Drug Development® & Delivery

November/December 2011 Vol 11 No 9 www.drug-dev.com

Industry Outlooks & Perspectives

IN THIS ISSUE

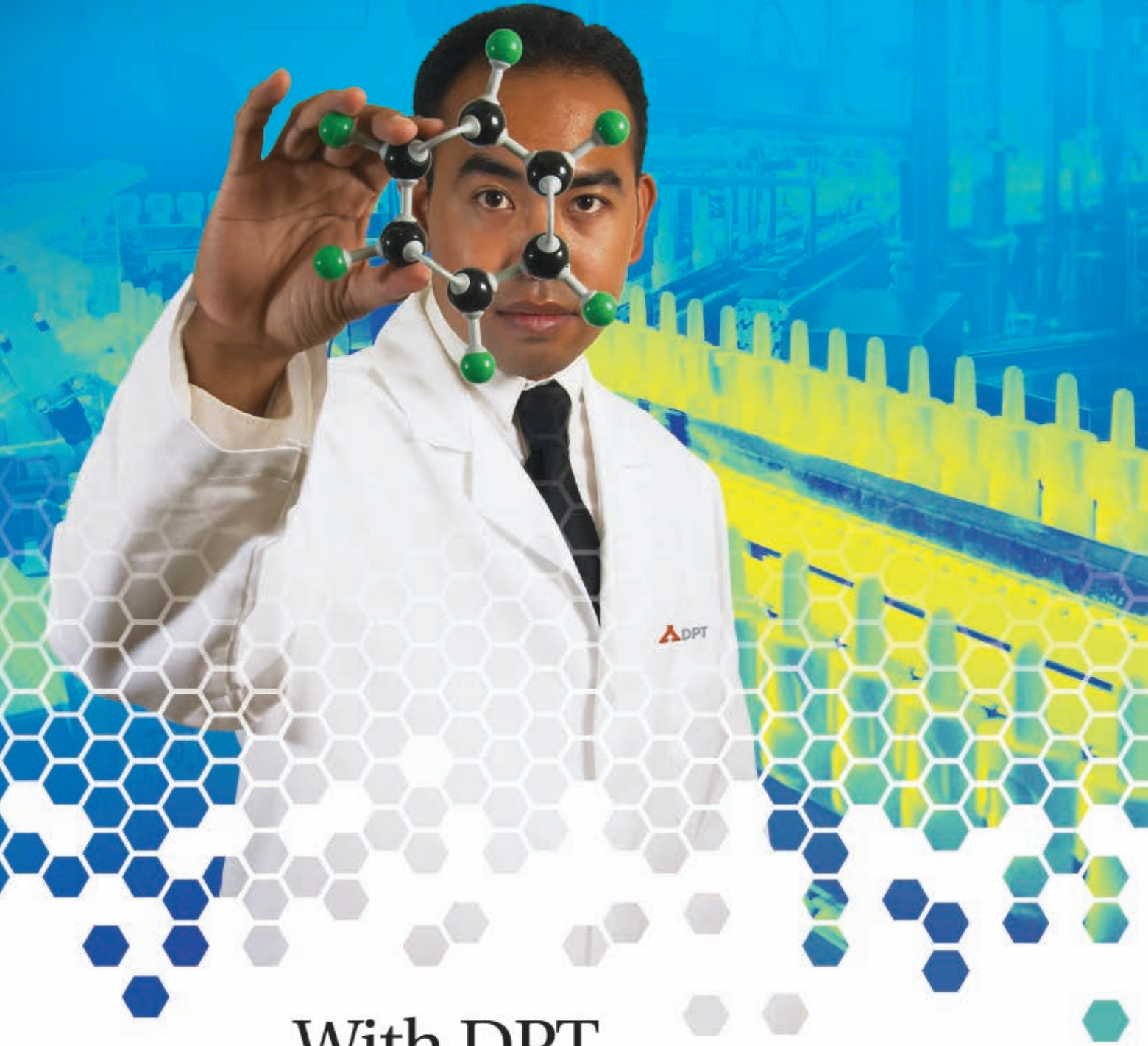
The science & business of drug development in specialty pharma, biotechnology, and drug delivery

10th Anniversary Issue!

Follow Us On

Frost & Sullivan, the Growth Partnership Company, enables clients to achieve best-in-class positions in growth, innovation and leadership. The company's Growth Partnership Service provides the CEO and the CEO's executive team with disciplined research and best practice models to drive the generation, evaluation and implementation of powerful growth strategies. Our mission is to research and analyze new market opportunities for corporate expansion. We are the world leader in growth consulting and the integrated areas of technology research, market research, economic research, corporate best practices, training, customer research, competitive intelligence and corporate strategy.

Exclusively Focused on Growth	Actively engaged in identifying new market opportunities, researching competitive strategies and developing implementation plans that enable clients to accelerate growth.
Industry Breadth	Cover the broadest spectrum of markets and technologies to provide clients with the ability to look outside the box and discover new and innovative ideas.
Global Perspective	Over 40 global offices ensure that clients receive global coverage and perspective based on local and regional expertise.
Continuous Monitoring	Continuously monitoring markets, technologies, careers and geographies for growth opportunities.
CEO's 360 Degree Perspective™	Disciplined research integrates all critical research methodologies to significantly enhance the accuracy of decision-making and lower the risk of implementing growth strategies.
Trusted Partner	Work closely with executive teams to leverage all of Frost & Sullivan's expertise to promote revenue-generating initiatives.



With DPT,
development and manufacturing piece together seamlessly.

DPT is the contract development and manufacturing organization (CDMO) that specializes in sterile and non-sterile semi-solid and liquid dosage forms. With unmatched technical expertise and fully integrated drug development and manufacturing services, we can help you successfully develop and commercialize your next product. Partnering with DPT gives you a seamless transition from pre-formulation to clinical supplies to commercial supply. After all, keeping it all together is what sets us apart. To get started, visit us at www.dptlabs.com or call 1.866.CALL.DPT.

DPT®

SOURCE WITH CONFIDENCE®

SEMI-SOLIDS • LIQUIDS • NASAL SPRAYS • PRESSURIZED METERED-DOSE INHALATION • AEROSOL FORMULATIONS • STERILE DOSE FORMS

1.866.CALL.DPT • WWW.DPTLABS.COM • SAN ANTONIO, TX • LAKEWOOD, NJ

Providing our partners the fastest path to market.

A Contract Diagnostics Organization (CDO) is your complete partner for diagnostics development.

We can manage all or any part of development from initial assay discovery through clinical research to regulatory approval. Our services include research project design, conduct, and FDA submission; laboratory assay development, validation, and sample testing in our CAP/CLIA lab; cGMP assay and reagent manufacturing; and expert guidance across the entire process.

"Our partnerships are based on flexibility, allowing us to either build and validate any assay without bias towards existing product platforms, or to work with emerging technology to ensure the best solution."

Mathew W. Moore *PhD, Principal, ResearchDx*

To learn more about how ResearchDx can help you, contact us at:
www.researchdx.com
or call **866-225-9195**

ResearchDX
Your Companion in Diagnostics

Drug Development & Delivery

November/December 2011 Vol 11 No 9

Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
Tel: (973)299-1200
Fax: (973) 299-7937
www.drug-dev.com

Advertising Sales Offices

International
Ralph Vitaro
219 Changebridge Road
Montville, NJ 07045
Tel: (973) 299-1200
Fax: (973) 299-7937
E-mail: rvitaro@drug-dev.com

West Coast
Warren De Graff
818 5th Avenue, Suite 301
San Rafael, CA 94901
Tel: (415) 721-0644
Fax: (415) 721-0665
E-mail: wjdegraff@drug-dev.com

Mailing List Rental
Candy Brecht
Tel: (703) 706-0383
Fax: (703) 549-6057
E-mail: cbrecht@mgilists.com

East & Midwest
Patricia Loyas
977 Wall St.
Diamond Point, NY 12824
Tel: (518) 668-4144
Fax: (518) 668-9794
E-mail: ployas@drug-dev.com

The Editorial Advisory Board

Dan Marino, MSc
Executive Director
Drug Development & Delivery

Table Of Contents

TRANSDERMAL TRANSCENDENCE

That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

As one of the world's largest manufacturers of transdermal patches offering a full range of research, development and manufacturing capabilities, Aveva transcends traditional limitations of patch technology and business partnerships to achieve new levels of product and corporate performance.

- Customizing solutions to the unique characteristics of each drug
- Masterfully balancing the patch properties of adhesion reliability and gentleness that lead to an enhanced patient experience.
- Managing a higher drug concentration in a smaller patch

A flexible, customer-oriented business philosophy that adds value to projects and exceeds customer expectations.

