

# Drug Delivery<sup>®</sup> Technology

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## Discussing Thermoresponsive Delivery

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# Formulation Development

## Changing Tides in Formulation Outsourcing

By: Cindy H. Dubin, Contributor



**Jeffrey E. Browne, PhD**

*Technical Director, Pharmaceutical Softgel Sales  
Catalent Pharma Solutions*



**Derek G. Hennecke, MBA**

*President & CEO  
Xcelience, LLC*



**Michael Ruff, PharmD CPIP**

*VP, Pharmaceutical Development  
Metrics, Inc.*



**Paul F. Skultety, PhD**

*Director, Pharmaceutical Development Services  
Xcelience, LLC.*

There appears to be a shift in the outsourcing industry, particularly as it relates to formulation development. CROs really saw increased usage from the early to late 1990s up until just recently. Many of the leading CROs are seeing revenues below \$25 million, according to a May 2009 report from PharmaFocus.com. Pharma and biotech companies do not appear to be aggressively growing their pipelines or developing “blockbuster” drugs at the same pace they had in previous years. Thus, the business strategy of outsourcing formulation development has slowed a bit; it is more cost effective to keep this process in-house while pipelines get reconstructed to their previous strength. However, as the economy turns around, CROs

are expected to see a revival.

*Specialty Pharma* magazine recently asked some formulation development contractors how they are setting themselves apart from their competition during these trying times and how their clients can benefit. Participants include Jeffrey E. Browne, PhD, Technical Director, Pharmaceutical Softgel Sales, Catalent Pharma Solutions; Derek G. Hennecke, MBA, President & CEO, Xcelience, LLC; Michael (Mike) Ruff, PharmD, CPIP, VP, Pharmaceutical Development, Metrics, Inc.; and Paul F. Skultety, PhD, Director, Pharmaceutical Development Services, Xcelience, LLC. Research Inc.

**Q: *Talk about the importance of being able to deliver fast-into-human formulations.***

**Dr. Browne:** The rapid delivery of FIH formulations is extremely important to virtual-small pharma and Big Pharma alike. Often, the ability of virtual-small pharma to obtain funding is predicated on the timely completion of milestones such as FIH studies. Tremendous product pipeline pressure exists for pharma companies of all sizes to identify viable drug candidates through FIH studies, and to weed-out those that are not. The focus of our FIH formulation approach is delivery of a formulation using the simplest approach possible, which minimizes the formulation and analytical efforts required, and achieves adequate drug exposure in a limited number of healthy subjects.

Recognizing this need, we now offer and promote “fast-track” FIH formulation programs. Catalent’s approach yields FIH supplies in 4 to 6 months from first receipt of the client’s API. This program builds on the client’s available API data, and runs many formulation and analytical activities in parallel. In addition to our extensive multi-dose form preformulation and formulation expertise, one of the greatest time-savings we provide Catalent clients is the streamlined turnkey ability to develop, manufacture, and package FIH supplies within our network of facilities. In addition, Catalent offers a range of FIH formulation options to best match up with the specific requirements of the client’s API. This means our clients only have to deal with one outsourcing partner instead of two or three, thereby simplifying the whole process.

**Mr. Ruff:** At Metrics, we understand that most proposed clinical programs are under significant time pressure for both public health and business reasons. More effective and safer drugs are urgently needed to treat a variety of diseases currently not adequately treated, such as cancer and hepatitis. Likewise, the viability of a client company may be entirely dependent on how quickly they can demonstrate an encouraging result from early human trials. Therefore, time to dosing in the clinic is frequently the most important concern to the client. Metrics prides itself in being able to deliver FIH formulations, in part because it has a 4 to 1 ratio of analytical chemists to formulators. This high ratio helps ensure that analytical method development, typically the critical path, can keep pace with formulation development.

**Mr. Hennecke:** It is absolutely vital that a contract developer provide solutions that enable clients to move quickly into first-in-human studies. Now, more than ever, pharmaceutical companies of all sizes are under pressure to reach critical milestones faster despite challenging molecular properties associated with their candidate, and with limited API.

Subsequent rounds of funding often depend upon it.

As financing is tight and pharmaceutical companies struggle to do more with less, Xcelience delivers solutions that help clients work smarter in order to move drug development candidates forward faster and to maximize the chance for success. We offer a number of formulation development approaches specifically tailored to enable speed to first-in-human studies while conserving API and other resources. Though not all are relevant for commercial scale, API-in-bottle, powder-in-bottle, API-into-capsule, and traditional formulations are all approaches worthy of consideration as possible formulation options for clinical supplies for a Phase I clinical trial.

