# Solid Dosage Manufacturing Trends

## Big Pharma continues to unload in-house manufacturing, partnering with contract service providers that can meet their cGMP needs.

## By Tim Wright, Editor

The oral solid dose form continues to play a major role in the contract manufacturing industry, representing about 60% of the market. After a period of uncertainty, the solid dose market is set for a new period of gradual expansion.

Solid dose manufacturing and oral delivery of new drug candidates, reformulation of existing molecules, fixed dose combinations, controlled release dosage forms and other life cycle management strategies will continue to have significance and a large market share, according to Anil Kane, executive director, global head of formulation sciences, Patheon. “Oral delivery using solid dosage forms will continue to be the preferred delivery route if drugs can be formulated and delivered in appropriate doses,” he said. “Patient compliance and cost of goods with solid oral dosage forms continue to be the biggest advantage.”

The current and near-term climate looks positive, according to the manufacturers we spoke with about the state of the business in 2015. “The market should stay strong as long as funding stays readily available,” said John Bender, vice president of commercial operations at Norwich. “However, competition is coming from pharma sites that have been converted to offer CMO services along with existing companies expanding their service offerings.”

While contract manufacturing opportunities appear plentiful moving forward, they often have complex processing and challenging handling requirements, according to Rob Goshert, vice president of business operations for AAIPharma Services Corp. “Due to many recent and near-term client product approvals, we expect a better mix of commercial manufacturing well into the future,” he said. “The outsourcing trend does not appear to be slowing while at the same time regulatory challenges are reducing the number of available facilities.”

Compared to last year, Ian Muir, managing director, Aesica, said the market continues to perform well and anticipates another year of strong growth for his company’s solid dosage business across formulation development and finished dose manufacture, packaging and artwork services. “The drivers of growth within the CDMO sector remain the same this year as has historically been the case, with continued mergers within the pharma sector, reduced pipeline activity and the rise in generic prescribing all driving decisions around make versus buy.”

David Watt, director, technical pharma services, WellSpring Pharmaceutical Canada Corp., believes the CDMO market is rebounding this year after many years of stagnant growth and that this growth will continue for at least the next 24-30 months, so long as the financial markets continue to rebound. “The opportunities for growth within this environment exist in the high potency products as well as the niche tableting such as bi-layer tablets,” he said.

### Market Trends & Drivers

The manufacture of solid dosage forms continues to evolve, with key drivers including functional improvements, safety and overall cost of development and commercial manufacture.

CDMOs and CMOs have become more mainstream and integral to the pharmaceutical industry and this has been driven by both capacity and capability needs, according to Randy Wald, senior research fellow at Bend Research, part of Capsugel Dosage Form Solutions. “As plant network strategies evolve and new products progress there has been more alignment between development and commercial for manufacturing process streamlining and improved quality,” he said. “While wet granulation remains required and preferred in some situations, this has resulted in more emphasis on direct blend and dry granulation processing for tablets and capsule manufacturing. This in turn has put more emphasis on raw material and process control.”

From a regulatory perspective, Quality by Design (QbD) and Process Analytical Technology (PAT) principles are increasingly being sought, and beyond this continuous manufacturing, particularly for finished dosage forms, has emerged as one of the rising star technologies.

“The major trend towards continuous processing where multiple continuous unit operations are coupled into an integrated system has occurred using joint industry, academia and process equipment supplier collaborations; and the genre includes the primary processes in oral solid dosage form manufacture direct blend, dry and wet granulation, tableting/encapsulation and tabletifilm coating,” said Mr. Wald. “Drivers include streamlined development, lower and more flexible manufacturing, higher quality product and lower net costs.”

Life cycle management strategies such as fixed dose combinations, extended release and pediatric forms continue to increase in demand. “Combining new chemical entities with an existing drug to explore new clinical benefits and newer indications is on the rise,” said Mr. Kane. “New chemical entities coming out of discovery continue to have poor solubility and bioavailability challenges, and the industry continues to invest in ways and means to deliver the drug with a better clinical outcome. Contract developers continue to support the industry in solving these challenges.”

Increasingly the CDMO sector, which traditionally focused on development and manufacture, is overlapping with other sectors involved in electronic data transfer and management and supply chain logistics as they look for areas of expansion in non-traditional sectors, particularly as the sector looks for a more efficient and integrated supply chain, said Mr. Muir. “Indeed, the longer term trend is towards integration throughout the supply chain with companies offering API manufacture all the way through to finished drug manufacture and packaging,” he said. “As a result, much of the expertise that is traditionally in pharma is now residing within the CDMO sector and this is undoubtedly changing the relationship between client and customer with even risk sharing models becoming more common.”

In addition, Mr. Wald said the industry has seen increased demand for specialized dosage forms such as pediatric/geriatric, taste-masked, abuse-deterrent and controlled release technologies. “Additionally, a significant increase in fixed dose combination products has occurred and continues,” he said. “Also, an increased percentage of compounds requiring high potency containment during drug product manufacture, and the corresponding increase in equipment and facilities with required specialized designs have transpired and are significant trends at all CDMO, CMO and pharma companies.”