To license a product or to see how we can add value to your project, call Robert J. Bloder, Vice President Business Development, at **954.624.1374** or visit **www.AvevaDDS.com**

NITTO DENKO GROUP

PARTNERSHIPS & ALLIANCES

The Reshaping of the Pharmaceutical Industry Landscape: Partnerships & Alliances Are the Core of New Business Strategy

By: Cecilia E. Van Cauwenberghe, Senior Research Analyst, Life Sciences & Biotech, Technical Insights, Frost & Sullivan

INTRODUCTION

Although the pharmaceutical market continues growing, it is more evident every day that the paradigm shift of industry capitalization creates underlying opportunities. In a few words, the biopharmaceutical industry is facing the tough reality that the drug development models that have served the industry well for many years, based on a vertically integrated structure with most of the R&D process performed in-house, have become unsustainable. On that note, the pharma industry is currently focusing on research and development (R&D) activities toward a more personalized and cost-effective approach to medicine. Principal motivations holding this change consist basically of the increment of the healthcare budgets around chronic disease, market pressures resulting from declining R&D productivity, limitations for doctors to prescribe drugs according to policy restrictions, rising costs of clinical trials, patent expirations and higher regulatory hurdles, new advances in microelectronics for medical devices promoting point-of-care (PoC) systems, crucial necessity to avoid the increasing individuals' self-medication, expansion of the medication demand in emerging economies, governments' trends in focusing on prevention instead of treatment, and increasing caution regarding regulatory and ethical issues, among others.

Such landscape changes can be seen not only as challenges, but also as major opportunities for the markets evolution, driving the industry to review all business models to determine and pursue new R&D paradigm shifts that inject vitality to the whole process. The following reviews a brief analysis of the current pharmaceutical industry landscape as well as the different business strategies adopted by main players.

INDUSTRY LANDSCAPE

The pharmaceutical industry addresses current unfilled needs in the healthcare world by calling for the right treatment for the right individual at the right time. As with any other major societal and technological transformations in the world, such a novel discipline is expected to bring along great value creation and resource reallocation among various stakeholders in the healthcare industry. Given its fundamental impact and implications on all different businesses related to healthcare, it is critical to achieve a clear understanding of the present and future of personalized medicine in order to become the involved organizations ready to capture the most value in this evolution.

Latest approaches to pharmaceutical development, including a variety of actors among Big Pharma and Big Bio companies, mid-size players, and specialized service providers (CROs, Health IT, etc.), have been shaped under the up-to-date impetrating landscape of the

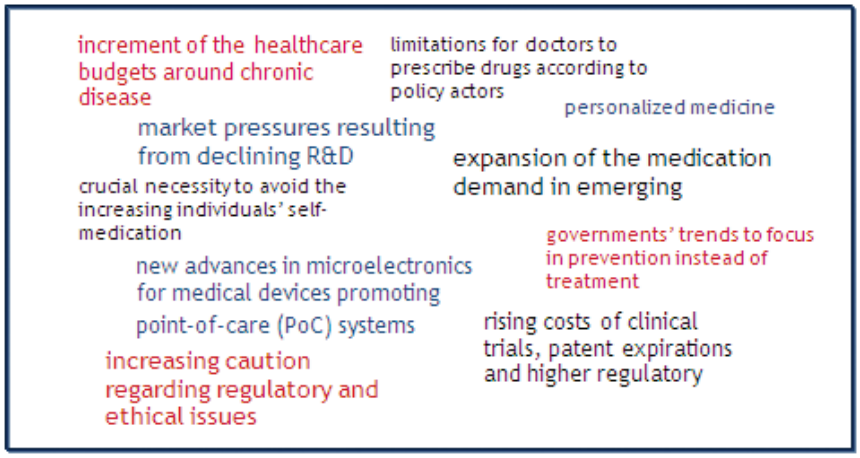
blockbuster strategy. Such an approach is focused on developing drugs to exploit these large potential markets. The objective was one drug for large markets with typically 15 million-plus chronic patients and annual revenue potential of at least $1 billion.

Nowadays, this strategy has been observed to gradually decline over time, leading to narrow product portfolios (usually aligned with chronic disease treatment markets), a relatively small number of genuine innovative compounds, and a proliferation of incrementally improved drugs. Based on these observations, it is expected that this landscape should experience a radical change.

Such a change brings a more personalized approach to medicine, on the base of novel technologies flourishing at the post-genomic era. Precisely at this point, phenotyping of diseases is being replaced by an understanding of disease at the molecular level. Hence, stratification of patients based on observable characteristics, that is, phenotyping, is being replaced by stratification based on genotype. In this regard, biomarkers and molecular diagnostics appear as preponderant technologies.

Although the complexity of a personalized medicine environment results in enormous, genotyped clinical trials, biomarker-measured responses are expected to result in more efficient treatments. Similarly, the complexity of the company's positioning into the market and product-related decisions are also expected to increase. Therefore, a deeper understanding of diseases at the molecular level and increasing usage of genotyping and biomarkers to develop targeted treatments is crucially needed. This is expected to expand the patient-disease matrix from a few phenotype paths to many genotyped paths, ending in consequent opportunities and challenges.

FIGURE 1



The Most Relevant Promoters of a Paradigm Shift in the Pharmaceutical Industry (Source: Frost & Sullivan)

Indeed, even though changes are expected to occur gradually, future financial success will require different capabilities and different ways of deployment. While Big Pharma faces a great challenge in making this landscape profitable according to current capabilities, through a huge restructuring task, Big Bios will experience the need for financial success by taking advantage of their biological-based R&D operations. Thus, new business models based on partnerships and alliances, as well as other collaboration networks, including the participation of different industry service providers, such as contract research organizations (CROs), contract manufacturing organizations (CMOs), etc., are arising.

In the current healthcare value chain, patients typically represent the starting point. A variety of disease symptoms triggers the patient-physician interaction to finally conduce to the diagnosis, prognosis, and treatment processes.

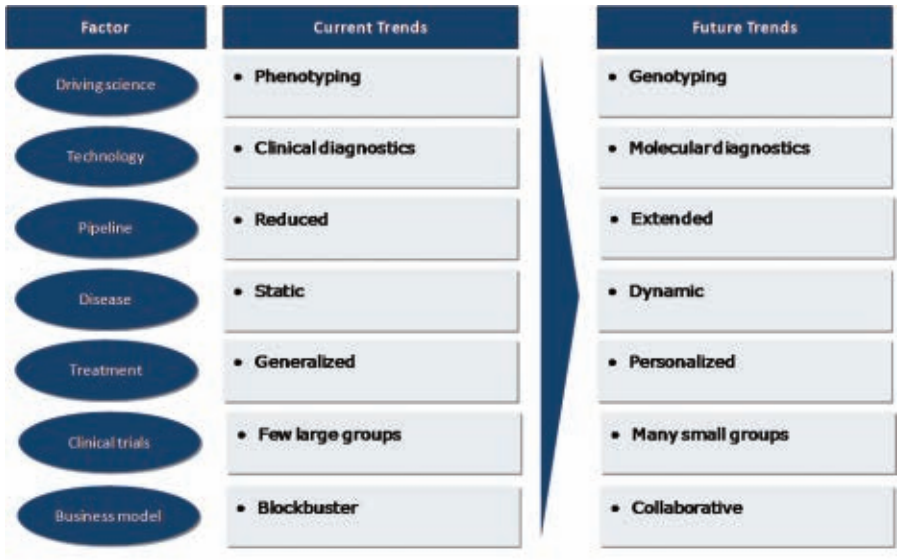
Regarding the current value distribution in the healthcare-related industries, providers constitute the most inherent part of the chain in virtue of care delivery and patient-physician interaction. Thus, diagnostics product manufacturers and service providers play an important role in promoting novel solutions to healthcare professionals. In this matter, several medical device companies supply products as part of the diagnosis and treatment solutions, and align themselves with the pharmaceutical and biotech industries to provide market research information for their marketing, sales, and R&D functions, as well as strategic solutions.

An essential driver in healthcare development is constituted by the currently emerging genomics and pharmacogenomics companies. Novel molecular-level diagnosis and treatment products, closer to the concept of individualized or stratified medicine, are starting to arise.

INDUSTRY VALUE DISTRIBUTION

The combination of the broad spectrum of scientific fields involved in biomedical technology and life sciences moves toward a more personalized approach to medicine, resulting in expectations for a unique cooperation across the value chain of healthcare R&D. Under this scientific approach, the order will move from fundamental to applied research to clinical research to clinical practice.

FIGURE 2



The Current & Future Trends in the Biopharmaceutical Industry Landscape (Source: Frost & Sullivan)

The foundations for these novel approaches to medicine and biology, and therefore, for the pharma and life sciences industry, rely on the basis of molecular diagnostics and, in general, in a deeper understanding of human biology at the molecular level. An example of such a development is pharmacogenomics, which studies the differences in drug response in a drug-patient interaction and behavior based on molecular profiling and genotyping. It is expected that disease diagnosis and prognosis protocols enable diagnosing a certain disease condition based on molecular-level indicators in a more accurate manner, as well as, a more reliable prognosis, conducing to the optimization of the clinical routine.

The most radical difference between the current healthcare value chain and a personalized platform is given by the last start by individuals instead of patients, emphasizing the social impact of such a discipline and those associated activities. Prediction plays the most crucial role of denoting individual genetic predisposition to develop certain diseases in the future, so that appropriate decisions can be fortunately made.