**Q: *Once a proof-of-concept has been established, how rapidly can the drug development program advance through to Phase II and III studies?***

**Mr. Ruff:** It depends on the definition of proof-of-concept, which is different for different clients and different disease indications. For some clients, this means getting through Phase I studies examining pharmacokinetics and side effects from dose-escalating studies in healthy volunteers. For others, it may also mean completing a small Phase II study to demonstrate some proof of efficacy. Regardless, it is always important to be able to move quickly into subsequent Phase II and III studies.

At Metrics, the transition from Phase I to manufacturing larger, Phase II supplies is typically rapid and seamless if the client has adopted our recommendation of developing a formulation for Phase I trials. Unfortunately, if the client has adopted a non-formulated dosing approach for Phase I (API alone in either a bottle or a capsule), Phase II studies cannot proceed until the formulation and analytical methods are developed, along with the necessary stability data. At Metrics, this can usually be achieved in about 12 weeks, including a month of stability data. The client must weigh the likelihood of success in Phase I and subsequent need for quick entry into Phase II trials against any possible time savings by starting clinical trials with a non-formulated product.

Early Phase III studies can commence as soon as the client feels confident about the Phase II results. Formulation and process optimization and scale-up will be performed before large, pivotal Phase III efficacy studies commence to ensure that clinical material is identical to the proposed commercial product, an FDA requirement. The optimization and scale-up typically is completed in 12 weeks, depending on the complexity of the formulation and process.

**Dr. Skultety:** On average, the total timing from start of Phase II through filing an NDA can range anywhere from 18 months up to years, depending on the approach used to establish clinical proof-of-concept, the intended therapeutic indication, and considerations for scale-up to commercial formulation. For example, if a powder-in-capsule approach was used for Phase I, then a formulated product will need to be developed for Phase II. A typical traditional formulation development would include dosage formulation, time to gather sufficient stability data, and the manufacture of clinical supplies, which may take between 4 to 6 months. The therapeutic indication may greatly impact product development timelines. Some indications require larger and longer clinical trials than others. For example, it is much easier to find patients with high blood pressure for an anti-hypertensive indication than it is to find people with certain cancers. This applies to both Phase II and Phase III studies. Lastly, the Phase III dosage form should be quantitatively and qualitatively close to the formulation that will be commercialized.

**Dr. Browne:** The length of time from proof-of-concept to Phase II and III depends on a number of factors, some within the control of outsourcing providers, while others are not. Often, the availability of API or the time for completion of the Phase I study is rate-limiting factors, over which the outsourcing provider has little control. When these are not at issue, the time it takes to develop an acceptable formulation, select the right drug delivery technology, and perform the related analytical support can often determine the length of time it takes to advance to Phase II studies. Where feasible, some clients run their early Phase II (IIa) studies using the same formulation used for their Phase I studies, allowing the quicker initiation of Phase II studies, while a more optimized formulation and advanced dose form is developed for later stage Phase II (IIb) and III studies.

Development cycle times depend on choosing the right formulation approach from the start, taking into consideration the known API properties, as well as any formulation work that might have been undertaken to date. For example, trying to formulate a poorly water-soluble (BCS II) API into a conventional tablet, using the one-size-fits-all approach can lead to excessively long development times, when a lipid-based formulation approach could have been more rapidly and successfully employed, allowing for the more timely initiation of Phase II studies. Challenging API properties and formulation complexity can add to the formulation development cycle times, and these are areas to which Catalent brings a wealth of problem-solving experience.

We have 75 years of experience as a company in developing formulations for oral dose forms, and we've learned to be

practical and pragmatic. We believe in using the simplest formulation approach possible to meet the desired formulation attributes, such as manufacturability, stability, drug release, etc. Because we have formulation experience across so many dose forms and routes of administration, we have a great deal of practical know-how, which frequently gives us an edge to get to a stable formulation very quickly.

We work hard to effectively manage those factors within our control to provide our clients with a quality formulation for Phase II and III studies in the shortest time possible.

The last thing we want to do is to delay our client's development programs. To achieve this, we have built state-of-the-art development and manufacturing facilities around the world, and staffed these facilities with experienced formulation and analytical personnel. Being able to apply the right type and level of scientific expertise is important to ensuring the timely completion of development programs. We have found, for example, that it is important to maintain a ratio of 2.5 to 3 analysts to every formulator, recognizing that inadequate analytical support can often lead to project timeline delays. Typically, our project plans call for 6 to 12 months to complete the activities needed for progress into Phase II studies.

