IN-DEPTH PROCESS AND PRODUCT EXPERTISE

THIS IS KEY TO CDMO SUPPORT OF ORPHAN DRUG AND BREAKTHROUGH THERAPY DEVELOPMENT & COMMERCIALIZATION

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Kristine Senft is a professional, inspirational sales and business leader with a proven track record of success in the pharmaceutical and fine chemical industries. She has achieved a distinguished 25+ year career introducing strategies to drive global growth within intensively competitive markets. Before joining Hovione, Kristine served in various roles as a Business Unit Director, DSM Biomedical, and SVP, Marketing and Sales, DSM Pharmaceutical Chemicals, where she led both regional and global marketing and sales organizations. She also worked for Albemarle Corporation for many years in mainly sales and business management roles in their Fine Chemicals and Pharmaceutical API businesses. Kristine is an active supporter of the Drug, Chemical and Associated Technologies Association (DCAT), DCAT Week, and has recently served on the DCAT Board of Directors. While residing in Europe she was also associated with the European Fine Chemicals Group (EFCG). Ms. Senft graduated from Eastern Illinois University with a BS in chemistry. In 2014, she completed the DSM Executive Leadership Program at Wharton, University of Pennsylvania.

ABSTRACT

As older blockbuster drugs lose patent protection and generic competition increases, many pharmaceutical companies are focusing discovery efforts on therapies with the potential to treat multiple niche populations. Increasingly, innovative small and emerging pharma firms are developing new drug candidates with orphan or breakthrough therapy status that are ultimately licensed or sold to large brand manufacturers. These companies rely heavily on contract manufacturing and development organizations (CDMOs) that can provide in-depth scientific expertise and achieve under rapidly accelerated timelines the development of cost-effective, robust, reliable processes that consistently yield high-quality products.

Until recently, most pharmaceutical firms were not interested in the development of small-volume drugs due to fears of limited returns. With the age of the blockbuster drug now history, many drug companies are finding that niche therapies, particularly those that may treat numerous indications, not only provide patients with life-saving medications, but also realize attractive financials if developed in a streamlined and cost-efficient manner. There are over 7,000 different types of rare diseases and disorders, yet only a couple of hundred approved therapies designated as orphan drugs. According to EvaluatePharma, although the average Phase III development time for orphan drugs is not shorter than that for non-orphan drugs, the Phase III drug development costs for the former are half those of the latter, and the anticipated return on investment for a Phase III/filed orphan drug is nearly twice that for a non-orphan drug.

As a result, EvaluatePharma estimates that the orphan drug market is growing at an annual rate of 11%, more than double that of the overall prescription drug market (5%), and by 2020 will reach $176 billion in annual sales and account for 19% of the total non-generic prescription market. In 2013 alone, 260 orphan drug designations were granted. In 2014, the FDA approved 15 NDAs and seven BLAs with the orphan drug designation, along with 24 supplemental approvals.

Many companies are also pursuing the new breakthrough designation established in 2012 by FDASIA, the Food and Drug Administration Safety and Innovation Act. A candidate qualifies for breakthrough therapy designation if preliminary clinical evidence suggests that the drug may have substantial improvement over available therapies on at least one clinically significant endpoint. The development and approval times for breakthrough therapies are typically half that of the seven years for conventional drugs, and both the sponsor and CDMO benefit from greater FDA guidance and communication with the agency. FDA's CDER approved 14 breakthrough therapies

in 2014 and nine in 2015 as of August 21.

Of the firms pursuing the development of orphan drugs and breakthrough therapies, many are small or emerging pharmaceutical or biopharmaceutical companies focused on niche, small molecule therapies. These companies often have limited resources in terms of laboratory, analytical, and manufacturing equipment (indeed, some are virtual companies in that respect) and depend heavily on service providers to perform crucial process and formulation development, validation, regulatory compliance, and manufacturing activities. The choice of CDMO can therefore have a direct impact on the success or failure of the new drug.

DEEPER SCIENCE

Whilst technical capabilities and synthetic expertise in a wide range of chemistries is necessary for any CDMO, the ability to accomplish practically any chemical transformation is no longer sufficient when supporting small and emerging pharma companies that are focused on the development of small-volume, niche drugs for targeted patient populations. Clearly, an awareness and understanding of their needs related to the development of orphan and fast track drugs and breakthrough therapies is a must.

Innovative smaller pharmaceutical organizations, particularly those in North America, also expect to have deeper discussions about technology and science. They no longer see CMOs/CDMOs as simple suppliers of manufacturing services; they select providers that can offer a unique depth of expertise, knowledge, and know-how that can help them address the challenges they face throughout the development and commercialization process, and increasingly at earlier stages. The same trend is also occurring with larger pharmaceutical companies that outsource discovery and early phase development.

All of these firms rely very heavily on CDMOs that have a deep understanding of both the processes and molecules they are trying to develop. Service providers with the right combination of technical capabilities and experience can help sponsor firms to reduce development times and costs, and provide assurance to regulators that the ultimately chosen cost-effective process will be robust and reproducible, and provide product with consistent quality, regardless of any need for technology transfer or scale-up.