By these means, a new value creation comes out, causing the avoidance of potential loss and enhanced quality of an individuals' life. Such new value creation has had a main focus on distinctive areas. Molecular diagnosis and prognosis, as the basis of a more personalized approach to medicine, result in an essential target. Stratified medicine for a rational screening to attempt to find differences in drug response, including the possibility of adverse effects, also constitutes a crucial element for value creation. The design of optimal therapies and strategies to elude these adverse drug responses (ADR) becomes significantly important for the success of personalized medicine. Finally, the disease predisposition assessment and management constitutes the basis for prospective healthcare.

INDUSTRY EVOLUTION

External scientific affairs meet experts and specialists from science, research, and business, creating a prosperous situation for innovation and development, which constitute a crucial factor in the transition toward personalized medicine. This prospect generates opportunities for establishing parallel processes and, hence, for reducing the timeframe and costs of the R&D processes.

Focus on Partnerships & Alliances

R&D processes are divided into the phases of discovery and development. In that sense, partnerships and alliances are created throughout both phases of the process, usually under the definitions of upstream and downstream alliances, respectively. There exist many different partnership models, with numerous and diverse structures and outlines. From an economic point of view, the success can be devised through a profitability index; however, from a business perception, several factors should be taken into account.

Therefore, successful partnerships strongly depend on management, as well as its evaluation and fostering from the part of the corresponding partners. Over the years, special attention was gaining for the essential, but intangible, factor of reliability and confidence. Indeed, endeavoring parts working to generate a combination of both competence-based and character-based reliability has been demonstrated as a vital feature for the success of the alliance. The competence-based approach consists of the recognition that the partners possess the essential resources and competencies to generate a successful outcome of the partnership. On the other hand, a character-based approach is more related to personal values, such as integrity, discretion, openness, coherence, and helpfulness, just to name a few.

Another important factor contributing to a successful business relation between partners is given by a clear strategic purpose, well established from the beginning in order to avoid zig-zag movements and consequent erosion of the personal relationships. Similarly,

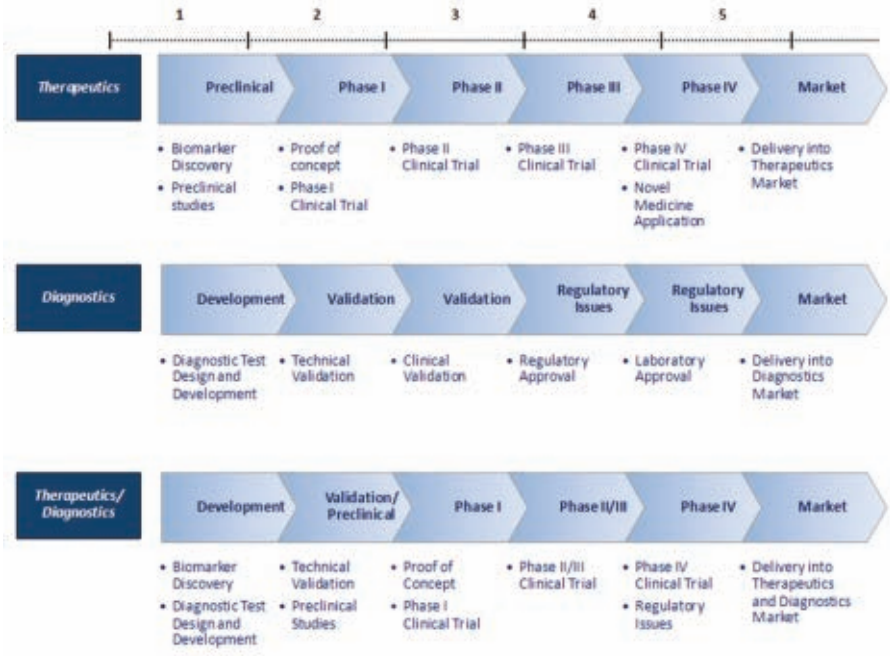
a definition of prospects can facilitate a smoother path toward success, in addition to the proposed strategy. In this regard, defining prospects means exchanging information on performance among the partners and identifying clear goals for the partnership, as well as aligning governance and organizational engagements to link both participants.

Notably, these new circumstances of interaction and collaboration with potential partners are a result of the internationalization of the pharmaceutical industry. In this regard, results are important to design cooperative principles and rules for the regulation of medicine development in the interaction with an external scientific partner. It can be seen that as the pharmaceutical industry becomes increasingly internationalized, the global healthcare community will make claims for new pharmaceutical norms and standards that guarantee the safety of the processes.

It is remarkable at this point that the industry becomes more international every day, resulting in expectations of the evolution of a new generation of companies. Intermediary facilitators to collect and assemble the excessive amounts of global data are essential to personalized medicine. This is in addition to the importance of scouting organizations that act as conciliators for large pharmaceutical companies by recruiting external scientific partners, such as biotech companies, CROs, federal and academic research, among others, who play a crucial role in the new scenarios of the pharma industry.

On this same point, an increase in partnerships among federal and academic institutions with pharmaceutical companies is becoming a reality. Intermediary companies facilitating the transition from upstream to downstream processes are expected to perform an essential role in the translation to routine clinical practice.

FIGURE 3



The Industry Value Distribution, Focused on Therapeutics, Diagnostics & Companion Medicine (Source: Frost & Sullivan)

Another aspect to take into consideration is the internationalization of the industry, given by the increase in competition from a section of the technology developers, which can benefit the pharmaceutical industry in the long-term. The challenge here for pharmaceutical companies is making the best selection for investment in innovative and prospective technologies in which investments reach leadership positions in the near future. Again, intermediary players can help in the evaluation of the most promising technologies that work towards the future development of personalized medicine.

Accordingly, and by considering the global development of this discipline, the industry transition toward personalized medicine also involves highly specialized niche markets, in addition to the constitution of external scientific and international business alliances. This is so that the focus of pharmaceutical companies is on the right selection of their business strategy and the collaboration networks that lead toward their goals.

Focus on R&D Improvement

Measured over the past half century, the pharmaceutical industry has been markedly successful in terms of financial results, innovation, and performance, or generated societal benefits. Nonetheless, in the late 1990s, some leaders began to caution about the outcomes related to blockbuster New Molecular Entities (NMEs), which were projected significantly below the level needed to generate the required revenues to sustain the stock market valuations of pharmaceutical companies.

In addressing this concern, some approaches led to a substantial expansion of R&D efforts. Over the past decade, R&D budgets have grown significantly. However, massive scale without a consistent improvement in the R&D process results in less efficiency in productivity, as it can be seen from the FDA approvals statistics for NMEs,

with only a handful of these approvals being truly innovative, first-in-class molecules.

Major efforts focused on increasing the efficiency of the R&D process have been based on integrating knowledge management processes to classified information, correlating and assessing the R&D information generated, and fostering the constitution of decision support mechanisms to continually realign R&D efforts based on potential risk and rewards. On the same line, stand-alone R&D centers that focus on specific therapeutic areas and outsourcing attempt to move the process into increased flexibility in order to adapt have also been conducive. Nevertheless, reengineering, realigning, and restructuring are only some of the potential factors to improve the process, and they do not constitute a paradigm shift alone. Changes should be thought as the basis for the clinical translation into personalized medicine so that the complete R&D process needs to be altered.

Key elements to improve the R&D process in the transition toward a new perspective of medicine are those related to a reduction in the timeframe and costs during the research activities for the NMEs' discovery and subsequent development. Here, the virtualization of different parts of the process in order to perform a variety of tests in silico gives real-world solutions for accomplishing in vitro clinical investigations, and further in vivo studies in humans with improved success. Such an approach relies on perfect agreement with novel regulatory issues claiming minimal use of animals for laboratory assays, as well as the recent classification of a variety of genetic tests as Class III (most strict level) disposals. Frost & Sullivan recently published research titled "Bioinformatics in Drug Discovery," detailing important aspects of in silico proves of concept and market assessment.

A deeper understanding of the mechanisms governing specific diseases results in a vital tangible asset in the development of personalized medicine. Intellectual capital constitutes a key element to enhance the R&D process, focusing on the most suitable therapeutic area to achieve a profound knowledge of the disease mechanism and the biological pathways involved, which provides the ability to leverage all resources, including the existing patient data and technology. Succeeding with the improved R&D process requires the essential comprehension of the disease nature to enable the evaluation of therapeutic interferences and the discovery of relevant targets for therapeutic intervention. Furthermore, a directed selection of the pool of candidate patients for clinical trials according to their prospective therapies results is essential when identifying the commercial feasibility of each therapy. From there, it is important to have a thorough understanding of the composition of the given disease to spot both NMEs and biomarkers and focus on the relationship between the molecular intervention and the disease pathophysiology.