Mr. Wald continued, “Drug absorption enhancing technologies rapidly matured in the past decade, yet new technologies continue to be developed. Primary examples include maturation of amorphous solid dispersions especially via spray drying and hot-melt extrusion, submicron particle size reduction and lipid based formulations that are soft and hard shell based, and the emergence of high surface area carrier technology.

“New excipients, excipient grades and blends (e.g., co-processed, multifunction, and ready-to-use) were also developed and utilized. Given the prohibitive cost of developing and gaining approval for a new excipient, suppliers have coupled processing advances for the development of innovative dosage forms. Very recent examples of these that use GRAS excipients include new cellulose grades specially designed for spray-dried dispersions and hot-melt extrusions for enhancing bioavailability and functional enteric capsules that eliminate the need to enteric film coat for gastric resistance or full enteric protection.”

Mr. Watt said while roughly 50% of the drug development pipeline is comprised by biologics, the rest are in the other dosage forms, which means that there are fewer solid dose products being developed now than there were in the past. “Those that are seem to be more in the areas of high potency compounds and niche forms, such as bi-layer, tablet-in-tablet, sub-lingual tablets, bio-adhesive tablets, floating tablets, quick dissolve tablets and compression of coated beadlets into tablets,” he said. “This will require investment in granulation and tableting capabilities to meet the needs of these specialty tablet products.

“On the other hand,” he continued, “the rise of generics in the last few years has compensated for the decline in the development and commercialization of new NCEs. These generic solid dose products do require conventional granulation and tableting capabilities, so what was once considered old technology seems to be new again.

“The opportunities for growth within this environment exist in the high potency products as well as the niche tableting such as bi-layer tablets. High potency compounds require the environmental controls as well as handling expertise; containment solutions are expensive and require engineering solutions to provide the level of environmental health and safety to protect both the manufacturer as well as the drug. The niche solid dosage forms such as bi-layer require highly specialized equipment, which can be cost prohibitive to a CDMO.”

## Consolidation Continues

Consolidation in the market is another growing trend. “We continue to see the venture capital community invest in R&D, small biotech and emerging companies, as well as promising clinical programs, which will continue to grow,” said Mr. Kane. “We foresee outsourcing to grow as Big Pharma continues to consolidate, reducing the number of plants and facilities worldwide. This will create opportunities for contract development and manufacturing organizations to support the industry.”

He continued, “As the pharmaceutical industry continues to consolidate through mergers and acquisitions, there is an increasing trend in in-licensing and out-licensing of clinical candidates and partnering to co-invest for different markets. These trends offer opportunities for emerging companies, and Big Pharma companies, as well as contract manufacturers.”

Mr. Muir concurred that the market does seem set for another round of consolidation, which will undoubtedly provide

increased opportunities. “Pharma is increasingly looking to reduce the numbers of contract manufacturers it works with and technological capabilities, alongside financial stability and pedigree, undoubtedly play a part,” he said. “Our inclination is that people are looking more at quality-based decisions rather than purely cost led ones. Similarly, finished product contract manufacture across complex formulations, controlled drug and high potent capabilities are still showing strong growth and sales into developed markets will remain key targets.”

He continued, “A key obstacle for the industry as a whole is the fragmented timing and approach to serialization. After years of harmonization activity, the industry seems to be heading in the direction of regionalization for local packaging and eventually for local manufacture. This trend is being complicated further by the changing geopolitical environment in many of the affected regions and markets. Another key challenge will be ensuring that enough value can be distributed in the supply chain to ensure reliability, and to prevent an unstable supplier base.

“We predict a trend in which CDMOs are changing themselves with merger activity driving both scale, breadth of technology and geographic reach. At the same time we are finding as well that there is a strong trend in the market towards generics away from branded drugs. The CDMO market is a hotly contested environment and we predict that a number of the smaller companies will drop out of the market due to the fierce level of competition that is being experienced.

“The key trend across the CDMO market remains the gradual shift towards more strategic partnerships with pharma, and this is lending itself to an arms race of technologies across the biggest providers. What we are likely to see is increased consolidation as a result and larger players looking for novel technologies to add to their service offerings.”

## Meeting Customer Expectations

Staying in tune with what customers on the sponsor side are looking for is key to success in this business.

“Customers require responsiveness, flexibility and open communication while operating on tight deadlines,” said Mr. Bender. The cornerstone of what customers are looking for is reliability and consistent high quality across all stages of project service offering and the ability of CDMOs to deliver on time in full, according to Mr. Muir. “Beyond that, customers are looking for partners with innovative technologies such as continuous manufacture,” he said. “The ability to provide specialist offerings will differentiate the stronger CDMOs in terms of being responsive to current customer demand and expectation.”

According to Mr. Goshert, clients always expect quality, speed, service and value. “Most want all four and some chase price over value, and get what they pay for,” he said. “Some Big Pharma companies attempting to get out of manufacturing, or offload nuisance manufacturing, are attempting to bully the service providers with onerous demands —payment terms, pricing, risk, etc. In order to be successful and compliant long term, CMOs will need to stand firm on their requirements and not give in to pressure for unfair balance.

