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Solid dosage outsourcing: Mergers, expansions, and new technologies

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As the number of "virtual" companies grows and as Big Pharma shifts away from fixed infrastructure, CDMOs are shouldering more of the work load in product development and manufacture. This article summarizes how four companies with a strong presence in solid dosage forms—Capsugel, Metrics Contract Services, Patheon, and Rottendorf—are capitalizing on this new business and technological environment.

In the past, companies we now call contract development and manufacturing organizations (CDMOs) were seen as hired hands. Some offered niche technologies and expertise, while others focused on clinical or commercial manufacturing. But today's CDMOs are larger, more diversified, and offer more services than ever.

Capsugel, Morristown, NJ, is a good example of how the industry has evolved. It's one the oldest and largest suppliers of empty hard capsules but until recently, it offered few product development or manufacturing services. Its transformation began in 2011 after KKR, an investment firm, bought the company from Pfizer and launched its Dosage Form Solutions (DFS) business.

In March 2013, it acquired Scotland's Encap Drug Delivery, giving it more expertise in liquid/lipid-filled formulations and a commercial manufacturing facility. In October 2013, it acquired Bend Research, Bend, OR, which specializes in enhancing bioavailability and modifying API release using spray-dried dispersions and hot-melt extrusion. In January, Capsugel acquired Xcelience, Tampa, FL, which specializes in formulation development and the manufacture, packaging, and distribution of clinical trial supplies. It also bought Powdersize, Exton, PA, which uses micronization to improve the solubility of APIs.

"We could have just focused on the capsule business," said Amit Patel, president of DFS. Instead, the company planned to make Capsugel a leading provider of innovative dosage forms and solutions to healthcare customers. "That vision statement doesn't mention capsules. It doesn't mention gelatin," Patel said. "So we took all the things that Capsugel was already doing beyond hard capsule supply and brought them together as the Dosage Forms Solutions business, and went beyond just the capsule." He cited bioavailability enhancement, modified release, high-potency handling, and clinical trial services as examples of high-growth areas. "No matter which lens we look at the business through, geography-wise, segment-wise, or offering-wise, we're seeing growth across the board."

Business is also good at Metrics Contract Services, Greenville, NC. "We've seen tremendous demand for formulation development projects that involve potent or cytotoxic compounds," said John S. Ross, executive vice president. The company is owned by Mayne Pharmaceuticals, a publicly traded Australian pharmaceuticals manufacturer. But Metrics is exclusively a development company, and Ross estimates that 75 percent of Metrics' new clients are "virtual" companies with little or no infrastructure to develop or manufacture a product.

In fact, all its work is pre-commercial and novel. It doesn't work on generics and it doesn't—at the moment—offer commercial manufacturing. But that will change once Mayne Pharma completes a $65 million, 126,000-square-foot oral-dose facility adjacent to Metrics' current operations, doubling manufacturing capacity. The company will also introduce commercial-scale fluid-bed processing to make modified-release multiparticulate dosage forms.

"In the past, we didn't really offer a viable solution for commercial manufacturing," Ross said, so most customers took that work elsewhere. "With the expansion, fewer clients will have to exit, and because the expansion is right here on-site, it will not involve a tech transfer. It will be the same FDA establishment."

Patheon, Durham, NC, is also expanding. In October 2012, it acquired Banner Pharmacaps, the world's second-largest pharmaceutical business dedicated to softgel formulations. In 2014, it combined with DSM Pharmaceuticals, which added US capacity for sterile, oral solid dosage, and API manufacturing. In 2015, it bought Agere Pharmaceuticals, Bend, OR, which enables it to manufacture solid dispersions that improve API solubility-bioavailability. It

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also bought Irix, which specializes in APIs for high-potency drug products.