Once the discovery aspect of the R&D process has been modified to meet the requirements of personalized medicine, the development procedure must also be customized. Biomarkers constitute a source of accepted indicators of success. The aforementioned in silico platforms based on the mathematical modeling and simulation of the broad spectrum of mechanisms involved in a certain disease, at different scales from molecular level to organisms, are also gaining special attention in this part of the R&D process.

Such improvements in R&D procedure attempt to decrease the development costs in clinical trials and reduce the timeframe for development. In addition, new opportunities for faster recouping of invested capital arise. Failures detected at earlier stages during the process can limit the investments leading to large savings.

The key element in the evolution of the R&D process toward a propitious scenario for personalized medicine development relies on the advance of a few steps at a time, giving time to learn from the experience. This transition assumes a very complex landscape, which is expected to shift in the direction of a more personalized sense of medicine by logical incremental approaches, including gradually transforming visions, strategy, and R&D processes.

Focus on Regulatory Issues

The paradigm shift regarding personalized medicine approaches also comprehends regulatory issues. Thus, the translation of personalized medicine to routine clinical practice involves the approval of new drugs on a real-time basis, including contingencies and more exhaustive life trials.

Following this point, the FDA has developed a program known as the Critical Path Initiative (CPI), created to formulate new analytical tools for improving safety and efficacy of medicines. In parallel, the European Commission and European Federation of Pharmaceutical Industries and Associations (EFPIA) have stated the Innovative Medicines Initiative (IMI), a pan-European cooperative agreement concerned with producing new medicine development tools. In addition, the European Medicine Agency (EMEA) has created and launched a new European Risk Management Strategy (ERMS), requiring all European pharmaceutical companies to provide comprehensive data and information about the risks associated with medicine developments. To this respect, transparency is vital for succeeding.

Focus on New Strategies for Intellectual Property Protection

Regarding intellectual property (IP) protection, certainly, many challenges exist that are associated with these types of personalized medicine inventions. Experienced patent counsel can enhance the ability of personalized medicine companies to capture appropriate claim scope.

Thus, an institutional platform as well as IP strategies helps stakeholders in both the private and public sectors make better and more productive use of their developments. These include biomarkers and small molecules, which represent a crucial need for the translation of personalized medicine and are available for high-throughput screening (HTS).

Some approaches, attempting to bridge the gap between patents and the public domain or open source information, include the creation of novel search engines to explore a larger and higher quality pool of molecules and genes that could result as attractive options for personalized medicine use. This is followed by the design of a contractual framework in which publicly funded university research could identify and characterize potential lead compounds without compromising patents on those compounds. Finally, the administration of such a framework from public-private partnerships need to be carried out for the effective translation of upstream research into genuine innovative therapeutic advances to contribute to the overall public health.

CASE STUDIES & FINAL REMARKS

While a variety of opportunities traditionally derived from Big Pharma activities still continue to come into sight, the specialty pharma (SP) sector faces significant competitive pressure. SP market maturity brings with it the necessity to innovate and become increasingly outstanding in shaping the ability to focus on a specific range of unmet needs through new specialization strategies. Market features, including trends toward the commoditization of drug delivery technologies and competition from foreign bulk generics manufacturers, force companies to develop new growth models and targeted portfolios. These factors also establish novel policies regarding license agreements, merger and acquisition (M&A) activities, and partnership and alliance opportunities.

Precisely in addressing this concern, Shire has adopted an insightful use of strategic partnerships and alliances, as well as a judicious approach to licensing and acquisitions settlements, through the active dedication of its business development division. Furthermore, Shire has carefully evolved its strategy to avoid performance fluctuations and traditional pitfalls that are typical in the Big Pharma industry, such as patent protection loss, oscillation in sales volumes, and expensive research, among other hazards.

Shire's strategy is founded on a "search and development" (S&D) approach, seeking out rare and uncured diseases while also acquiring new drugs that are almost ready for launch on the market. The expedited and focused character of Shire's management team facilitates a strong market position by overcoming the inertia of the business. Thus, by leveraging its internal expertise ranging from the initial scientific evaluations to its full commercial projections, the company reaches the final transaction stage with admirable diligence.

Therefore, Shire's tactical approach focuses on products in specialist markets with strong IP protection and global rights. In this regard, Shire has completed seven M&As in 10 years. This activity is constituted as a priority for the company, and includes 20 products on the market, along with a pipeline of seven projects, including six that are at or post Phase II.

Market trends for personalized medicine are principally governed by the continuously increasing healthcare costs and timeline of the drug discovery pipeline. Additionally, the current outcomes have become insufficient for a population seeking a better quality of life, which requires cures instead of chronic treatments. Thus, in addressing this growing sense of urgency, focus has been on achieving a more personalized approach to medicine, through better diagnostic tests at the molecular level to deliver more effective therapies to a reduced pool of patients, potentially lessening costs and time.

On the other hand, the emergence of a wide variety of small and medium enterprises (SMEs), derived from early stage companies and university spin-off companies, have a profound impact on the development of personalized medicine. These SMEs also play a crucial role in the new business models through the downstream alliances with big players into the pharmaceutical industry.

On the base of such alliances and collaboration networks, personalized medicine will see a revolution, moving into routine practice in the next decade of the 21st century. Shire's strategic goal focuses on meeting the current medical needs in specific therapeutic areas, maintaining special emphasis on attention deficit hyperactivity disorder (ADHD), human genetic therapies (HGT), gastrointestinal (GI), and renal diseases, among others.

The company looks for products at the appropriate stage of development with growth potential and IP protection to incorporate them

into its existing balanced sales portfolio. Shire's specialty sales and marketing platform operates across the major North American and European markets through its existing distributors and licensees, reaching a preponderant role in seven of the eight major SP markets. By these means, partners benefit from Shire's excellent record of accomplishment for product development and commercialization, which constitute the base of a flexible and creative approach to novel collaboration models.

Shire's improvement in market positioning can be measured by analyzing the exceptional results obtained from the recent past, with product sales up 32% to $794 million (In 2009, this figure amounted to $603 million) and total revenues up 31% to $874 million (In 2009, this figure was $667 million), as a result of higher product sales and royalty incomes.

As mentioned earlier, external scientific affairs meet experts and specialists from science, research, and business, creating a prosperous situation for innovation and development. This constitutes a crucial factor in the transition toward novel conceptions of integrative healthcare, and, therefore, toward a more personalized approach to medicine. This prospect generates opportunities for establishing parallel processes, and, hence, reduces the timeframe and costs of the R&D processes. Such improvements in R&D process attempt to decrease the development costs in clinical trials and reduce the timeframe for development. In addition, creating new opportunities for faster recouping of invested capital are of focus. On the other hand, failures detected at earlier stages during the process can limit the investments in this area, leading to larger savings.

In this regard, there exists many different partnership models with numerous and diverse structures and outlines. From an economic point of view, success can be achieved through a profitability index. However, from a business perception, several factors should be taken into account, including reliability, clear strategic purposes, attractive goals for every involved part, etc.

Such a tactical movement of internationalization in the pharma industry helps to pioneer the S&D business model and enables the ability to spread risk to avoid dependence on one or two products. In this regard, Shire S&D outsources all non-essential aspects of the process, utilizing CROs for all clinical aspects.

Concerning competitive intelligence, Shire closed an outstanding year in 2010, beyond any expectation. Observed growth across the company's core portfolio enabled Shire to make targeted investments in its pipeline, as well as enhance its international market structure by shaping novel collaboration lines according to emerging rules and scenarios.

Boehringer-Ingelheim (BI) is well-recognized for having steadily established itself as one of the largest and most successful bio pharmaceutical CMOs globally. According to research carried out by Frost & Sullivan, strategic alliances and support services for start-ups have further reinforced BI strategic superiority in the bio pharmaceutical contract manufacturing market.

To date, BI has successfully introduced 19 DNA-derived biopharmaceutical products - significantly higher than any other company in the biopharmaceutical contract manufacturing market. Its strong in-house technologies and strategic alliances (such as those with Pfenex Inc, Fresenius Kabi, Probiogen AG, and VTU Technology) have enabled the company to offer cutting-edge solutions. Furthermore, four of the biopharmaceuticals produced by BI rank among the top 20 globally of biopharmaceutical products. These include Enbrel produced for Amgen Inc. and Pfizer/Wyeth Pharmaceuticals, Synagis for MedImmune Inc, Betaferon for Bayer Health Care, and Erbitux for Merck Serono.

Based on this strategy, BI counts among its customers many of the world's leading research-oriented biopharmaceutical companies and pharmaceutical organizations, such as Genentech Inc., Genzyme Corp, GlaxoSmithKline, InterMune Inc., Bayer Health Care, Pfizer Inc., and Amgen Inc.

Similarly, as drug development and outsourcing industries continue to mature and as cost pressures continue to increase, the focus is kept on looking for more valuable relationships. That is the case for progressive players, such as Novartis, which has based its alliance partnership models and strategic relationships on optimizing performance and outcomes. According to the company's management, Novartis explores the definition of clinical delivery alliances and carefully studies the value of these alliance partnership models in order to accomplish conjunct efforts associated with drug discovery and development processes.

