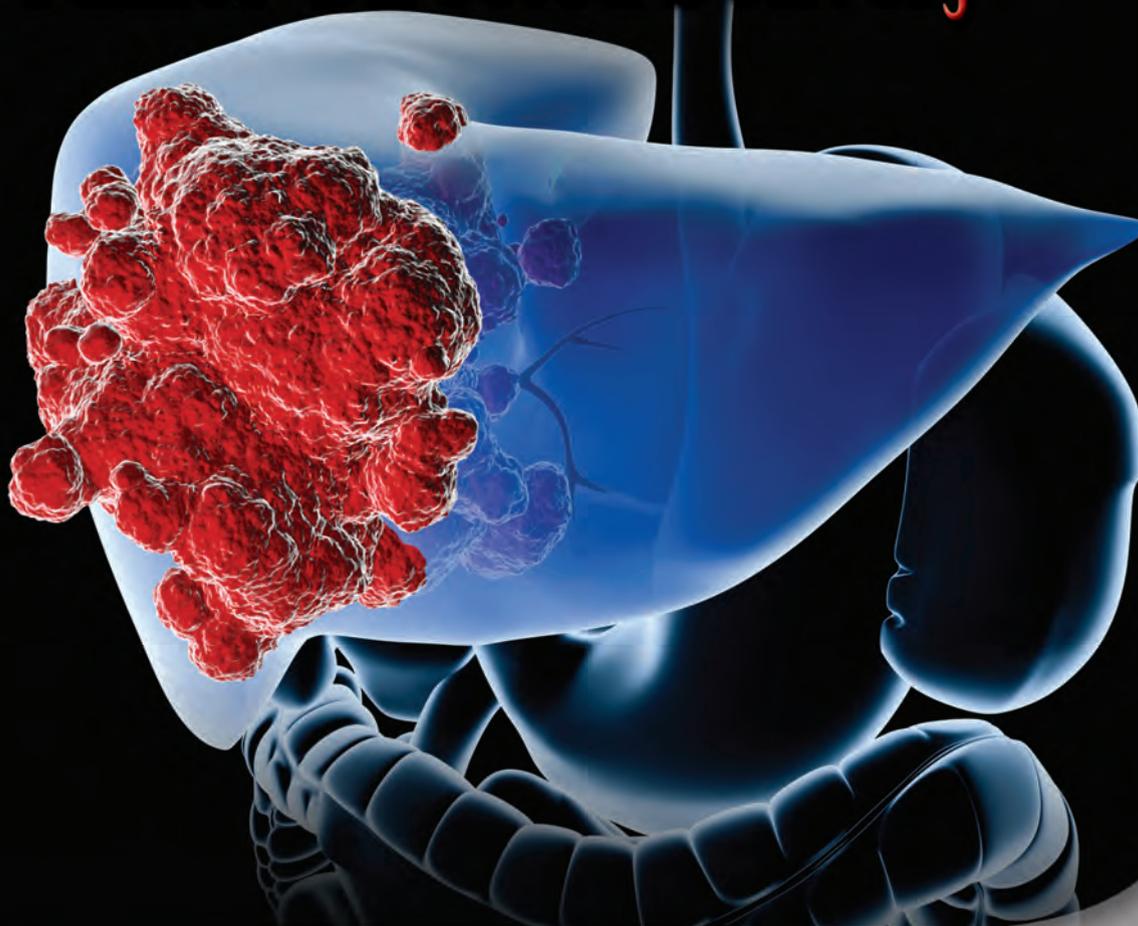


# Drug Development & Delivery<sup>®</sup>

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## Encore™: Optimizing Tumor-Directed Delivery



The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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# SPECIAL FEATURE

## Outsourcing Formulation Development & Manufacturing: Using a Single Provider Reduces Costs & Risk

By: Cindy H. Dubin, Contributor

The depth and breadth of outsourcing by pharmaceutical/biopharmaceutical companies realized last year is expected to expand significantly in 2016, particularly with regard to formulation development and manufacturing activities. In fact, a recent survey from That's Nice finds that 69% of the pharma/biopharma respondents expect to increase their use of contract development and manufacturing providers (CDMOs).