**Q: *How knowledgeable is your team with regard to dosage forms, formulation requirements, and commercialization?***

**Dr. Browne:** Given that Catalent is a world's leading provider of advanced dosage forms and outsourced dose form manufacturing, we have proven experience in bringing products from preformulation or the clinic to the market. We are also very fortunate to have a team of scientists with considerable knowledge and expertise in formulation development and commercial manufacturing. Investment in highly talented, experienced people has always been a priority for us, and we have experts in every major route of administration, dose form, and package. The technical personnel in each of these capabilities are experts in their field. Most also have significant pharma industry experience. Just as importantly, we have invested heavily in our other development and commercial support functions, such as quality, regulatory, and project management. Globally, we have more than 1,000 scientists supporting formulation, analytical, and other client-focused activities. We also offer commercial manufacture and packaging services and regulatory consulting, and call on all of these disciplines to help our clients bring their products to market faster and more successfully.

**Mr. Hennecke:** The Xcelience team is very experienced in the area of oral, solid, and semi-solid dosage formulation. Our team consists of a number of individuals with greater than 10 years industry experience taking products from preclinical development through commercialization. In July 2008, Xcelience was fortunate to attract top industry talent in Paul Skultety, PhD, who has served as Director, Pharmaceutical Development Services at Xcelience, LLC. Dr. Skultety has a unique background in pharmaceutical development combining extensive experience with contract development and pharmaceutical companies. He has a successful track-record of developing NCEs from pre-IND to commercialization.

**Mr. Ruff:** We have a seasoned pharmaceutical development team of 10 formulation scientists with an average of 12 years of experience in formulation development, scale-up/optimization, and commercial manufacture. Some of the senior scientists and scientific management have more than 20 years of experience. All scientists have earned degrees ranging from BA to PhD. They are supported by 15 pharmaceutical technicians with an average of 14 years experience in the same disciplines.

Metrics has successfully developed dosage forms, including tablets (uncoated and coated), capsules (powder, bead-filled, and liquid-filled), and topical and oral powders. To meet the dosing requirements for each drug, we have developed the following drug delivery characteristics: instant release, sustained release, controlled release, delayed release, enteric-coated, and zero-order release. The Metrics facility is fully equipped with modern GMP assets to support all typical solid dose manufacturing processes. Our equally experienced commercial manufacturing group, working with the pharmaceutical and analytical development teams and regulatory affairs, has successfully scaled-up, validated, filed, and launched six commercial products during the past 5 years. This is demonstrated proof of not only our excellent technical ability but also our understanding of the sometimes complicated regulatory requirements.

**Q: *Talk about the financial and schedule benefits of outsourcing formulation development activities.***

**Mr. Hennecke:** A Specialty Pharma company can save a great deal of time, infrastructure costs, and capital expenditure by outsourcing formulation development activities. Outsourcing enables Specialty Pharma companies to remain virtual or avoid increased headcount throughout periods of fluctuation, all the while ensuring that their project remains on track. In addition, outsourcing enables companies to avoid wasteful spending

upward of \$500,000 on a new piece of equipment that may be project dependent and therefore used only once or twice.

At Xcelience, we can use the same piece of equipment multiple times and spread that capital cost over several additional projects that year alone. Our experience with a broad range of formulation and manufacturing equipment translates into time savings by reducing the learning curve that would have been associated with operationalizing a new piece of equipment. Experience with encapsulators is a good example. Each new model has novel features or quirks that require experience to master. Xcelience provides immediate access to scientific and instrument expertise and custom-tailored solutions designed to accelerate drug development and reduce risk for Specialty Pharma companies.

Xcelience API-into-capsule services are a great example of how much time and money can be saved by outsourcing formulation development activities. We have earned a reputation for being an experienced provider of API-into-capsule services, having processed more than 30 APIs and 90 batches using Capsugel's Xcelodose® 600 and 600 S precision powder micro-dosing systems. Our defined API-into-capsule program enables clients to shave an average of 17 weeks from a traditional formulation program, and our confidence in filling such a variety of APIs enables us to offer a guarantee.