Those acquisitions, coupled with other internal initiatives, prompted Patheon's "OneSource" campaign, which promotes the company as a single-source solutions provider, from API to commercial production, said Kaspar van den Dries, Patheon's senior director of formulation sciences for solid dose and softgels. He said the end-to-end capability includes "supplying the API and drug product from the early phase to late phase, and doing all the work around that, including the compliance, where we have a good history. It is quite unique in the industry."

Bioavailability enhancement, modified-release capabilities, and high-potency handling are among the areas of new investment.

Customers include Big Pharma companies that are cutting back in some areas of development, and small and emerging companies. "Many times they are virtually based and while they certainly have the clinical or medical expertise, they don't necessarily have the infrastructure, supply chain, and logistics to support CMC development," van den Dries said. "For this reason, we see a very broad range of companies who are interested in these services."

Naturally, not every client or project needs every service, especially in early development. "Some want to establish proof-of-concept and spend as little money as possible on the upfront formulation work, so they choose fit-for-purpose formulations just to make it work," he said. Other companies, mostly midsize and bigger pharma companies, usually take a more comprehensive approach to eliminate the need for pharmacokinetics bridging studies and a new formulation in a later stage of clinical development. "We also see companies that want to have a bona fides formulation developed that starts from a tablet or a capsule from phase 1 onward."

Rottendorf is a German company dedicated to solid dosage forms. In March 2011, it formed a US corporation led by Gordon Haines, but manufacturing and packaging remains in Germany and France. "Because we have a presence in the US that manages the time difference, the physical distance is much less a barrier than it would've been 10 years ago," Haines said. "We're not finding that to be an insurmountable barrier whatsoever." Indeed the US market, which accounted for less than 5 percent of the company's total revenue in 2011, now represents more than 20 percent of total revenue.

The company's development group employs more than 40 scientists, all of whom work on a broad range of solid oral dose products. "That's all we do, because that's our area of expertise, hard-core solid dose technologies," Haines said. The company manufactures about 600 different SKUs annually, including multilayer tablets, fixed-dose combinations, as well as timed-release, controlled-release, and tablet-in-tablet products. "It's across the board and across multiple therapeutic areas, even OTC products."

As for new technology, Haines said Rottendorf takes a "5- to 10-year look" to see what it should explore and the company may begin making high-potency products. It's also working with Bosch on micro-dosing technology and with a consortium of universities and companies evaluating nano-dosing. "We want to ensure that we're offering the technologies that the solid oral dose world is looking for and will be looking for. That's driven by our customers and we will expand into the new technology that works for them," Haines said.

Rottendorf recently bought more land near its headquarters to accommodate an expansion. It might also build in the USA. "Our long-term vision is to have, at a minimum, packaging operations here, and potentially offering manufacturing. It'll be driven by the business," Haines said. And business has been good. "Our focus in the USA when we started was midsize, smaller, and virtual companies that could use a full range of our services. But Big Pharma has found us, so it's really been across the board."

CDMOs become "technology-agnostic" experts

According to Patel, "There's an increasing desire for the pharmaceutical companies to tap the best expertise possible, and outsourcing is one of the best ways to do that." He said that 10 years ago, there was some question about the future success of the outsourcing model, but the recession of 2008 led to a lot of downsizing at Big Pharma and prompted companies to seek more partnerships, which led to successful launches. "That's given the entire industry much more confidence to collaborate on unique technologies and unique capabilities. Those are two of the growth drivers in the CDMO market."