The survey identified the following as the primary reasons for this anticipated increase:

- A pipeline of drug candidates that is more robust than has been witnessed in more than a decade;
- An increasing rate of FDA NDA/BLA approvals, with 2014 and 2015 seeing near-peak numbers and similar

levels expected going forward, largely due to the greater number of accelerated approval pathways (Fast Track and Breakthrough Therapy Designations and Accelerated Approval and Priority Review processes);

- The growing number of biologic drugs in development, many by traditional pharma companies that lack biotech expertise;
- The entrance of numerous small, virtual startups into the market that have no manufacturing capacity;
- The increasing complexity of both small- and large-molecule drugs, such as poorly soluble compounds, antibody-drug conjugates (ADCs) and highly potent Active Pharmaceutical Ingredients (APIs), that require



**Lipid multi-particulates in a sprinkle capsule shell that can be utilized for pediatric formulations (Xcelience).**

specialized facilities, equipment, and operational expertise; and

- The movement away from blockbusters, many of which have or will soon fall off the patent cliff, to small-volume, niche and targeted treatments that require unique skills and expertise.

As pharma/biopharma companies look to expand their use of outsourcing in the areas of development and manufacturing, they want to do so with a single provider. Approximately 40% of the survey respondents believe it is very important to use a one-stop-shop CDMO to fulfill their needs from R&D through to commercialization.

This annual *Drug Development & Delivery* report highlights how CDMOs are evolving their models to become their clients' single provider and to accommodate their more potent, challenging products.

### **Almac—A Single-Provider Model From Trials to Commercialization**

Traditionally, biotech and virtual companies have embraced integrated drug substance and drug product services. Now, with Big Pharma looking to both rationalize internal capabilities and consolidate their supplier base, these companies are embracing an integrated services approach within their outsourcing model.

Almac offers a full suite of drug



**This Xcelodose 600s micro-encapsulation machine at Almac helps negate a need for expensive and time-consuming tablet/capsule development.**

substance and drug product development and manufacturing services, including processing of highly potent materials. "All services are delivered from a single site, thereby reducing risk and cost while simultaneously expediting time to the clinic," explains Brian Eastwood, Head of Business Development (Europe), Almac. "Vendor management is simplified, allowing our clients access to single-project management teams covering chemical and pharmaceutical development."

Within development, as pharma companies seek to address the need for pediatric versions of their new chemical entities, formulation development and clinical manufacture

of minitabiet presentations are on the increase. This dosage form, whether filled in sachet, capsule or bottle, offers the benefit of increased dose accuracy and flexibility, as required for the pediatric population.

Almac, in partnership with its clients, has recently expanded its minitabiet capabilities through the purchase of mid- to high-speed encapsulation machines, capable of filling minitabets, powders, and pellets into capsules. "In addition, the acquisition of both a stick pack machine and additional standard sachet filling technology has given our clients access to this in-demand dosage form for pediatric presentations," says Mr. Eastwood.

**Highly potent API production at CordenPharma Colorado.**



In addition to the pediatric population, continued focus on oncology therapies has led many CDMOs to develop and manufacture dosage forms for highly potent molecules. “We are witnessing a transition to low-dose API in-capsule presentations for Phase I and, in some instances, Phase II clinical trials within the oncology field,” he says.

To meet this increasing demand, Almac has acquired a third Xcelodose

600s micro-encapsulation machine.

“This API in-capsule route accelerates time to clinic, negating a need for expensive and time-consuming tablet/capsule development, with the added advantage of significantly reducing API burn for early-stage development.”

Recently, Almac partnered with a US-based client for the development of both the API and formulation of drug product. Having manufactured clinical,

registration, and process validation batches, Almac now produces the commercial product from its UK headquarter facilities.