Industry players, including VDDI Pharmaceuticals, UBC, and Pfizer, have demonstrated similar strategies. At this respect, it is important to identify the variety of factors driving changes in the industry to enable the exploration of new business paradigms for partnering with clients, thus enriching business relationships.

PAREXEL International Corporation, a leading global biopharmaceutical services provider, is also well committed to addressing best practice strategic partnership models to increase operating efficiency and improve development effectiveness. Good examples of such model applications are the cases of Merck and Bristol-Myers Squibb partnerships, based

on leveraging global resources and a worldwide technology infrastructure, as well as the implementation of innovative approaches to achieve significant value creation.

Another remarkable configuration is exposed by Takeda Pharmaceuticals International, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The company entered into strategic partnerships in the past year with Covance and Quintiles, two of the world's largest full-service CROs, to plan and execute global development programs to support new compounds in all therapeutic areas, excluding oncology. By means of this agreement, Takeda is able to access clinical development capabilities and central laboratory services of Covance and Quintiles, with each partner company providing dedicated resources to support Takeda's development pipeline. This significantly improves its efficiency while moving the company toward a fully virtual outsourcing model, which combines the expertise and capabilities of Takeda with those of Covance and Quintiles.

Similarly, academic and clinical institutions are also participating in such an important paradigm shift regarding partnerships and alliances models. That is the case of Tufts University, which launched the Tufts Institute for Biomedical Partnerships. The institute developed and managed by Tufts University School of Medicine and Tufts University's Advancement Division is a university-wide, global pharmaceutical partnering initiative designed to create and manage a diverse portfolio of drug discovery and development partnerships. The principal goal underlying such a decision relies on culturing innovative drug discovery and developing alliances between Tufts Institution with the pharmaceutical industry based on existing assets of strategic interest, while generating revenue streams to benefit both the university and industry. As part of the strategy, the Web platform has been custom developed and designed to educate and engage pharma partners as well as qualify allies and create distinctive alliances by facilitating communication vehicles, strategic market resources, and information repositories.

Thematic areas covered by the involved players include: the development basis for innovative therapies for cancer, infectious diseases, cardiometabolic and pulmonary disorders, neurological and psychiatric disorders, as well as technology platforms, including biomaterials and biological scaffolding, genetics, genomics and cell function, translational and clinical pharmacology, functional tissue engineering, functional proteomic screens, drug discovery and development for target identification and validation, structural and chemical biology-based drug design, metabolic analysis of drug candidates, in vitro models of drug transport, experimental and spontaneous models of disease, drug disposition and clinical pharmacokinetics, clinical pharmacology, drug development and regulation, protocol design and complexity, new models of pharmaceutical innovation, pharmaceutical economics; and research constellations through the establishment of non-traditional networks of robust research activities (including regenerative medicine, biology and aging, and inflammation, among other scopes). ◆

BIOGRAPHY

Cecilia E. Van Cauwenberghe is a Senior Research Analyst for Frost & Sullivan's Technical Insights practice. She has more than a decade of professional expertise in chemical and biomedical engineering arenas, which include R&D activities in several well-renowned universities and multinational companies. Ms. Van Cauwenberge has particular expertise in leading and executing projects related to life sciences and biotechnology, healthcare and biomedical devices, biomedical and clinical engineering, and energy and geophysics. Before joining the Frost & Sullivan team in 2010, Ms. Van Cauwenberge worked with Dr. Rene G. Favaloro Foundation University, South National University, Comahue National University as well as YPF S.A., The Techint Group and the National Institute of Industrial Technology (INTI).

Roundtable Discussion

Pharma & Biotech Contract Services: Then & Now

By: Cindy H. Dubin, Contributor

Most outsourcing activity in the past decade has revolved around contract research outsourcing, which includes discovery research, preclinical, and clinical studies; and contract manufacturing outsourcing, which includes active pharmaceutical ingredients, formulation products, and their intermediates.

According to BCC Research, revenue for global pharmaceutical contract manufacturing and contract research organizations reached $196.5 billion in 2010 (it will further grow to $217.9 billion in 2011) and is projected to reach $360.6 billion by 2016, increasing at a compound annual growth rate of 10.6%. These numbers reflect contract manufacturing of OTCs and nutraceuticals, and bulk and dosage form drugs, as well as contract packaging.

A downward spiraling economy, a client base besieged by mergers and acquisitions, and the constant struggle to do more with less have packed a punch. However, service providers have fought back admirably. The contract manufacturing market is expected to grow at a CAGR of around 11% during 2011-2013, according to a new report *Global Contract Manufacturing Market Analysis*. The study equates the demand for contract manufacturing services to the rising cost pressure on pharmaceutical companies. Additionally, leading pharma companies are looking at the outsourcing model as a means to expand into the biosimilars and generics segments.

In a similar story of success, the contract research market grew to $28 billion last year, increasing by 15%, according to Biopharm Knowledge Publishing's *Contract Research Annual Review 2011*. Sales growth in the contract research industry accelerated to around 16% year on year in 2010, generating a worldwide market worth $27 billion. However, many major CROs have seen profit fall by more than 50%. In response, the industry is rapidly reshaping itself to match the changing needs of a pharmaceutical industry that is realigning its R&D strategies to improve effectiveness and to face a new set of demands from the market.

The skyrocketing cost of drug development throughout the past decade, coupled with stiff competition for limited numbers of potential trial participants, has compelled pharmaceutical and biotechnology companies to seek more cost-effective ways of conducting clinical research. This quest has led to outsourcing clinical trials to developing countries where large numbers of qualified patient volunteers await, the cost of doing business is far cheaper, and new therapeutics can be brought to market faster. Clinical trials conducted in the US typically cost about $150 million, 60% more than in India, according to a study by Rabo Bank. China, too, is becoming an increasingly popular site for clinical trials, with sponsors drawn by its "potentially lucrative market for new drugs, which some estimate will be worth $50 billion in 5 years," according to a June 20, 2011, statement from the Parkinson Pipeline Project.

During 2007-2010, the global clinical trial outsourcing market grew at a CAGR of 14%, reaching sales worth more than $22 billion. IMARC Group expects the rapid growth of this market to create huge opportunities for cold chain logistic providers.

Leading contract service providers recently spoke exclusively and candidly with *Drug Development & Delivery* magazine about their strategies to innovate, compete, save costs, and still deliver quality services. Participants included Mark Alexay, President, ChemOutsourcing; Jeff Basham, VP, Business Development, Metrics Inc.; Todd Daviau, PhD, CEO, and President, CoreRx, Inc.; Philip Diamond, VP, Corporate Market Development, Almac Group; David Exline, Senior VP, Gateway Analytical; Rick Hancock, President, Althea Technologies, Inc.; Derek G. Hennecke, CEO & President, Xcelience, LLC; Robert

W. Lee, PhD, VP, Pharmaceutical Development & Quality, Particle Sciences, Inc.; Terry Novak, President, Norwich Pharmaceuticals; Robert Odenthal, Global Business Director of Inhalation, 3M Drug Delivery Systems; Cornell Stamoran, VP, Corporate Development & Strategy, Catalent Pharma Solutions; Vanlee Waters, Marketing Manager, Dow Pharmaceutical Sciences, Inc.; and Kristie Zinselmeier, Director of Marketing, BioPharma Solutions, Baxter Healthcare Corp.

Q: What has had the greatest impact on the contract services sector in the past 10 years?

Mr. Hennecke: With our industry going through a period of such rapid change, pharmaceutical companies are re-evaluating how they outsource. The need to accelerate drug development has taken on a greater significance in the recent economy, but not at the expense of quality/regulatory compliance, price-to-value ratio, and the service performance metrics that are necessary to remain at the top of the consideration set.

Mr. Basham: The collapse of venture funding in 2008 was a significant development in the contract services industry. Prior to 2008, the funding of new chemical entity development by both venture capital and large pharma organizations served as a force for growth for CDMOs. Since 2008, the constriction of venture funding of development has shrunk the available projects to be contracted out. So quality, service, and pricing have become significant drivers in the latter part of the period. Cost control versus quality will always be the pendulum that swings back and forth. While the pharma pipeline is slowing, cost controls continue to be a focus.

Mr. Stamoran: The most material change in R&D impacting outsourcing providers throughout the past decade has been the changes in innovation sourcing by large pharma and biotech companies. Ten years ago, nearly 60% of industry-wide revenues were from "home grown" products–organic innovation, with a majority of the remainder from in-licensed products. In 2011, we're seeing the inverse–nearly 60% of industry-wide revenues are from inorganic sources, meaning that fundamental product innovation is most often coming from outside the walls of in-house R&D. Even more importantly, this "outside innovation" is more often coming via company acquisition than by product in-licensing. This has very specific implications for development solutions providers–it's important to partner earlier with the emerging, specialty, and virtual companies who account for more than half of the active R&D pipeline today.

