Drug Development & Delivery

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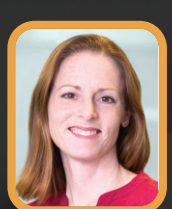
Prefilled Syringes & Biologics: The Perfect Partnership

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



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Special Feature

Outsourcing Formulation Development & Manufacturing: Specialized Capabilities for Small & Large Molecules

By: Cindy H. Dubin, Contributor

The demand for outsourcing pharmaceutical formulation development and manufacturing is on the rise for drug developers at all levels.[1] A new report predicts that the global contract development and manufacturing organization (CDMO) outsourcing market will to reach $44.17 billion during 2020-2024.[2]

Sectors of the CDMO market – sterile injectables, prefilled syringes, biologics APIs, and viral vectors – are expected to expand quickly, driven by an accelerating shift in the pharmaceutical market toward innovative biologic and cell and gene therapy products. Nonetheless, small molecules will continue to represent the majority of prescribed drugs for the foreseeable future and thus are the major growth driver for the CDMO market.[3]

Experts see a strong correlation between size of a company and its likelihood to outsource.[3] In 2017, manufacturing of 20% of newly approved drugs was outsourced by Big Pharma; this increases to 80% of all manufacturing being contracted out by small biotech/pharma. And all 15 newly approved drugs in 2017 owned by small companies were supplied by CDMOs.[4]

A Höfliger ModuleC LS is the centerpiece of precision filling capabilities at Experic, Cranbury, NJ.

In this annual *Drug Development & Delivery* magazine report, some of the key players in the CDMO market present case studies about how they are helping pharmaceutical and biopharma companies overcome a variety of formulation and manufacturing challenges.

Ascendia: Three Platforms Enhance Formulations

Ascendia offers tailored formulation approaches, leveraging its suite of technology platforms: NanoSol®, EmulSol®, and AmorSol®. The technologies are used to formulate biological therapeutic entities that could help address delivery issues associated with solubility, stability, and permeability.

NanoSol helps produce nano-sized drug particles; EmulSol is a technology for production of oil-in-water nano-emulsions; and AmorSol is for the production of amorphous solid dispersions.

Jim Huang, PhD, Founder and CEO of Ascendia, explains that the versatility of these technologies for use in both small and large molecules has grown the company's oral and injectable business. In some cases, the technologies have been used to deliver large molecules orally by enhancing GI stability and permeability.

"A client approached us with a peptide that has a high molecular weight for delivery by oral route of administration," he describes. "There were three delivery challenges facing the peptide: solubility, permeability, and GI stability. Using Ascendia's EmulSol technology, we dramatically improved bioavailability of the peptide in animal models to enable further development of the project by oral route," he says.

Catalent: Providing Small-Molecule Options for Expedited Programs

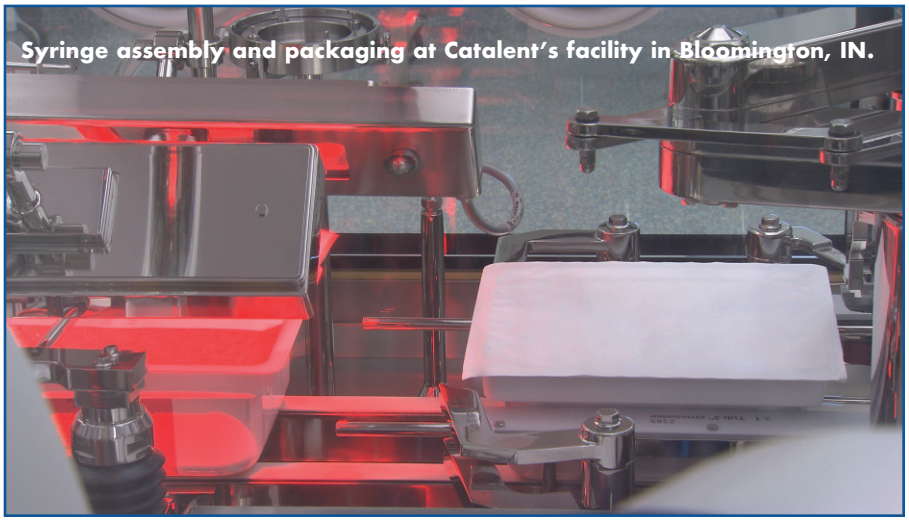
Rare diseases, fast-tracked drugs, and oncology treatments now account for much of pharma's development pipeline, so it is important that CDMOs provide specialized capabilities, technology, expertise, and experience relevant to these types of programs. For expedited pathways, it is important, too, that development partners understand the interwoven and related steps essential to progressing a program efficiently and quickly. To that end, Catalent has invested in technology and capabilities such as hot melt extrusion, spray-dry dispersions, and lipid formulation to provide options for small-molecule development, often to address the all-too-common hurdle of poor solubility and bioavailability.