“By leveraging our integrated API and drug product expertise, prior to and through NDA submission and approval, our client was able to take advantage of a single-partner approach with smooth transition through the drug development process and commercialization, saving time, transfers, and other uncertainties inherent in a multi-supplier process,” says Mr. Eastwood. “By doing so, Almac played an integral part in bringing a much needed treatment for a previously unmet medical need to the market.”

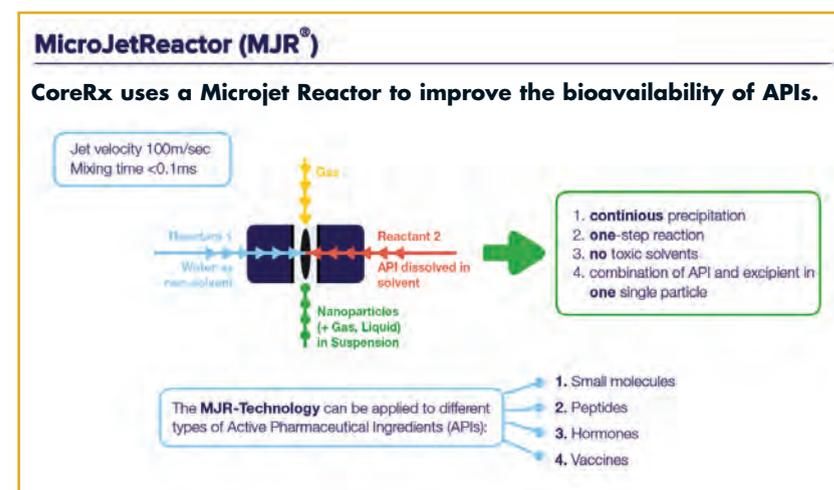
### **CordenPharma—Full-Service Capabilities Geared to Meeting Aggressive Timelines**

CordenPharma has seen increased outsourcing activities for formulation development and manufacturing, especially in some niche or specialized technologies (e.g. contained products such as antibiotics, oncology, highly potent, etc.). Due to this higher demand, pharmaceutical customers have moved towards shorter preferred supplier lists for development and commercial manufacturing. To meet the demand, CordenPharma is expanding capacity in all R&D groups, both in terms of personnel and equipment, explains Luca Porcu, Director, Global Small Molecules Platform, CordenPharma International.

CordenPharma provides full-service contract development and manufacturing to customers from early development (Phase I clinical studies) to commercialization. "Spanning from cGMP intermediates to APIs to final drug products, CordenPharma's integrated supply is especially effective for products in the clinical phase, where customers are looking for more flexible timelines, with preference to managing a unique supplier," says Mr. Porcu. To fill the gaps of existing market needs, CordenPharma is investing in new development and commercial capabilities and capacities, including the acquisition of new manufacturing facilities, which are also focused in forward and backward integration.

CordenPharma works closely with customers to provide a comprehensive development plan for all clinical phases to achieve product compliance, quality, and safety. "In addition, a Quality by Design (QbD) approach enables customers to gain robust manufacturing processes that will provide a stable supply throughout the development and commercialization phases, while still meeting their often very aggressive timelines," he says.

One recent development and manufacturing project involved support in meeting a customer's market demands for patients to gain or maintain access to their product after a shortage. The project required quick response time and expertise in all related production and regulatory activities. "CordenPharma was



selected for our ability to manage on very short notice, with a flexible, dedicated team that successfully provided a documentation package that enabled favorable and fast approval by the relevant health authority," explains Mr. Porcu. The approval was granted without need of a pre-approval inspection, resulting in an immediate restoration of supply to the customer's patients.

### CoreRx—Simple to Complex Formulation Handling

Formulation strategy has shifted in the last few years towards direct compression and roller compaction. Moving away from wet granulation, which is costly and has more potential issues with product stability, however, is still a necessary evil for dosage forms with high percentages of API that are not amenable to processing by any other method.