While Capsugel offers a variety proprietary technologies, it doesn't insist that customers use them. "Our goal is to be flexible and adaptable enough to align with the customer to do what makes sense from a science-driven perspective," Patel said. "Technologies by themselves are just a means to an end to solve problems. The most important statement I would make of Capsugel and DFS is that our strategy and our business model are built around being

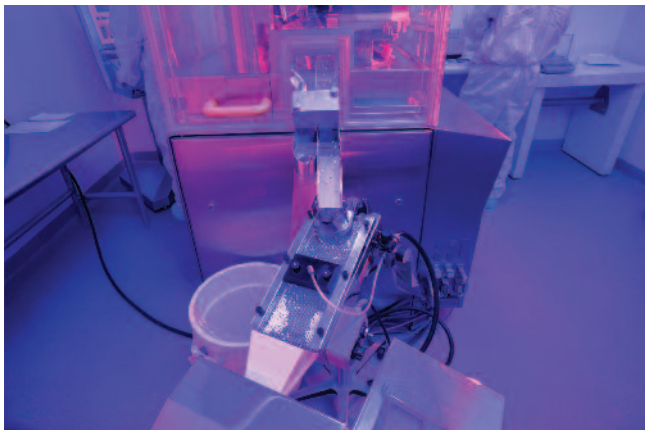

Photo courtesy of Capsugel

Capsugel's acquisition of Xcelience increased the its solid dosage formulation and manufacturing capabilities, including microdosing in capsules, clinical supplies and services, and tabletting. The photo shows a Fette P1200i tablet press in operation at the company's cGMP production facility in Tampa, FL.

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Photo courtesy of Metrics

Metrics' expertise includes developing high-potency drug products and using fluid-bed technology to create multiparticulate dosage forms.

technology agnostic." Nor does every customer's product involve a capsule. Among the products DFS helped customers formulate and file with the FDA in 2015, there are a variety of dosage forms, including hard capsules, multiparticulates, softgels, and tablets, Patel said. "We do have deep capsule-related expertise, but we're also dosage form agnostic."

At Metrics, many customers must reach certain milestones to get their next tranche of funding, and for them, "speed is everything," Ross said. It's one of the reasons Metrics expanded its product development area last year to include a non-GMP space. "That's been the key factor for us. It's really allowed us to make tasks that once happened consecutively to now run in parallel. Prior to that expansion, we didn't really have any space on site that was suitable for non-GMP, quick-in, proof-of-concept work. It mitigates some of that upfront investment in time and overhead," he said. "You can be a little bit more expedient in your experimentation." Last year, one project went from inception to the clinic in 9 weeks. "That was aided by some early formulation activity in that space. Now we're kind of wishing we had made it bigger."

The quest for speed has also led Metrics to start making more changeovers when its equipment is idle and by doing more off-shift cleaning and swabbing. "That way we can get the analytics done on equipment—at least in some cases—overnight. We're principally a one-shift operation but we're starting to add bits and pieces to take advantage of the time when equipment is typically idle." For yet more speed, the company also continues to look for simpler or less expensive containment options. "The diversity of compounds that we introduce into our site is incredible," Ross said. "Anything that can expedite cross-contamination control without losing any effectiveness would be huge. It'd give companies like ours a better ability to manufacture and package potent substances or cytotoxic substances, exploit equipment turnover, and ensure employee safety," he said.

At Patheon, solubilization enhancement is a key initiative, van den Dries said. "We can look at different technologies to overcome your bioavailability issues in parallel, supported by in silico modeling and predicting formulation properties. We can also do some molecular modeling to see what solutions work best." That may mean creating a solid dispersion or something else entirely. "There's no single solution to overcome bioavailability issues; it depends on the API's properties. But we have no presumptions on what the best approach is. We approach it agnostically."

The company has also begun work on a system to continuously manufacture tablets and capsules at its Greenville, NC, site. "The concept is very clear, as are the benefits," van den Dries said. "It addresses the time and money lost in the development cycle on scaleup. It also can be a nice benefit to existing manufacturing processes." (See the related article on page 14.)

Cost and time savings are also a priority at Rottendorf. "We consider ourselves a very good value-based company, meaning we bring a high level of skill, capabilities, and commitment at a very reasonable price," Haines said. "We partner with you to ensure that we understand what you're trying to do and we help you achieve your overall goal, not just produce a pill." The company also seeks opportunities to improve products and save money. "It's not just 'Give us a recipe and we'll make it.'" In some cases, the company might suggest switching to an excipient that Rottendorf buys in bulk. "If you're OK qualifying a new supplier for a like excipient, we can cut the cost of your formulation."