"By leveraging relevant experience and drug development knowledge, we can demonstrate strategies that maintain the integrity, quality, and timeliness of the development and manufacturing processes at the accelerated pace required of expedited programs," says Elliott Berger, Vice President and Chief Marketing Officer, Catalent.

As an example, MGB Biopharma, a biotech company based in Scotland, is developing a new class of anti-infective medicine based on Minor Groove Binder compounds. MGB-BP-3, a novel small molecule, is currently in Phase 2a in the US and Canada. The drug is being developed for the treatment of clostridium difficile-associated diarrhea. Catalent offered a tablet formulation through its OptiForm® Total Supply solution, incorporating formulation development, clinical trial material manufacturing, and supply and distribution to patients. The first clinical trial kits were successfully delivered to MGB's patients within six months.

Catalent recently announced biologics-related COVID-19 programs, including helping to accelerate the availability of manufacturing capacity for Johnson & Johnson's lead vaccine candidate. Additionally, Catalent partnered with Arcturus Therapeutics to support the drug substance manufacture of its COVID-19 mRNA-based vaccine candidate. "Catalent continues to expand its biologics drug substance capabilities and capacity significantly with a fourth and fifth biomanufacturing train in Madison, WI, and the recent completion of a $14 million commercial packaging expansion, in Bloomington, IN.

In February 2020, Catalent completed the acquisition of MaSTherCell to add cell therapy to its technology-focused cell and gene therapy CDMO capabilities.



Syringe assembly and packaging at Catalent's facility in Bloomington, IN.

The acquisition complements the specialized expertise in gene therapy and adeno-associated virus (AAV) vectors that Catalent acquired with Paragon Bioservices in May 2019.

HERMES PHARMA: ODG Formulation Expanded Sponsor's Brand

Many people experience swallowing difficulties with traditional tablets and capsules, so pharmaceutical companies are looking for ways to address this problem. Sponsors look to HERMES PHARMA to access experience in user-friendly oral dosage forms, for existing products or as part of new product development. As a full-service CDMO, HERMES PHARMA can take a product from technical through to regulatory and clinical development, a capability its customers increasingly require.

As specialists in innovative, user-friendly oral dosage forms – such as effervescent and chewable tablets, orally disintegrating granules (ODGs), and instant drinks – HERMES PHARMA is actually seeing a growing market for such products as patients increasingly exercise choice and manufacturers compete to deliver what consumers want.

"Taste masking is critical to the acceptance of many orally administered products, especially those with a long residence time in the mouth, such as ODGs," says Dr. Martin Koeberle, Head of Analytical Development & Stability Testing, HERMES PHARMA. "We recently deployed a solvent-free hot melt coating (HMC) technology capable of masking even very sour and metallic tastes. HMC involves covering the API solid core with a molten coating at a controlled temperature, which then solidifies to create a homogeneous coating."

He explains that HERMES PHARMA used this technology for a client whose generic, over-the-counter (OTC) drug was formulated as an effervescent tablet, but wanted an additional 'on-the-go' oral formulation to meet consumer demand. "However, the taste characteristics of the API were poor, making the desired re-formulation difficult. Our use of HMC to mask the taste enabled the successful development of a new formulation in the form of ODGs that require no preparation and can be administered directly, extending our client's product range and adding greater value to the brand."

Dr. Koeberle points out that while the ease, convenience, and relatively low manufacturing costs of orally administered formulations means there will always be a strong market for them, there are challenges, such as making sure that regulatory bodies receive and fully understand data that is appropriate for novel approaches.

Hovione: Particle Engineering for Small & Large Molecules

Hovione has strategically decided to explore niche areas that are difficult to tackle and can benefit from its expertise in particle engineering. Examples include the oral delivery of Amorphous Spray Dried Dispersions and the manufacturing of dry powders for inhalation.