"To facilitate this switch, CoreRx has embraced the more highly designed excipients from either a particle engineering or co-processed perspective for both immediate- and

modified-release dosage forms," says Brian McMillan, Vice President and Chief Technology Officer, CoreRx. These include co-processed excipients such as Retalac and Parteck SRP-80 for modified-release formulations and Prosolv and Kollidon VA-64 for immediate-release dosage forms.

In some cases, enabling polymers to be used for direct compression where they previously could only be used for wet granulation can lead to more rapid formulation development, he says.

In addition to enhancing release profiles, CoreRx is focused on improving API solubility. "These APIs require more processing for particle size reduction, solid/spray-dried dispersion preparation, lipid complexation, and nanoparticle preparation in order to improve bioavailability," says Janice Cacace, Director Formulation Development, CoreRx. "For these processes, we recently acquired a microfluidizer and a Microjet Reactor."

For solubility enhancement and modified release, solubility/dissolution screening can become a burdensome

task. Six months ago, CoreRx acquired a Pion Rainbow fiber-optic system that can be used for real-time solubility and dissolution screening. "Because this is real time, and does not require the use of HPLC on the back end, the turn-around time has been decreased from days to hours," she says. "This rapid screening technique has become very important to us in the early formulation development stages."

### **Metrics Contract Services— Flexibility, Simplicity, & Scalability**

Metrics Contract Services (MCS) is embarking upon a \$65 million oral-solid dose site expansion, scheduled to become fully operational in late 2017. The expansion will double the current clinical manufacturing footprint and offer dedicated non-GMP development lab space for small-scale formulation development, GMP clinical trial materials for both pilot and mid-scale batch manufacture, and GMP commercial-scale manufacture. "The site expansion will increase our potent and non-potent commercial capacity by more than six times, and the expanded facility will position Metrics Contract Services to meet client needs ranging from Phase I to commercial," says Thomas B. "Brad" Gold, PhD, Vice President of Pharmaceutical Development, Metrics Contract Services.

Dr. Gold points out that flexibility and simplicity are key to successful formulating and manufacturing of

clinical trial material batches at Metrics Contract Services. "We can accelerate timelines and provide drug candidates to clinics more quickly. Often, we choose to employ simple API-in-capsule using our Xceledose simple formulation capsules or tablets for First in Man (FIM) Phase I clinical studies, depending upon the API physicochemical characteristics and clinical timeline. We have the ability to manufacture GMP batches at very small scale (100g). This is useful when API availability is limited, which is common in early project stages."

Regarding flexibility, a dedicated development area helps initiate projects quickly; within two weeks or less following contract approval. Potent-capable manufacturing suites in the R&D and the clinical manufacturing areas accommodate OEL Category 3 compounds. Granulators and supporting fluid bed dryers can be used for batches ranging from 1kg to 400kg; roller compactors for batch sizes as small as 10g facilitate continuous batch processing; blenders handle batch sizes between 100g to 450g; and tablet presses and encapsulation equipment on the R&D and clinical manufacturing side are capable of scaling up to commercial equipment.

The ability to scale up projects successfully is demonstrated in this late Phase I/early Phase II project that Metrics Contract Services handled a few years ago. "The client was managing multiple changes in the development/clinical timeline and API, something many companies experience with projects at that stage