In addition to service seekers looking for a stellar regulatory history and speed, Mr. Goshert said more than ever, prospective clients are not only looking for a suitable facility fit for their product, but also looking for a cultural fit with its employees. “Flawless execution on commitments will lead to continued growth,” he said.

Mr. Kane added that customer expectations in the following are increasing: on time delivery (OTD); right first time (RFT); quality; and scientific expertise.

He said, “Customers are looking for the best scientific solutions, and those who can provide speedy, flexible and quality deliverables will be ahead of the game. Although competition in solid oral contract development and manufacturing is always increasing, the companies who can consistently deliver the above requirements will be able to grow.”

New Developments & Technology

**CDMOs and CMOS respond to client-specific needs and the general market trends with continued expansion, service offerings, capabilities and capacity.**

Capsugel in November announced the expansion of its lead-user customer-collaboration program for its intrinsically enteric capsule technology to address the need for targeted drug delivery for gastric-sensitive APIs. This new approach to enteric drug-delivery combines Capsugel’s drug formulation, polymer chemistry and capsule-design expertise.

Most recently, Capsugel acquired the intellectual property pertaining to proprietary Ionic Liquids Technology (ILT) developed at the Monash Institute of Pharmaceutical Sciences (MIPS), Monash University. This novel technology relies on an innovative salt screening strategy, producing liquid forms of drugs, which show higher solubility in lipid-based liquid, semi-solid and multiparticulate formulations.

In Patheon's European network, the company has invested in early phase clinical manufacturing by installing an Xcelodose automated encapsulator to support a speedy Quick to Clinic Program for Phase I studies. The company has also installed solid dose manufacturing equipment to support formulation and cGMP clinical manufacturing of tablets, capsules and other forms. In the North American network, Patheon has built capability to support development and manufacturing of high potent compounds using processes like roller compaction, tableting and encapsulation with full containment. Patheon offers end-to-end services from drug substance and drug product through its new Patheon OneSource integrated offering.

AAIPharma has expanded its service offerings to include API with the recent integration with Cambridge Major Laboratories, which ties in well with its clients First-in-Human (PIC & PIB) and later phase manufacturing programs. The company also enhanced its solid dosage manufacturing with an 11th flexible GMP manufacturing suite; on-site formulation development suites; new equipment including a Korsch XL 400 multi-function press; and additional packaging equipment and capacity. The company is also currently engaged in design of an additional solid dosage facility at its Wilmington, NC campus to accommodate future growth at larger scales.

Aesica has set in place strategies to grow its existing solid dosage business. It recently announced that it has received continuing FDA approvals for both its bulk manufacturing and packaging operations in Germany. As a consequence, it can continue to grow its manufacturing and packaging services for pharmaceutical products destined for distribution and export to the strategically important U.S. market. The short-term and medium-term goals for Aesica are to continue to expand its market penetration as it looks to continue growth across the European and U.S. markets.

WellSpring has invested in three major pieces of equipment to meet the demands of its existing clients, including an Alexanderwerks Roller Compactor, a second O'Hara Tray Drying Oven, a 450L Collette Planetary Mixer and an IMA Precisa Capsule Weight Sorter. The O'Hara Tray Drying oven provides double the capacity of the current drying allowing the company to meet client capacity. The company's facility has entered the foray into high potency compounds in liquid and semi-solid manufacturing and has engaged Safebridge for assistance on high potency compounds. Safebridge provides EH&S categorizations for Actives as well training on high potency handling and the use of IC Dover soft containment has been implemented at the site.

**Tim Wright** is the editor of Contract Pharma. He can be reached at twright@rodmanmedia.com

ALSO ON CONTRACT PHARMA WHAT'S THIS?

**Virtual Outsourcing**
1 comment • a year ago
Darius Carney — Well, that's interesting - more industries are turning to outsourcing to work on varying …

**Sanofi Selects New CEO**
1 comment • 15 days ago
sdavid — Thesepharmaceutical company executives exemplified the most greedy, callous andhypocritical …

**SGS Granted French R&D Tax Credit Recognition**
1 comment • 4 months ago
Miles Reid — It's good of SGS.

**Preparing For The End**
1 comment • 5 months ago
Eileen Sullivan Scully — MS Scott makes interesting commentary. Most of us don't realize the scope and expense …


**Focus on your patients. Focus on you.**
With a focus on improving patient outcomes via product development and commercial manufacturing, you can depend on Norwich — a reliable partner for all stages of your product's lifecycle.

Contact us to help you focus on your patients at
www.norwichpharma.com

NORWICH
CELEBRATING 125 YEARS

**Focus on your patients. Focus on you.**
With a focus on improving patient outcomes via product development and commercial manufacturing, you can depend on Norwich — a reliable partner for all stages of your product's lifecycle.

Contact us to help you focus on your patients at
www.norwichpharma.com