Historically, Hovione has mainly focused on small molecules and their pre-formulation, by means of particle engineering, to overcome solubility limitations or to render them suitable for inhalation. In recent years, Hovione has experienced some challenges with large-molecule particle engineering, but intends to increase its activity in this area. "The delivery of large molecules is leading us to novel areas of aseptic particle engineering that we will be introducing in our portfolio," says Teresa Alves, PhD, Senior Director, Science & Technology, Hovione.

Dr. Alves adds that there are opportunities to apply lessons learned with small molecules to large molecules. "We see a trend in the increased delivery of biologics by inhalation, particularly dry powder inhalation, including the delivery of peptides, proteins, hormones, DNA, RNA, etc. We are also actively working to process low bioburden biologics to solve difficulties that our clients experience in limited shelf life, high viscosity, and new areas of administration."

Márcio Temtem, PhD, Site Manager, R&D services, Hovione, explains how the company's sponsors have benefitted from Hovione's experience in spray drying. "Spray drying scale up runs with minimum work at scale," he says. "This is what we call Development by Design. By relying on stasticial and mechanistic models, databases, and scientific know-how, we can save API and time required for CMC process development. We have successfully applied these tools to biologic molecules, namley proteins, antibodies, and fragments of antibodies, and some of these solutions have evolved to commercial manufacturing."

Lubrizol Life Science Health: Early Engagement in Complex Formulations Ensures Scalability

Getting a CDMO engaged in the development process as early as possible avoids spending time exploring the wrong solutions and coming up with suboptimal formulations that need to be corrected be-

fore manufacturing.

"By bringing us in earlier in the process, we can more accurately assess which technologies and approaches can work on a project," says Robert Lee, President of Lubrizol Life Science Health, CDMO Division. "To help with this, we have created feasibility programs for nanomilling and microspheres designed to accelerate product development and provide early-stage support. If a feasibility program proves successful, we are positioned to provide ongoing optimization, scale-up, and manufacturing."

He says Lubrizol's proprietary LyoCell® technology combines a lipid-based approach with nanoparticles, while leveraging the power of a reverse cubic-phase matrix. This assures that the hydrophobic and hydrophilic domains in these nanoparticles are never more than a few nanometers apart, which may lead to unique solubilization properites, he says. Intended for a broad range of applications, LyoCell technology uses Generally Recognized as Safe (GRAS) ingredients and is useful in virtually every route of administration, including injectables.

"Although nanomilling has been around for decades, it is a go-to technique for certain APIs," he says. "The value is especially significant for parenteral dosage forms because this may provide a pharmaceutically elegant formulation, i.e., neutral pH, isotonic, minimal excipients, and the bulk of the composition being water followed by API."

Clients come to Lubrizol with complex development challenges. "Often, these are great product ideas, but their formulations were developed in an R&D environment by organizations without much experience in developing complex dosage forms intended for cGMP manufacturing for clinical use," says Mr. Lee. "We transfer in these lab-scale formulations and create a viable product by using a scalable process in conjunction with optimizing the formulation. This translates it into something that is acceptable for GMP production and ultimately commercial production."

An example is when a client requested that Lubrizol develop a transdermal patch to deliver two APIs – one very potent and at a very low concentration, and the other not as potent, but at a much higher concentration. After evaluating the physicochemical properties of the APIs, loading, and target flux, Lubrizol recommended a gel, rather than a patch.

"At first, our client was not fully convinced, however, due to limitations with the composition of the delivery system, very little of the APIs were released and the levels were unable to reach therapeutic concentrations," Mr. Lee explains. "After this, we were given approval to develop a gel. The gel development program was extremely successful, and our formulation was progressed into Phase 2 studies."

Metrics Contract Services: Full-Service OSD Development

Metrics Contract Services, a division of Mayne Pharma, is a targeted specialist in the novel oral solid dosage (OSD) development space, providing early-stage development through global commercial supply. A recent major expansion of its North Carolina campus brought a new commercial manufacturing facility online, enabling Metrics to offer services under a single FDA registration service, ranging from first-in-human development and clinical trial materials to global commercial supply. Potent handling and analytics round out clinical-to-commercial capabilities.

John Ross, President, Mayne Pharma USA, says the small-molecule OSD segment remains the largest market within pharmaceuticals, and continues to grow at a rate of 6% annually, representing significant opportunity for growth. Occasionally, some large-molecule OSD opportunities exist, and Metrics is currently engaging in some of those.