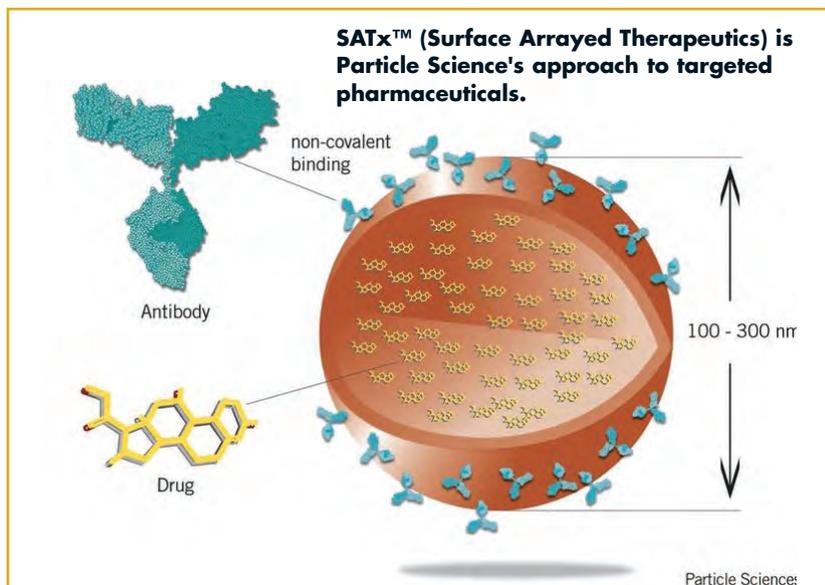
of drug development," explains Anshul Gupte, PhD, Associate Director of Pharmaceutical Development at Metrics Contract Services.

MCS provided analytical development and manufacturing support, and produced the clinical trial supplies throughout the Phase II and large Phase III trials. "To accommodate clinical requirements, we scaled up the formulation from 1kg to 400kg batch size, largely done while the product was still being manufactured under GMP, as API supply was limited along the way," says Dr. Gupte. Several QbD studies were conducted at various scales.

"The client recently had the drug product approved for commercialization in both the United States and the European Union," states Dr. Gupte.

### **Particle Sciences—Targeted Drug Products Using Nano Formulations**

More and more CDMO clients are demanding a model that provides end-to-end solutions. With the acquisition of Particle Sciences (PSI) by Lubrizol LifeSciences, PSI now offers exactly this—starting from polymers, through formulation development, and into commercial manufacturing on a global scale. "This minimizes the cost and risk of tech transfers plus shortens overall development timelines," says Robert W. Lee, PhD, VP, Pharmaceutical Development Services at PSI. "We also have established relationships with other providers offering



complementary services, including pre-clinical *in vivo* testing.”

PSI has a repertoire of formulation technologies focusing on BCS II and IV molecules. Dr. Lee says there are only a handful of viable drug delivery approaches—particle size reduction, amorphous forms, permeation enhancers, lipidic and polymeric systems, etc.—but each has different flavors and one size does not fit all.

One area of growth for PSI is in the formulation of biologics. “We can use standard delivery methods for biologics and have also developed proprietary approaches, including SATx™, which is our approach to targeted pharmaceuticals, and can be used for therapeutics as well as vaccines,” explains Mark Mitchnick, MD, CEO of PSI.

Targeted drug products are a key objective of pharmaceutical development, especially since the advent of monoclonal antibodies. These targeted pharmaceuticals are typically composed of monoclonal

antibody-drug conjugates (ADC). ADC technologies, however, do have several challenges that have limited and slowed their development and commercial use. New formulation technologies that use nanoparticles circumvent these limitations. In fact, more than 100 different APIs can be encapsulated by solid lipid nanoparticles (SLNP), claims Dr. Mitchnick. Physicochemical attributes can be tailored through inclusion of surfactants into the formations. The resulting particles can interact with either the hydrophobic or electrostatically-charged domains of amphipathic and hydrophilic molecules. These particles efficiently bind to, and are coated by, pharmaceuticals and biopharmaceutical molecules, and are being developed for monoclonal antibodies that target tumor cells and other tissues.