Haines said the company is committed to "total process ownership. We act as if we're part of the customer's company to help them reach their goals." It also entails close process supervision. In one case, Rottendorf workers noticed that a batch of excipient had extremely low pH compared to other batches. "By definition, it met all the critical parameters, but based on our experience, it raised production issues," Haines said. After tests showed it would be a problem, Rottendorf made small process adjustments, and the excipient was approved for use. "So the customer was happy because we didn't just blindly accept the excipient and because we figured out how to use that excipient and not create bad product."

More services and more partnerships

Clearly, the business and technology landscape for CDMOs has changed. "The number of organizations that have now decided, fundamentally, that they're not going to invest in infrastructure has grown dramatically," Ross said. "When I started 15 years ago, the CDMO was rarely the expert and most customers were only looking for additional capacity." Not so today. "Clients are looking to us and our

Photo courtesy of Rottendorf

Rottendorf's development group employs more than 40 scientists, all of whom work on solid oral dose products. The photo shows a worker loading ingredients into a granulator.

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competitors for answers. CDMOs are hugely relevant now, and in many cases we are the experts. That's evident in the projects that we participate in. We're not just a pair of hands. We're a partner in their manufacturing development endeavor."

Patel agreed that companies rely on CDMO expertise more than ever. It stems, he said, from Big Pharma's focus on two activities: discovery research and commercialization of pharmaceutical products. "The competencies required to do those two things are very different. In fact, they couldn't be further apart in terms of what's critical to being a really strong discovery engine and what's critical to being a really strong commercialization engine."

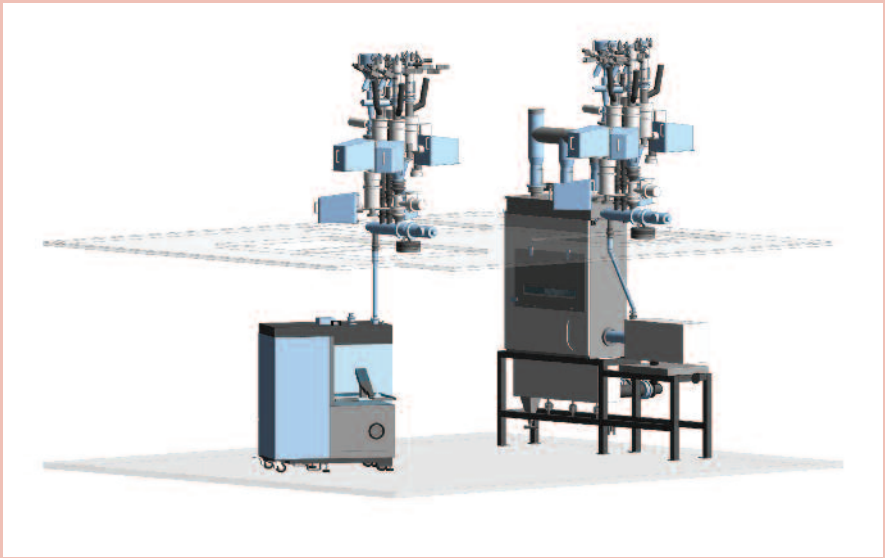
As a result, more companies will turn to outsourcing for help with formulation development, clinical supply, scaleup, manufacturing, and implementing unique technologies, Patel said. "There's an increasing desire for the pharmaceutical companies to tap the best expertise possible in those areas of specialization. It turns out that outsourcing—that is partnering and collaborating—is one of the best ways to do that." *T&C*

Patheon plans continuous manufacturing line

Patheon plans to continuously manufacture tablets and capsules at its Greenville, NC, site. The project is led by Eric Jayjock, director of continuous manufacturing. "We're pursuing it for many of the same reasons that Big Pharma would," he said, but the company isn't following the industry's "natural model" of letting Big Pharma go first. "We see this is a superior approach to manufacturing products. We want to be on the leading edge."