With regard to small-molecule OSD, a Metrics client had developed a simple direct-blend capsule formulation consisting of three potencies: 2mg, 10mg, and 50mg capsules. The manufacturing process had been scaled up to an automated encapsulation process. While the 2mg capsule drug load was about 1.5%, the drug load of the dose-proportional strengths 10 and 50mg were 10%, respectively, explains Thomas B. "Brad" Gold, PhD, Vice President, Pharmaceutical Development, Metrics Contract Services.

This presented a few problems. First, blend uniformity values for the 2mg potency were unacceptable and were confirmed with content uniformity that likewise did not meet specification. Second, the capsule sizes used were on two extremes (Size 4 and Size 00), which were considered to pose patient compliance issues (size 00) and manufacturing issues (size 4) during the automated encapsulation process.

To resolve these problems, Metrics scientists improved blend uniformity by incorporating a geometric blending strategy with alternate blending and sieving steps. The blend was milled before adding the final geometric portion of excipients. Also, Metrics scientists collected and tested blend uniformity samples at pre-determined points during blending to optimize blending time. Bend uniformity improved significantly with this strategy, says Dr. Gold.

Subsequently, scientists developed a granulation process for a compressed

tablet dosage form, which theoretically would address both blend uniformity and capsule size issues. "The result was a successfully developed and manufactured lead tablet formulation using a dry granulation process," he says. "Blend uniformity improved significantly for the tablets, as did content uniformity. Moreover, scientists made all the required tablet strengths in patient-friendly sizes and shapes." Clinical trial material is scheduled for manufacture in Q3 2020, pending stability results of the tablets.

Quotient Sciences: Translational Pharmaceutics Streamlines Development

"Biotech and pharma sponsors select Quotient Sciences as their formulation and manufacturing partner because they need program acceleration," says Nutan Gangrade, Global Vice President, Pharmaceutical Sciences, Quotient Sciences. "Scientific expertise, technical competence, and quality are paramount, but being able to shorten drug development times for our customers by more than 12 months is a game changer."

One way to improve efficiency and shorten development timelines is to break down the barriers between product manufacturing and evaluation in clinical trials. Quotient Sciences has bridged this gap by establishing an operational platform called Translational Pharmaceutics® that integrates formulation development, real-time product manufacturing, and clinical testing. "By combining the work of CDMOs and contract research organizations (CROs) in one offering, outsourcing and program management are simplified and streamlined, and development times and costs are significantly reduced," he says.

The outcomes from a recent study by Tufts Center for the Study of Drug Development (CSDD) demonstrate that Translational Pharmaceutics creates substantial benefits to pharma and biotech companies compared to traditional multi-vendor development approaches. The Tufts CSDD team evaluated data provided by Quotient for a range of programs conducted over the past decade, including actual dates taken from executed Translational Pharmaceutics project plans. A group of independent industry consultants provided benchmark data for conventional timelines for similar programs to enable comparison and identification of time and cost savings.

Although the Translational Pharmaceutics platform can be applied to nearly any development project, the Tufts study focused on three applications with small molecule oral drug candidates: the transition from first-in-human to proof-of-concept; the development of drug products that required enhanced solubility through formulation control; and the development of modified-release formulations. The Tufts CSDD research concluded that applying the integrated approach of Translational Pharmaceutics to the programs resulted in mean time savings of >12 months and R&D cost reductions of >$100 million per approved molecule.

Mr. Gangrade says that Quotient Sciences has developed state-of-the-art facilities in the UK and US for formulation development, GMP manufacture of clinical trial materials, and for running adaptive development programs. To date, Quotient has completed more than 400 programs using Translational Pharmaceutics with molecules across the development spectrum, including the acceleration of first-in-human to proof-of-concept programs, the optimization of clinical formulation compositions, and as part of late-stage or lifecycle management programs (505(b)(2) projects).

"Biotech and pharma sponsors also achieve other benefits with Translational Pharmaceutics, including formulation screening and bridging within a single clinical protocol, maximizing potential for "right first time" by using clinically driven decisions, seamless supply of drug product(s) into subsequent patient studies, significant reductions in drug substance (API) consumption, and supply chain efficiencies," he says.

Recipharm: Tackling Complexity in Scale Up

There is strong interest in orphan drugs, specialized treatments, and innovative drug products based on existing molecules. Recipharm solves different challenges and manages complexity when developing and scaling up these innovative products, explains Torkel Gren, Science & Technology Officer, Recipharm. "Our end-to-end development and manufacturing offering is one of the advantages of working with Recipharm as it means we can simplify a molecule's journey to market."