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It should also be noted that the rapid pace of advancement in chemical and biological technologies ensures that no one company can have expertise in all of the latest techniques and methodologies. Therefore, in addition to having specialized expertise in several scientific areas with applicability to pharmaceutical development, such as particle engineering and chromatographic purification on the lab to commercial scale, CDMOs viewed as preferred partners also have capabilities designed to aid in process understanding, and belong to a network of providers with other specialized expertise that they can tap if needed.

One technical area of particular importance is particle engineering. Because 40-60% of all NCEs are poorly soluble, CDMOs with the ability to identify solutions to solubility challenges have a real competitive advantage. Experience in particle engineering and the ability to create a wide range of physical forms with enhanced solubility is becoming a necessity today. State-of-the-art technologies such as spray drying and hot melt extrusion, combined with advanced modeling tools, enable significant reductions in development times and costs while providing high quality APIs with desirable pharmacokinetic properties.

RELATIONSHIPS MATTER

Indeed, relationships also play a crucial role in the success of accelerated drug development projects. According to a recent report by the Tufts Center for the Study of Drug Development (CSDD), to better serve public and patient communities by reducing rising development costs, shortening cycle times, and delivering better innovations, many pharmaceutical firms are also implementing highly collaborative approaches to validating drug targets; integrating real world data into the R&D process; employing flexible and adaptive clinical trials; and using green manufacturing techniques that include the sharing of precompetitive information among government agencies, academia, patient groups, payers, and providers.

Because there is much less time to develop and validate the manufacturing process and analytical methods and generate safety and efficacy data, it is important that the CDMO and sponsor company have established a more strategic relationship, with the CDMO acting as an extension of its customer rather than only as a vendor. Strong sponsor-CDMO communication is particularly vital, so that potential problems can be caught and addressed before they become major setbacks.

Good relationships with FDA representatives are equally important. Orphan drug, breakthrough therapy, and fast track designations require increased interactions with the agency to ensure that the shorter development times can be met. CDMOs that have experience working with the agency and recognize the value of additional meetings and guidance from

Focused Expertise for Accelerated Drug Development and Manufacturing

Hovione has been providing support to small and emerging pharma and biopharma companies since the start-up of our New Jersey plant in 2002, which will double its size to support increased demand from our sponsor partners. Today we provide support for all stages of the drug development and commercialization cycle to customers large and small.

With our in-depth process and product knowledge, we are able to rapidly develop robust, reliable, and predictable processes with attractive long-term economics that provide products of very high quality. As a result, Hovione is ideally positioned to support the development and commercialization of orphan drugs and drug candidates with breakthrough and fast track designation.

+ Small-volume API manufacturing
+ Development by design (application of quality by design and process modeling technologies) for streamlined development
+ Advanced particle engineering capabilities (spray drying, hot melt extrusion capabilities, and jet milling)
+ Expertise in overcoming poor solubility and permeability
+ Facilities for the production and handling of highly potent compounds
+ Advanced cryogenic and hydrogenation capabilities
+ VPP Star Award facility as designated by the Occupational Safety and Health Administration (OSHA)

the FDA will be able to not only provide enhanced service and support to their small and large pharma customers, but also help reduce risk and facilitate earlier approvals.

To address the development challenges presented by the increasingly complex drug candidates of today, pharmaceutical companies are also seeking CDMOs that emphasize collaboration within their own firms. For accelerated development projects in particular, effective cross-functional teams are needed to ensure that CMC data development and stability studies are completed in a timely fashion, a suitable plan for scale-up and production is in place, the needs of other international authorities are considered for global products, and lifecycle management issues have been addressed. In fact, CDMOs with integrated capabilities across all stages of development and commercial manufacturing are increasingly preferred over traditional CMOs.

DEVELOPMENT BY DESIGN

There is very fundamental science behind all of the phenomena that occur during chemical/biochemical processes. The use of modeling technologies based on first principles provides the ability to design robust processes that behave the same regardless of scale. The application of quality-by-design (QbD) and process analytical technology (PAT) methodologies during both the development and commercialization stages, combined with the use of advanced modeling, allows simulation of the full design space well beyond what is possible using a design-of-experiment approach alone. At Hovione, this approach is a very powerful one that leads to the development of highly robust and reproducible processes, and in turn ensures smooth and rapid technology transfer and scale-up of the same high quality products regardless of volume or location. The enhanced process understanding and reproducibility obtained are also well-regarded as strengths by the FDA and other authorities. This approach ensures that only value-adding activities are performed, and are performed at the right time and in the most efficient manner.

IN CONCLUSION

Despite the turbulent times currently facing the pharmaceutical industry, there are many opportunities for both smaller emerging and larger established pharmaceutical and biopharmaceutical companies to develop novel medical treatments that will improve the lives of patients suffering from a myriad of as-yet-untreated diseases. CDMOs with a deep understanding of the process development and commercialization needs of both small and large sponsor firms faced with accelerated timelines can help speed new safe and efficacious drugs to market while ensuring that they are produced using cost-effective, robust processes.

Hovione, with years of experience developing and producing small-volume APIs at its US site, is ideally positioned to support accelerated orphan drug and breakthrough therapy projects. This is of particular benefit to emerging pharma clients, which enables the transition to commercial production regardless of the ultimate owner of the IP. We recognize that each customer has unique needs, and are therefore focused on meeting those needs through the tailoring of our comprehensive set of chemistry, particle engineering, process and formulation development, manufacturing, analytical, and regulatory capabilities. P


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because assurance of supply
is a top priority for our customers.
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