Mr. Waters: There have been a couple of very important structural changes in pharma contract development in general, which have changed the landscape for all companies in our business. The first and foremost is the incredible skyrocketing cost and time associated with new prescription pharmaceutical drug development and approval. Drug R&D costs have risen approximately 25 times in the last 28 years with a new molecular entity now costing somewhere in the neighborhood of $1 to $1.25 billion. Add to that the increased time to market it takes for approval of an NME (~15 years), which directly reduces the patent protected life of the product. This results in the loss of billions in ROI for the product. Bottom line–it doesn't pay to develop NMEs in house.

Q: How has the economy affected the contract services industry, and how has your company responded to the economic recession?

Mr. Exline: The current economical conditions have forced the industry to streamline operations and focus resources on the most critical needs. Much more attention is placed on cost-effective testing with efficient turnaround times. Also, pharmaceutical companies are hesitant to invest long-term in areas that are not considered routine in nature. The effect on Gateway Analytical has been very positive throughout this period. The services that we offer combine non-routine testing with critical need and regulatory implications.

Dr. Lee: The sputtering economy has impacted contract services pretty significantly in the past 10 years, with a more profound impact in recent years. This is due to significant and continuing downsizing by pharmaceutical/biotechnology companies that still need to get the work done, but may not have the internal resources to accomplish this. As a result, more companies are turning to CROs, including those that offer CMC services, such as Particle Sciences.

Mr. Waters: In the most recent 2 to 3 years, the overall macro-economic status of the world, and most importantly the US

and EU, has been negative, which increases both consumers' and investors' uncertainty, thereby causing more doubt in the minds of pharma executives. This makes it crystal clear that growing and thriving for most contract development companies is a long way off in the distant future.

Mr. Diamond: Looking at decade cycles, in particular during the course of the past 10 years, we have seen a significant change in our market's landscape. Our multinational customers have undergone numerous mergers and acquisitions, resulting in fewer, larger pharmaceutical conglomerates. These changes, combined with the current economic climate, has resulted in customers continually attempting to drive down costs while still demanding the highest levels of customer service and quality they have always received. In response, we have built up strong relations with multiple clients, tailoring our services to their very specific needs.

Dr. Daviau: The contract services industry really saw its growth phase from the mid-1990s until just recently. As a whole, the economic downturn has really affected the pipeline of many emerging pharmaceutical and biotech companies. The focus in pharmaceuticals no longer seems to be discovery- and development-driven. Rather, the focus seems to be on mergers and acquisitions. At CoreRx, we have responded to the economic recession in two ways. The first is by efficiently using existing resources to achieve a customer-centric approach. Secondly, we have reinvented ourselves by adding capacity with a new facility scheduled to open early next year. In this new space, we will not only be expanding our formulation laboratory, but also increasing the size and capabilities within our analytical, formulations, and manufacturing departments.

Ms. Zinselmeier: The economic environment has proven to be challenging for many industries and businesses, and contract manufacturing is not exempt. Being part of a large, multinational corporation that operates in several distinct healthcare-related spaces provides us with additional stability in difficult market circumstances. The recession has also driven increased demand for CMO services, as some companies are unable or unwilling to make infrastructure investments, resulting in a positive effect on our business. The economic volatility will continue in the near-term, necessitating increased maximization of resources. The phrase "making more with less" continues to be the mantra for development and commercialization teams. There is little room for error.

Mr. Novak: The challenge is filling capacity with the right products and services that do not require large outlays of capital and can also generate cash flow for future investments. One way of overcoming the challenge is to be proactive in evaluating the industry pipeline to understand the technologies that are, and will be, needed to develop and commercialize products. In the interim, it is a matter of targeting business development efforts at those products that fit the development and manufacturing trains currently installed. Add to that the need for the CDMO to invest the capital necessary to provide the services requested as pharma has an even greater reluctance to fund any capital needs.

Mr. Stamoran: From 2007-2009, many larger companies slowed the pace of R&D spending or took other steps to reconfigure their R&D activities, in some cases, including ceasing activities in certain therapeutic areas completely. Likewise, many smaller, earlier stage companies had substantial issues obtaining follow-on funding to support ongoing preclinical and clinical development activities. Both of these factors caused a substantial amount of volatility in clinical trial-related spending, which cascaded to many of the development solutions providers as well.

Q: How much more competitive has the contract services landscape become in the past few years?

Mr. Basham: The addition of outsourcing management at all levels of the organizations has brought a more formal review process of the whole business. Historically, there was a focus on the quality and audit aspects, and if you performed there, then you were usually in the running. Evolving in the future will be even more formalized RFIs and RFQs stemming from the need to control costs.

Dr. Lee: Perhaps gone are the days of drug delivery companies with one technology. One size does not fit all for drug delivery/formulation development, so it is in the client's best interest to have access to several orthogonal technologies. A few CROs grew too rapidly or too large without having a sound business strategy in place. In some notable cases, this has meant the demise of the company. In other cases, the quality of the services slipped,

so this directly affects clients. Contract service providers need to make sure the quality of the work they perform is maintained at a high level, otherwise their clients will find alternative service suppliers.

Ms. Zinselmeier: Throughout the past decade, there has been a steady trend toward increased collaboration with manufacturing service providers. In our experience, this trend has exponentially increased throughout the past 3 years. Brought on by struggling pipelines and an effort to reduce costs, pharmaceutical companies are experiencing increased competition for scarce resources, and this is driving intense prioritization. Practically speaking, in an environment where only critical imperatives can be supported, unnecessary duplication of existing market resources cannot be justified. Therefore, we are seeing an increase in substantial contract manufacturing collaborations. We see greater scrutiny and time spent in the evaluation process of manufacturing service partners, particularly in the areas of experience and expertise. This has traditionally been a difficult aspect of the evaluation process due to the difficulty of reliably predicting the ability of a service partner to overcome obstacles. In the past few years, we have seen an increase in useful assessment tools, including requiring case studies to be shared during this process as a way to, for example, understand how a CMO might respond to a development challenge. It also allows the pharmaceutical company to evaluate more than just the physical resource of the facility. As pharmaceutical companies reduce the number of manufacturing service providers they collaborate with, it becomes critical that the remaining providers offer a wide selection of supporting services.

Mr. Hennecke: The fundamental shift to a service focus has made a tremendous impact on the contract services industry. Ten years ago, there was very little differentiation amongst service providers; they set themselves apart only on basic levels, such as capabilities, pieces of equipment, firm size, and price. But today, the hypercompetitive market has driven providers to become more sophisticated in their differentiation, and more client-focused. Sure, firms still have to hire the right people, purchase the right equipment, and maintain the quality of their facilities, but this alone no longer provides sustainable competitive advantage. So you see firms focus on taking these building blocks and fitting them together in ways that are difficult to imitate. Accelerated drug development programs, lean sigma applications that eliminate waste and variation from processes and reinforce quality, disciplined project management with enabling technology that facilitates real-time communication and information sharing, flexible scheduling models, and relevant area expertise are what define contract service leadership today.

Q: How have contract services evolved to keep pace with pharma's demands?

Dr. Daviau: Change can be advantageous or a challenge that cannot be overcome. The recent issues with contract service organizations, such as Azopharma and its sudden demise, and the regulatory issues at Cetero Research, have given us all reason to pause and think retrospectively about who we are, and what things we need to change. At CoreRx, we have taken this time to rework our entire network for a more customer-centered approach.

Mr. Novak: The biggest change in customer expectations is a move toward a more full-service model where the CDMO is responsible for everything from securing the API through finished dose manufacturing. In the past, most customers have secured the API and simply entered into toll manufacturing agreements. CMOs are now expected to be more involved in the pharma supply chain, which can be an advantage as we can become more integrated with our customers' entire process and be better suited to ensure security of supply. One way that service providers have changed is to develop relationships with API suppliers in order to provide the full-service offering now expected from many companies.

Ms. Zinselmeier: At the start of the past decade, the focus was on the efficiency of collaborations, but essentially all service providers were seen as interchangeable. As a result of the intense market conditions, it's no longer sufficient to provide only a basic level of efficiency. In order to be sustainable, each party to the collaboration must provide the value they are uniquely qualified to do. Thus, pharmaceutical companies are more heavily relying on the manufacturing service partner to provide a critical component in the value chain. We have seen an increased demand for highly skilled and technically sophisticated program management. The stronger the manufacturing service provider's program management capability, the stronger the

collaboration. Strong program management identifies potential challenges and related solutions before they impact the program and, thus, are why this proactive aspect of program management is a key new demand from pharmaceutical companies.

Mr. Hennecke: In the early phase development space, the most significant change in pharma expectations has been related to the pace of drug development, and I expect this need for a faster pace will continue into the future. This need translates into increased expectations for responsiveness by CRO partners. Established Big Pharma and virtual pharmaceutical companies alike can face significant pressure to swiftly adapt to changes in organizational priorities. So much rides on the ability to quickly implement those changes, and the contract provider had better be able to respond.