**Mr. Ruff:** There are two types of savings Specialty Pharma can achieve using an outsourcing plan. The first is time, both to proof-of-concept and to NDA filing. With significant experience executing first-time-in-man and subsequent Phase II and III plans, the client can be assured of meeting aggressive delivery dates for clinical materials, method validation, development reports, and regulatory documents. Metrics has completed well over 100 first-time-in-man plans for clients, which provides a significant level of confidence for our clients in our plans for their new chemicals. Each week that we can shorten the timeline to completion of proof-of-concept is a week of savings and an earlier arrival to the next level of development and ultimately, the NDA filing.

The second type of savings is in actual dollars. By outsourcing, the client does not need to invest in the significant staff and capital expenditures associated with development and clinical manufacture. Whereas most Specialty Pharma are focused on just a few projects, an experienced contract development company has proven expertise in a variety of dosage forms and can apply that experience to each unique project. This means the Specialty Pharma company can keep its focus on research and key knowledge of its molecules.

**Dr. Browne:** The time and money saved by outsourcing can be significant. If outsourcing reduces the development cycle time, the product can be potentially launched earlier. The potential to start generating revenues weeks or months ahead of schedule can be huge for a large-volume product. Clients can reduce development cycle time by outsourcing if they have limited or no in-house resources that can be applied toward the program. Often, with specialized dosage forms, the client does not have the capability to develop or manufacture the dosage form in-house even though it represents the preferred dosage form for their API. In this case, the client can add significant time to the development cycle by choosing instead to “force-fit” the API into an existing in-house dosage form technology. Bringing specialized dosage form technologies in-house for a given product just doesn’t make good business sense given the money and resources necessary to do so.

Outsourcing results in time and money savings, and the magnitude of these savings does depend on the competency of the outsourcing provider. Having knowledgeable and experienced people can make a world of difference. Not only does it increase the probability of first-time success, but when problems do arise, experienced partners know how to deal with them - quickly and effectively. As mentioned previously, it is equally important to have strong staffing in the development and manufacturing support areas, such as quality, regulatory, and project management. If a client has to spend significant in-house resource to babysit a contract developer, it kind of defeats the purpose of outsourcing.

**Q:** *One outsourcing consultancy is claiming that the contracting sector is “ripe for consolidation,” and many have revenues below \$25 million, particularly in formulation development. How are you competing in this market to ensure long-term support?*

**Mr. Ruff:** Metrics management has a serious commitment to the local community, which is reflected in the extremely low turnover of employees. Consequently, Metrics is not as prone to consolidation as other contractors in these volatile times. However, it does recognize the need to stay competitive in a market where consolidation may take place and so will maintain a marketplace watch on these issues and how they might affect our organization.

The key competitive tool that Metrics utilizes is quality. We use quality people to deliver quality results to quality clients. We try to do this time and time again as this is what allows the client to be confident in our plans, results, and working relationships.

Finally, while we focus on meeting our current clients’ needs,

we work with each new lead as if they are already a client, so that they can get a feel for the way our teams work with each project. Each client or potential client knows that we look at their project as if it is the only project in our system.

**Mr. Hennecke:** Consolidation in an industry happens when clients are better served by fewer companies. If the industry is better served by more vendors, then that’s what will prevail in the long run. Formulation development has diseconomies of scale. The larger you are, the slower you get. Xcelience knows that better than anyone - we were once part of a larger company that was trying to consolidate the drug development chain. It was too wieldy and slow. Once we were separated off from the company, we were able to become lean and mean and more client-oriented, rather than mother-company-oriented. Our bottom line exploded upward. I guess that means we were doing something right. Formulation services have been affected as pharma companies put their limited resources into late-stage drugs, hoping for quicker payoffs. This has been particularly damaging to smaller companies with only a few clients. Xcelience is fortunate to have a range of client companies of varying sizes from all over the world. We have been able to weather this storm solidly, and remain in an excellent cash position. Privately owned and debt-free, we look forward to the next stage, when we expect companies to resume pipeline development for early stage drugs.

**Dr. Browne:** Catalent is currently the largest outsourcing service provider of advanced technologies and outsourced development, manufacturing, and packaging services serving the global pharma and biotech industry. We have a strong business, with fiscal 2008 revenues of approximately \$1.8 billion, 9,500 employees, and a strong and stable financial position. We have built this business by understanding the needs of our customers and deploying our experience and expertise to solve the challenges our customers face. Simply put, we ensure our long-term viability by doing each day what we’ve done for 75 years: combining the talent of our people, our extensive intellectual property, and our world-class scientific and manufacturing network to solve our customers hardest challenges, and to act as a catalyst to their products’ success. ♦