Jayjock's experience in the field includes post-doctoral work on a continuous manufacturing collaboration between Rutgers University and Janssen. In 2013, he joined Janssen to help implement continuous manufacturing at its Puerto Rico site. Patheon hired him in 2015.

"This is the future, a paradigm shift in technology," Jayjock said. The advantages include higher efficiency and the ability to develop products faster while using much less material. Currently, he said, manufacturing 20- or 50-kilogram batches of clinical trial material requires three to six unit operations and takes a long time. "You have to get the material, run it through the first unit operation, test it, wait for the results, take it to the next one, test it, wait for the results, and so on." That could take several weeks. "In the continuous manufacturing world, we'll turn the line on, and in less than an hour we'll start producing product. We can make enough for a clinical supply in an afternoon."



Patheon's continuous manufacturing line will use modular components to perform dry granulation, wet granulation, tabletting, and capsule filling. This rendering shows the direct-compression and wet granulation modules positioned below a manifold of six feeders.

Patheon's line will be built using modular components that interface with each other. "That's the most important overall concept of the line, that we can snap together whatever configuration we need for whatever challenges we have," Jayjock said. There will be modules for feeding, blending, dry granulation, wet granulation, compression, and encapsulation. A coating module will come later. "We can be super flexible on the new product development level and the tech transfer level and solve process problems by using the equipment. That's going to give us all the more power to be specific to our clients needs in each individual case."

Process control is key. "The advantage comes not in what equipment train we're using, but in how we understand our process and how it's controlled. Then we can make a high-confidence product with fewer deviations."

The new line will apply the "S88" approach, a concept used in batch manufacturing and packaging that separates the product's recipe from the process equipment. "The idea is that if you know how to specify what you're doing using the fundamental physics, then you can transfer your product to another piece of equipment, and that

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piece of equipment figures out how to do the operation," Jayjock said. "It means when clients come to us with a product they've developed, we can help transfer it in. If for some reason it must be transferred out, that'll be a big advantage for them. Even internally, it will enable us to transfer between different sites with a high chance of success. It's another aspect of the modular future for CDMOs."

Patheon expects to install the process equipment mid-year, after which it will be connected to the control system. "We'll make sure that our process has the capability to run stable so that we can bring our client's valuable material to the line with the confidence that we can produce the best product on it and not have a waste issue or deviations." In the meantime, Patheon is talking with clients about which products are a good fit for the line.

Large production volumes favor continuous manufacturing, but that's not likely to be the primary consideration, Jayjock said. "I think the most value will come from developing a product on a continuous line because it will save API early and you'll get more knowledge about the line, and thus more confidence in your process." It will also eliminate scaleup. "Those are huge advantages for a new product."

Patheon is the first CDMO to undertake continuous pharmaceutical manufacturing. "There's only a handful of companies that have the technical capability and the depth of staff to handle it at this point. At Patheon, we're working to be an industry leader. Our goal is to be the go-to place for continuous manufacturing in the oral solid dosage realm."

- M.K

For more information about continuous manufacturing of solid dosage forms, see the May 2015 article, "Arden House conference: Continuous manufacturing gains momentum." It summarizes a 3-day AAPS event that featured Jayjock and other speakers from the pharmaceutical industry, the FDA, and academia.

Another article, "Evaluation of a continuous-cycled film coater in applying a high-solids coating," appeared in the October 2015 issue. It summarizes a study conducted by Colorcon and Driam. The coated tablets were assessed for weight gain consistency, color uniformity, surface roughness, and gloss.

Both articles are available at no cost when you log in to **www.tabletscapsules.com** and at these links:

bit.ly/Arden2015

bit.ly/TC1015ContinCoat