“These nanoparticle formulations effectively link biopharmaceutical and pharmaceutical molecules, like ADC, but without the need for, and

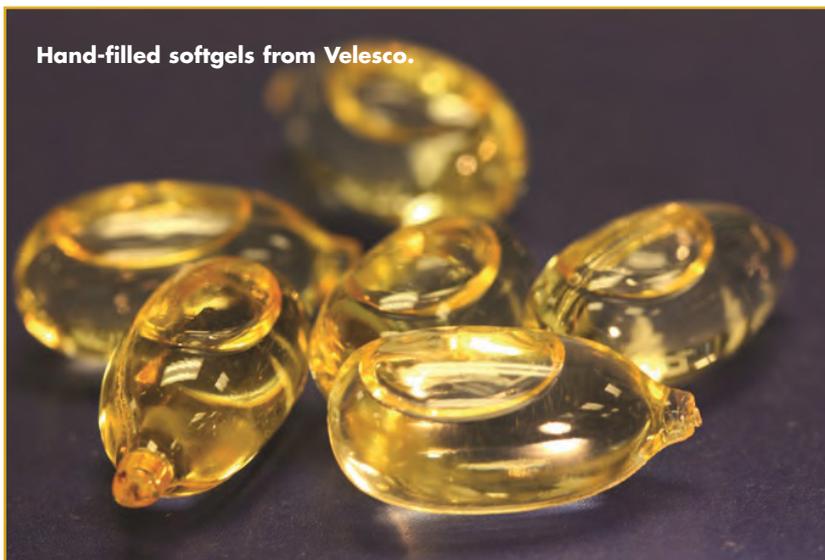
limitations of, conjugation chemistries,” says Dr. Mitchnick. “This results in final products with unique and useful physicochemical and biological attributes, including improved vaccine potency and safety, and targeted pharmaceutical and biopharmaceutical drugs directed against specific disease targets.”

### **Velesco Pharmaceutical Services—Air-Filled Softgel Capsule Shells Overcome Challenges With Highly Lipophilic Compounds**

Early-stage development of highly lipophilic drugs is considered challenging as such compounds typically have low and variable bioavailability, as well as questionable stability. In these cases, the traditional formulation strategy is to use liquid-filled softgel capsules. While generally this strategy is successful, it comes at a considerable cost as there could be a need to manufacture large batches due to equipment considerations with a commensurate high cost in terms of API utilization, says Lisa Crandall, MS, PMP, Associate Director CMC Project Management, Velesco Pharmaceutical Services.

“It is possible to manufacture one large batch of the lowest strength product and then dose subjects with ever increasing numbers of capsules to achieve higher doses,” says Ms. Crandall. “This is not a tactic to be recommended as the excipients used in softgel capsule fills can, at larger

**Hand-filled softgels from Velesco.**



doses, cause significant gastrointestinal side effects. Thus, the early development of highly lipophilic compounds is widely viewed as problematic and costly.”

To address this challenge, Velesco Pharma has developed a strategy of hand filling pre-formed, air-filled softgel capsule shells. This allows small batches to be manufactured with minimal waste and, as there is little set-up, the batches can be manufactured quickly.

The initial pre-formulation and liquid-fill development activities for these capsules are no different than those conventionally followed. This has the advantage of allowing the liquid-fill vehicle’s use in later, larger batches produced in the traditional manner. Having determined a suitable vehicle, and after qualifying the analytical methods, Velesco Pharma then prepares the first stability batches. These typically bracket the lowest and highest strengths envisaged by the client. Filling the capsules admittedly

requires some dexterity and a steady hand, but the process is fairly straightforward, says Ms. Crandall.

The air-filled softgels look like regular filled softgels with the addition of a narrow, hollow “tail.” Using a small syringe fitted with a very fine-bore needle, the liquid-fill solution is slowly introduced into the body of the shell. When the correct amount of liquid has been filled, the tail is sealed as close to the capsule body as possible by using heated forceps. In this way, batches of up to a few hundred liquid-filled softgel capsules can be prepared in a day.

The addition of a new, lower or higher dose to a stability program can be achieved quickly and at minimal cost both in terms of API and time needed to prepare the supplies. In the same way, as the clinical trial progresses, the preparation of additional, unforeseen strengths can be accomplished in a timely fashion with minimal expenditure of bulk drug.