As an example, Recipham was selected by the Swedish speciality pharmaceutical company, Lobsor Pharmaceutical AB, to devlop its Lecigon gel designed for the treatment of advanced Parkinson's disease (PD). The gel is administered to the small intestine via a portable pump, overcoming the traditional challenges associated with alternative IV-based solutions. "Throughout the development process, we performed all the formulation work, as well as developing the necessary analytical methods," Mr. Gren explains. "However, the complexity of the formulation meant that we faced several hurdles during the process."

In this instance, combining multiple APIs into a single formulation created some

challenges, primarily because each compound called for specific formulation features to ensure optimal properties, such as stability. There was also a heightened risk that the APIs would affect the stability of each other, especially in a gel formulation. The presence of several APIs also increased the complexity of the analytical methods required, making the development of suitable analytical chemical methods even more complex.

"Our team formed a project group during the initial stages, which brought together experts across various areas in the organization: formulation, manufacturing technology, packaging, analytical chemistry, and quality assurance," he says.

This helped ensure any processes developed remained suitable during the scale-up phase. To initiate the development process, a risk-based assessment of the intended product, including identification and assessment of the Quality Target Product Profile (QTPP) and corresponding Critical Quality Attributes (CQA), was undertaken. Mr. Gren says: "This provided a solid starting point and ensured subsequent work focused on the critical aspects of the product."

Singota: Preserving APIs in Biologics Manufacturing

The biologics market for fill/finish has been growing considerably, and many CDMOs are catering to pharmaceutical companies that have high-value, small batch-filling needs. Handling high-value, complex active ingredients requires an aseptic dosage manufacturer to protect against unnecessary loss of active ingredient.

"Special handling of biologics starts the minute the materials enter the facility by supply chain operators," says Laura Englander, Senior Business Development & Marketing Manager, Singota.

The Vanrx SA25 Aseptic Filling Workcell at Singota Solutions' facility.

Once received at the finished product manufacturing facility, the bulk drug substance is subject to numerous sampling and testing procedures. When manufacturing small batches, the portion of the total bulk active consumed by QC-related activities can amount to a large portion of the overall consumption of active for any given production batch, she explains. "It is important to consider sampling requirements and to minimize the consumption of the precious material while still meeting stringent testing requirements," she says.

An important early task for pharmaceutical companies, often in conjunction with their CDMO, is to produce a prospective estimate of the non-production-related needs for active ingredient to ensure that sufficient material will be available to support the manufacture of the required number of units of finished drug product to meet production goals. "Especially for early clinical trial production, working with a CDMO who understands the areas in which to minimize client material loss can be an effective means of reducing the use of precious active ingredient while remaining compliant with regulatory guidelines," says Ms. Englander.

To help biotechnology and pharmaceutical clients meet the challenges they face in producing small to medium-sized batches of sterile injectable products, Singota invested in the Vanrx SA25 Aseptic Filling Workcell in 2016. The technology combines gloveless isolator technology with high-precision robotic handling and filling equipment.

At Singota, formulation and sterile filtration are typically performed using single-use systems that are connected to the pre-sterilized disposable product filling pathway. Setup of these systems is simple and standardized across a variety of batch sizes and container/closure combinations. Assembly configurations minimize the product hold-up volume between the bag assembly and the filling needle. She explains: "For a batch with a fill volume of 1mL, the initial filling pump calibration consumes only a few doses of product, filtration loss, and end-of-batch holdup volume are negligible, resulting in overall product loss of less than 10mL. The result is a high yield of finished drug product."

Almac: Tailoring Solutions for Individual Drugs

Drug product type is always changing. Almac, a CDMO specializing in the development and manufacture of solid, oral dose, and small molecules, is witnessing a significant growth in developing and manufacturing age-appropriate formulations, especially for pediatrics, mainly multi-particulate formulations such as mini-tablets filled into stick packs.

Although Almac specializes in the clinical and commercial manufacture of solid oral dosage forms, the CDMO also has a range of solutions for labelling and packaging injectable drug products across its commercial facilities in the US, EU, and UK. "We continue to invest in our commercial packaging capabilities from vial and syringe labelling to semi-automated complex kit assembly," says John McQuaid, Vice President Technical Operations, Almac.