Mr. Odenthal: Sometimes it's about how clients have to evolve. We have observed that design for manufacturability and scale-up (DFMSU) is not always as carefully considered in the early development of a product as it should be. Companies must ensure that DFMSU has a prominent place in a product's evolution from the very early stages. DFMSU is a complex process, and pharmaceutical firms that do not have the in-house capabilities to apply the necessary guidelines should seek outside help from a reliable contract partner. The benefits to vigilance in this process early on can pay off in smoother navigation of the regulatory process, and more competitive manufacturing at commercial scale.

Q: What do you view as your biggest challenge?

Mr. Diamond: Ongoing mergers and acquisitions in the pharma industry have made it challenging to the contract services market to respond to the changing demands of the market. It is therefore essential that contract service organizations keep up to date with ongoing developments and pre-empt changes as soon as possible to ensure that existing relationships are not compromised as a result of M&As. We anticipate that market changes of this nature will continue going forward, and it is critical that contract service providers must make immediate adjustments and manage the change effectively to retain competitive advantage.

Mr. Exline: Due to the uniqueness of the services we offer in laboratory analysis, the biggest challenge is educating companies about the methodologies we employ and significant return on investment that can be achieved when using them. We work quite closely with our customers to ensure that the most difficult problems they face are understood and addressed with every analysis.

Mr. Waters: Certainly within the past 5 years is the ever increasing M&A activity we've seen within both the pharma and biotech sectors. This activity has directly led to a significant consolidation within both sectors (~30% reduction in biotech companies in the past 3 years) and has lead to a downsizing of the industry as a whole. The increased M&A activity has resulted in a two-pronged impact on contract service companies. The first and foremost being there are a significantly smaller number of customers to work with. The second factor is larger companies that have been involved in the M&A activity (the big fish who've swallowed the small fish) have to regularly re-prioritize all their "new" pipelines and development priorities, often resulting in much greater uncertainty for the contract services company's revenue stream. The single biggest challenge we currently face is pricing our services competitively to justify continued development of products in early phase development because the increased M&A activity has resulted in companies devoting most, if not all, of their R&D spend (dollars and time) into products in late-stage development (a drug in a Phase III trial). The current focus, solely on late-stage development projects, has resulted in a major downturn in the number of early stage development programs, which combined with a reduction in the number of companies involved in developing new prescription drugs, has resulted in a small perfect storm for many companies in our industry.

Ms. Zinselmeier: Neither pharmaceutical companies nor manufacturing service providers are immune to the decreased ability to access capacity and the resulting prioritization challenges. Stand-alone contract manufacturers carry this burden alone. It is essential to collaborate with a provider that is able to find capital to maintain or grow the business as necessary. Investment plans are becoming another important consideration in provider selection, including understanding how the service provider assesses the planning horizon. As pharma looks to create collaboration partners for the life of a molecule, the planning abilities of the provider, along

with their ability to make necessary investments through the life of a program, will continue to be important.

Mr. Alexay: The contract service industry has to change direction on a dime and make the right bets on where the industry is going. Because the drug discovery and development machine is suffering lower productivity, staffing cuts, outsourcing of R&D, and a tighter regulatory environment, the worldwide pharma services industry has seen many new opportunities crop up where previously there weren't so many. I am struck by the huge supplier base compared to the number of pharma projects. Because many of them are making a lot of money, it's clear the stakes are high. Many pharma service providers service both the pharma companies and other contractors. What a complex food chain!

Q: How has the growing presence of biotech companies in the past decade affected contract services?

Mr. Alexay: The other thing is the emergence of hundreds of small molecule biotech companies with much lower cost structures and so far, greater innovation. It looks like Big Pharma as we know it has gone away, and the next generation of companies is small, efficient, and highly specialized around a technology, family of targets, or therapeutic class. Lots of these companies are taking their molecules forward until they can license to Big Pharma for the expensive clinical development. Many are contracting or outsourcing everything except their molecules and IP. This is the future of our industry.

Mr. Diamond: From the biotech sector, we have seen a significant increase in the requirement for cold chain shipments throughout the past 2-5 years, and we forecast this growth to continue. It is essential, therefore, that contract providers can respond to this escalating demand by investing in appropriate facilities, equipment, and specialist personnel.

Mr. Hancock: When the first biotechnology companies were founded almost 40 years ago, many of them structured themselves in the same way pharmaceutical companies were at the time. Specifically, these companies strived to operate as fully integrated pharmaceutical companies and established facilities to support preclinical research through clinical manufacturing. Investors are no longer interested in the brick and mortar model and only want to invest in R&D capabilities and platform technologies. Fast forward to 2011, and many of the pharma companies that were fully integrated are starting to operate similarly to the way biotech companies have been functioning for the past 10 years. Increasingly, these companies are outsourcing more of their clinical development and commercial manufacturing operations. Outsourcing allows these companies to focus on core competencies (including discovery, sales, and marketing) and reduce operating expenses.

Q: Describe the impact from Eastern markets to perform contract services more cost effectively.

Mr. Odenthal: A number of new business models are developing in the pharmaceutical industry, driven largely by the hundreds of new pharmaceutical companies around the world. With backing from venture capitalists and bioscience entrepreneurs, these companies are contributing to a significant rise in the number of highly skilled bioscience professionals working outside the West. Meanwhile, more established firms are seeking to save money by cutting back their research and development investments. Contract partners, therefore, must be ready to serve both these new start-ups and the older firms with their very different needs. This is one reason that 3M recently opened a facility in Singapore. This location gives us a greater presence in fast-growing Asian markets. The Singapore facility can handle companies' needs for both early stage product development and later stage registration support.

Dr. Daviau: Without doubt, trade is increasingly global in scope today. And, the pharmaceutical industry is no different. There are several reasons for this, and a significant one is technological; due to improved communication and supply chain opportunities today, international trade is now more practical. Businesses now have access to products and services from many different countries. The understanding and the implementation of a globalized set of rules and regulations are not only required, but necessary to participate globally. That

"Ten years ago, nearly 60% of industry-wide revenues were from "home grown" products–organic innovation, with a majority of the remainder from in-licensed products. In 2011, we're seeing the inverse–nearly 60% of industry-wide revenues are from inorganic sources, meaning that fundamental product innovation is most often coming from outside the walls of in-house R&D. Even more importantly, this "outside innovation" is more often coming via company acquisition than by product in-licensing. This has very specific implications for development solutions providers–it's important to partner earlier with the emerging, specialty, and virtual companies who account for more than half of the active R&D pipeline today."

said, while it may be difficult to compete with Eastern markets on price, I believe we, as providers in the West, should focus on providing first-in-class services and continue to focus on the quality that sets us apart. By continuing to focus on the services we do best, and partnering with like-minded providers that complement our services globally, we will be better able to provide the level of expertise that a one-stop-shop could never provide. At the end of the day, our clients need to weigh the benefit of price versus compliance and determine what gives them their best value.

Mr. Stamoran: The market for both development solutions and advanced delivery technologies has become more sophisticated and global. Global development and launch strategies require development using ICH standards, and frequently conducting complex, multi-geographic clinical trials, including in markets historically viewed as developing or emerging, but today viewed as growth markets. Providing simple supply chain and "good enough" formulation solutions for Western markets is no longer sufficient. They require sophisticated bioavailability solutions, sophisticated delivery, release, or targeting profiles, and increased focus on patient safety, convenience, and adherence in order to get through the regulatory approval process reliably and faster to launch differentiated, successful products. Successful drug delivery and development partners must be able to offer more sophisticated solutions with unique expertise, local/target market understanding, proven technologies, and reliable supply capabilities.

Q: Where do you envision the contract services industry in the next 10 years?

Mr. Hancock: As most industry analysts have projected, pharmaceutical and biotech companies will continue to outsource an increasing amount of their clinical development and commercial manufacturing in an effort to reduce their fixed operating expenses. Because of this increased reliance on external partners, we expect the structure of the relationships to continue to evolve. As consolidation occurs within the industry, this structure is one that allows a greater degree of operational control by the pharmaceutical company, reliable revenues for the CRO or CMO, and retention of jobs that may otherwise be lost overseas.

Mr. Diamond: Ten years ago, contract service companies would have simply been a supplier to the pharma industry; however, the relationship has changed significantly and it is now essential that they are thought of as a seamless extension to the pharma organization. Going forward, establishing and retaining long-term relationships is the key to remaining successful.

Mr. Hennecke: Some global CROs have done well with establishing strategic partnerships that have delivered real client value, while others have acknowledged that re-negotiations associated with these long-term partnerships didn't deliver the expected returns for either side. I believe the path forward in sourcing strategy for innovator companies of any size is to adopt a portfolio approach that de-risks their overall drug development program; one that integrates one-stop-shops where it makes sense to consolidate services and reduce costs, but one that incorporates best-in-class or best-in-niche providers for services that require a level of attention or expertise that a one-stop-shop could never provide. The key to a successful portfolio strategy would be finding service providers that are willing to coordinate with upstream/downstream providers to smooth transitions, accelerate timelines, and assure quality of supply. Throughout the past 10 years, I've seen global firms chop

themselves into pieces, only to be sold and built back up into one-stop-shops again. I've seen this often enough to know that all of this activity never really served the clients well at all. More and more, I'm convinced that successful growth will be driven by one fundamental question: What does it take to provide the best service to our clients?