As an example, one client, whose

drug’s initial estimated dosing range was originally believed to be less than 100-fold was able to dose over a 250-fold range as data became available during the study. The additional dose groups were added as the study progressed with the new supplies being made “just-in-time,” the strength being based upon PK data from the previous dose group.

### **Xcelience, a Division of Capsugel Dosage Form Solutions—Bi-Layer & Multi-Particulate Formulations**

There has been an increased interest in combination products, but there are challenges in developing these products, such as ensuring the two APIs will be compatible and if they need different release profiles. If it is found that a combination product can successfully overcome these concerns, then the product can be developed using several formulation development technologies, such as a bi-layer tablet approach, where one layer can have a controlled- or delayed-release profile and the other layer can have an instant-release profile.

“Xcelience currently offers the ability to make bi-layer tablets, and because of the increased interest in combination products, we are purchasing a second bi-layer tablet press so that our experimental formulation development lab will have its own tablet press,” says Paul Skultety, PhD, Vice President, Pharmaceutical Development

Services, Xcelience, a division of Capsugel Dosage Form Solutions. "In this way, formulation development can be accomplished quicker and without interrupting clinical supply manufacturing. As the tablet presses are similar, it will make for a smooth transition from the formulation development lab to the GMP manufacturing facility."

Xcelience formulators can develop bi-layer tablets with the specific release profile required for the desired product characteristics. "We routinely develop and manufacture bi-layer tablets that have different release profiles for each layer," he says.

In addition to bi-layering, Dr. Skultety says there is greater focus on multi-particulate formulations for combination or single entity-products manufactured by either extrusion/spheronization or drug layering insert cores using fluid-bed technology. The APIs produced by either process can be manufactured into separate bead formulations and then encapsulated as the finished dosage form. If desired, the separate beads can maintain their own unique dissolution profile. Another approach is capsule-in-capsule technology, where a smaller pre-filled capsule is inserted into a larger liquid-filled capsule, each containing a separate active ingredient. Xcelience expanded its access to capabilities and product technologies in these areas when it joined Capsugel Dosage Form Solutions earlier this year.

Within the multi-particulate

formulations space, there is growing interest in specialized applications such as lipid multi-particulate (LMP) technology for pediatrics. LMPs, which are produced using melt-spray-congeal technology, utilize a range of Generally Recognized As Safe (GRAS) lipid-based excipients to encapsulate active ingredients and achieve a high degree of palatability, as well as solubility improvement and/or controlled release—depending on the target product profile needs.

For pediatric use, beads produced by any of these processes can be encapsulated using sprinkle capsules. This allows for the beads to be emptied and sprinkled onto something like yogurt or applesauce.

"The advantage of the multi-particulate system is that it provides more flexibility in the dose range (by adjusting the fill amount of the beads) that can be developed, and it can be encapsulated with either a two-bead fill, or a bead fill with a powder fill," says Dr. Skultety. "We routinely perform extrusion/spheronization, fluid-bed processing, LMP, and mini-tablets in both the experimental labs and in GMP manufacturing. The resulting beads or tablets can be manufactured to have controlled-, delayed-, or targeted-release dissolution profiles using a matrix mechanism or by providing a membrane film coat to control the release."

As an example, a client was developing a bead-filled capsule utilizing extrusion/spheronization for

a Phase I study. At the very last minute, the client needed to change the dosing in the Phase I study and go to a much broader dosing range. "Because of the flexibility of dosing beads in a capsule, Xcelience was able to adjust the lower starting dose from 10mgs to 5mgs and change the highest dose from 50mgs to 75mgs. This was accomplished with the same amount of API, and without the need for additional experimental work or interrupting the product schedule," explains Dr. Skultety.

Also under the Capsugel umbrella are Powdersize, Bend Research, and Encap Drug Delivery, which Xcelience can go to for help with troublesome APIs. For example, if the particle size of the API needs to be reduced, Powdersize can perform experimental trials with minimal amounts of API and reduce the particle size to the size required.

## Reference

1. That's Nice, CDMO Buying Trends, online, accessed March 17, 2016.

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