Almac supports the launch and market supply of several gene/cell therapies from its European Campus in Dundalk, Ireland. "With each cell/gene therapy product having its own unique handling, packaging, and 3PL distribution requirements, flexibility, responsiveness, and providing a tailor-made solution for every client is paramount," says Mr. McQuaid. "An example of our tailor-made, ultra-low temperature product solutions would be upon receipt of an order, which, depending on the gene therapy, could be as niche as one vial per batch. Our specialist team picks the product from storage, labels, packs over dry ice, and distributes direct to the end user within 24-48 hours."

A recent case study involved a client partner moving from a transactional fee-for-service model to one that enabled dedicated capacity on key Xcelodose technology to support clinical trials. Mr. McQuaid says: "The key element that made the 'reserved capacity' business model a success was the establishment of dedicated teams on both the Almac and client side, underpinned by strong project management. By utilizing this flexible business model, the client partner was able to secure capacity on Xcelodose technology, providing full flexibility of resource utilization to meet any changes in demand for the development of their portfolio of early-phase drug products."

Experic: Process Feasibility Mitigates Process-Related Risks

Many organizations that develop drugs focus primarily on what to make and not how to make it, even though the way in which a product is made can impact its ultimate performance. That is where Experic steps in. "We help companies optimize their products for clinical trials — from manufacturing, packaging, and labeling to clinical supply logistics — and then transition to eventual commercial-scale production," explains Jeffrey P. McMullen, Chairman and CEO, Experic.

Experic currently serves companies with both small and large molecules in their pipelines. While the delivery platforms differ for small and large molecules, Mr. McMullen says Experic complements its oral capsule-based technologies with inhalation- and autoinjector-based manufacturing technologies, and provides packaging, labeling, kitting, and clinical supply management services for both types of molecules.

A primary goal at Experic, he says, is to ensure process feasibility and robustness as clients progress their products from clinical development to commercial-scale production. A Modu-C LS is a modular trolley-based system with fast interchange of dosing systems that can fill up to 25,000 capsules per hour with up to100% inspection via an in-process control check weighing or Advanced Mass Variation sensor. Features include quality checking of capsule integrity, a capsule polisher, and metal detection system.

Understandably, companies want to know how to best manufacture their products. As a recent example, a leading pharmaceutical company contacted Experic about struggling with a new process development project. "We conducted a series of manufacturing experiments to evaluate the characteristics of that client's product," says Mr. McMullen. "From this data, we found that its cohesiveness and propensity to adhere to equipment surfaces created barriers to achieving a robust manufacturing process. This led to revisions in the process that allowed development to progress."

Early development of pharmaceuticals rightfully focuses on efficacy and safety, but delays in optimizing process development of the finished dose can result in some unwelcome late-stage surprises. "That is why we strongly encourage companies to consider manufacturing feasibility assessments early in the development process," says Mr. McMullen. "This allows clients to best capitalize on the investments made in their product and avoid scale-up delays on the pathway to commercialization. Experic's approach combines the application of equipment capabilities, powder handling expertise, and an understanding of the critical quality attributes of a product. This gives us the perspective to solve both manufacturing problems and to identify and mitigate related process risks."

Spray drying of highly potent drugs at Idifarma's facility.

Idifarma: Highly Potent Small-Molecule Capabilities

The growing demand for high potency active pharmaceutical ingredients (HPAPI) in drug manufacturing is fueling the need for high potency handling capabilities. Idifarma has specialized capabilities for niche and highly potent drugs as well as spray drying capabilities. This attracts low-volume projects involving highly potent drugs.

"The capacity to handle highly potent compounds and the flexibility to manufacture small-scale batches are increasingly important for many of our customers and products," says Manuel Leal, Business Development Director at Idifarma. "While many firms offer spray drying, Idifarma is one of only a handful of firms worldwide that can do so for highly potent drugs, such as hormone and oncology drugs, while also integrating the manufacturing of finished drug products in oral solid forms in the same facilities."

Idifarma is catering to a growing segment in the small molecules field: oncology treatments. Within the small molecule space, oral drugs remain one of the preferred options (over 50% of total small molecule drug products are oral) due to its cost-effectiveness and patient friendliness. "Our ability to manufacture highly potent drugs and small batches, which is required for many of them, and our differentiating technologies, enable us to collaborate on projects involving innovative and hybrid drugs," he says.

He points out that Idifarma has collaborated on many projects with a focus on challenging drugs. For instance, in a recent project, Idifarma scientists increased the solubility of a BCS Class II product 8 times, helping achieve the same therapeutic effect with a lower amount of API. "Improving the bioavailability of poorly soluble APIs is one of the most common challenges in the industry," says Mr. Leal. "In another project, we reformulated an injectable drug for a severe indication as an oral dosage form, resulting in great advantages for the patients and for the sustainability of the healthcare systems."

MedPharm: Live-Agent Topical, Transdermal Formulations

MedPharm's growth over the last few years can be attributed to developers recognizing that the topical and transdermal area, while having many unmet medical needs and offering attractive returns, requires specialist knowledge that they typically do not have in house. This increased recognition has coincided with MedPharm developing sophisticated *in vitro* performance models based on fresh human tissue to ensure optimal formulation development and the de-risking of programs before important investment and/or clinical decisions are made. MedPharm has expanded its services in this area to cover applications to the eyes, nose, and lungs as well as skin and mucosal membrane epithelia. The most recent model allows clients to screen compounds targeting coronaviruses using infected cultured human nasal or lung tissue.

MedPharm works with a range of clients, including those who want to deliver topically live agents, such as bacteria or viruses/phages. The is partly fueled by the interest in the microbiome on skin and mucosal membranes. "These products have their own challenges, particularly with respect to scale up and manufacture," says Jeremy Drummond, Senior Vice President of Business Development at MedPharm. "At this point, MedPharm is supporting clients in product development and we have invested in the analytical procedures needed for these agents."

Cost-effective process development of complex cream ensures consistent quality and on-time delivery of product at a time when a quality failure or delay can have severe financial conse-

Recro Gainesville supports challenging development and manufacturing projects for oral solid dosage forms, such as those with complex modified-release requirements.

quences for a project. Recently, the MedPharm team was asked to provide multiple 25kg batches of a complex cream for a Phase 2 atopic dermatitis clinical trial by a large global pharmaceutical company. "Failure to supply or delay would increase the time to market (lost sales) and halt the start of the scheduled clinical trial (increased costs)," Dr. Drummond says.

MedPharm identified the Critical Process Parameters (CPP), such as homogenization speed and time, and cooling rates at different stages. A suitable factorial design of 12 runs using 1kg lab reactors, which model the large scale, was developed. Then, a key Critical Quality Attribute was identified to be the rheology profile of the final product. Dr. Drummond explains that this work showed that the rheology could be particularly sensitive to the homogenization time and speed, and appropriate parameters were set. An initial run at the larger scale confirmed that the selected process and parameters resulted in a product that met all specifications. This all could be achieved without delaying the project.

"Subsequently, more than 15 clinical batches were manufactured under cGMP with reproducible quality using the optimized process and used in clinical trials," he says. "Given the sensitivities to key parameters observed, this almost certainly would not have happened without the process evaluation work. Additional large-batch production would have wasted significant amounts of a high-value API and impacted the completion of the clinical trials and subsequent product launch."

Recro Gainesville: Handling Challenging OSD Formulations

All clients of Recro Gainesville have one thing in common: complex issues that need to be addressed and not a lot of time to address them. As an agile CDMO, Recro Gainesville shepherds projects through the development process and manufactures products as they progress through various clinical phases leading up to a regulatory submission.

"Clients have a certain peace of mind knowing they can start a development project with Recro and see that product all the way through to commercialization with the same company," says Myke Scoggins, PhD, Director, Product Development at Recro Gainesville. "This eliminates costly delays they would normally encounter having to conduct transfers between stages of development and then finally to a commercial manufacturer."

Recro was presented with a project that had two APIs that were incompatible with each other. In addition to incompatibilities, there was a need for an immediate-release pulse for both APIs as well as a modified-release portion for maintenance of plasma levels to achieve reduced daily dosing. Recro took the approach of formulating a multiparticulate pellet system using a rotary granulation process. Inert sugar spheres were used as a substrate onto which API was applied by powder layering. Each API was individually processed to form two separate populations of pellets. These pellets were coated with a nonfunctional (in terms of release rate) coating to provide a protective layer between the APIs to mitigate the incompatibility issue.

Dr. Scoggins explains that at this point in the process, Recro had manufactured two immediate-release sets of pellets. "We then took parts of each population of immediate release pellets and further processed them with a modified-release coating," he says. "We now had four individual sets of pellets, an immediate release for each API, and a modified release for each API. Using our encapsulators, we then filled pellets in specific ratios to obtain the correct strength. Formulation, process development, and desired dissolution profiles were successful for this product." ◆

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