Mr. Alexay: The industry has become global and more competitive, and the double-digit growth of Pharma in decades past is no more until science makes the next major leap forward. When it does, the best service providers will be ready and profit handsomely. In the meantime, it's still a good business overall, and many contractors are doing great. Not every company can survive but that's nothing new. All things considered, I'd rather be working in the intellectually stimulating, high-stakes pharmaceutical industry! ◆

Mark Alexay,
President,
ChemOutsourcing

Jeff Basham,
VP, Business Development,
Metrics Inc.

Todd Daviau, PhD,
CEO and President,
CoreRX, Inc.

Philip Diamond,
VP, Corporate Market Development,
Almac Group

David Exline,
Senior VP,
Gateway Analytical

Rick Hancock,
President,
Althea Technologies, Inc.

Derek G. Hennecke,
CEO & President,
Xcelience, LLC

Robert W. Lee, PhD,
VP, Pharmaceutical Development & Quality,
Particle Sciences, Inc.

Terry Novak,
President,
Norwich Pharmaceuticals

Robert Odenthal,
Global Business Director of Inhalation,
3M Drug Delivery Systems

Cornell Stamoran,
VP, Corporate Development & Strategy,
Catalent Pharma Solutions

Vanlee Waters,
Marketing Manager,
Dow Pharmaceutical Sciences, Inc.

Kristie Zinselmeier,
Director of Marketing,
BioPharma Solutions,
Baxter Healthcare Corp.

Biopharmaceuticals: Opportunities & Industry Dynamics

By: Ruplekha Choudhurie, MS, Research Analyst, Healthcare, Technical Insights, Frost & Sullivan

INTRODUCTION

The biotech/biopharmaceutical domain is innovation driven and continues to be one of the most R&D-focused and lucrative segments of the healthcare industry. Though therapeutic proteins have been around for more than a century, the first modern biopharmaceutical (recombinant insulin, Humulin) was approved by the FDA in 1982. In the past 30 years, more than 200 biologics have been brought to the market to address challenges in treatment for many diseases with unmet needs. Diabetes, cancers, infectious diseases, rheumatoid arthritis, and other autoimmune and inflammatory disorders as well as genetic disorders are some of the major target diseases for biologics, where conventional medicine generally fails. Antibodies, gene markers, and cell surface proteins are deployed as diagnosis and prognosis tools. In spite of the potential of gene therapy and stem cell-based products, it is still a few years away from the market.

Biopharmaceuticals are more "biologically relevant" compared to small molecules, produce fewer side effects, and can offer targeted treatment options, which fuels its high demands.

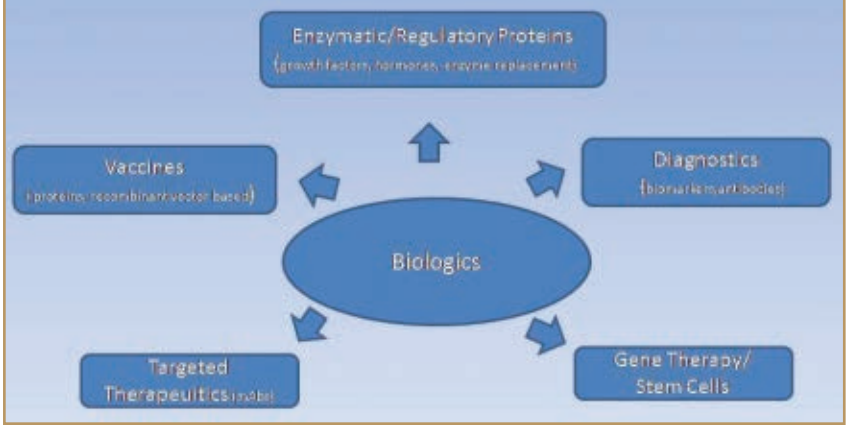
With top pharmaceutical companies adding biologics to their pipeline, this is definitely an area of interest from a utility and commercial perspective. Companies like Pfizer, Merck, Novartis, GSK, Roche, and AstraZeneca have shown significant interest in biopharmaceuticals, and the R&D intensity has improved in the past 3 years. Speciality biopharmaceutical companies, such as Amgen, Shire, and Genzyme, are renowned for their robust pipeline of biologics and continue to innovate in this field.

Increased global collaborations and more pools of funds and access to high-end technologies drive this market, while the deterrents are high R&D costs, huge capital risks, long development timelines, and ill defined/scattered regulatory norms. In spite of the potential biopharmaceuticals hold, the number of approvals in the past 2 to 3 years is not a clear indication of this. The year 2010 saw only about six approvals; however, the first approval of a cell-based therapeutic vaccine for prostate cancer (Dendreon's Provenge) was a noteworthy milestone. Many companies and investors are vigorously taking therapeutic vaccine candidates forward after this approval.

The funding scenario has evolved throughout the past decade and will continue to do so. After the failure of a number of drug candidates, many companies that were heavily reliant on Initial Public Offerings (IPOs) and venture capitalist (VC) funding have suffered a setback with the investor community showing decreased interest in companies without any products. The majority of funding for the biopharmaceutical industry comes from strategic partnerships, government funds, and other non-conventional financing modes.

The US leads the biopharmaceutical market in terms of innovation and R&D infrastructure, while Europe follows closely. There has been an increase in global alliances, and a number of major European pharmaceutical/biotech companies have established their footprint in the US. In addition, the usual academia-company partnerships are being replaced by joint development, licensing options, and mergers and acquisitions (M&As).

FIGURE 1



Some of the recent trends and developments in the biopharmaceutical industry are highlighted further.

MARKET OPPORTUNITY FOR BIOSIMILARS/BIOBETTERS

More than 35 biologics are going off patent in the next 5 years, providing an excellent opportunity for biosimilars and biobetters to enter the multibillion dollar market. Some of the successful biosimilars include human growth hormone (h-GH), erythropoietin and calcitonin. Development of bio-"generics" is more complex and expensive than small molecules, and because biological processes cannot be replicated, there are no known tools to compare the efficacy and safety of a biosimilar with that of the original drug. This has resulted in strict regulatory protocols and complicated development protocols.

Many of the biologics coming off patent are blockbuster drugs, currently monopolized by certain pharmaceutical companies. Many patients are not able to benefit fully from most biologicals due to high pricing and inability of companies to meet demands. A good example would be therapies for Fabry Disease and Gaucher's disease, where the biopharmaceuticals developed were not able to meet patient requirements (costs and dosage issues). The recent approval of Shire's therapies for both diseases has captured a significant portion of market share and is aimed at making it more "accessible." This is good news for many such companies with well-developed technologies and capabilities for manufacturing biologics.

Because biological manufacturing is a costly affair, it is likely that the biosimilar market will be penetrated more actively by large biopharmaceutical companies. These companies might also utilize glycoengineering platforms to develop biobetters, which will have a superior clinical value and might allow for creation of brand value. New recombinant protein production technologies are garnering increased interest from biopharmaceutical companies as they can provide patenting strategies for existing biologicals and also help develop more effective, safer monoclonal antibodies, hormones, and vaccines.

Development of simple, standardized tests to measure the bioequivalence of biosimilars is likely to improve the regulatory scenario. In an effort to reduce federal expenditure on drugs, the US government is formulating policies to encourage the development of biosimilars. Such a movement will bolster R&D in this field. There is a need to streamline regulatory approval processes, pharmacovigilance, especially in countries like India and China, to ensure only safe and effective biosimilars reach the clinic.

With competition on the rise, pricing will be a challenge for biosimilar manufacturers; however, if companies focus on developing biobetters instead, they can justify pricing, provided reimbursement bodies show positive response. Biopharmaceutical companies need to carefully balance innovations and incremental improvements to remain successful in this highly competitive industry.

FIGURE 2

Trade Name	Generic Name	Indication	Type of Drug	Company
Actemra	Tocilizumab	Rheumatoid arthritis	Humanized mAb	Genentech
Krystexxa	Pegloticase	Gout	Recombinant protein	Savient
Prolia, Xgeva	Denosumab	Osteoporosis/ osteopenia	Fully human mAb	Amgen
Provenge	Sipuleucel-T	Prostate cancer	Autologous, engineered, dendritic cell-enriched vaccine	Dendreon
Ruconest	Conestat alpha	Hereditary angiodema	Recombinant protein	Sanofi-aventis
Vpriv	Velaglucerase alfa	Gaucher's disease	Recombinant protein	Shire Human Genetics

New Biologicals Approved by the FDA in 2010

DEVELOPMENTS IN DELIVERY TECHNOLOGIES

Patient compliance is key to achieving success, and biopharmaceuticals have not been very successful in this aspect. Most biopharmaceuticals need to be administered via injection to achieve the required efficacy, which has greatly limited its utilization. Rapid degradation of proteins/peptides, and the large molecular size has resulted in inflexibility for delivery via the most preferred route (oral) and other potential means, such as pulmonary, intranasal, and mucosal.

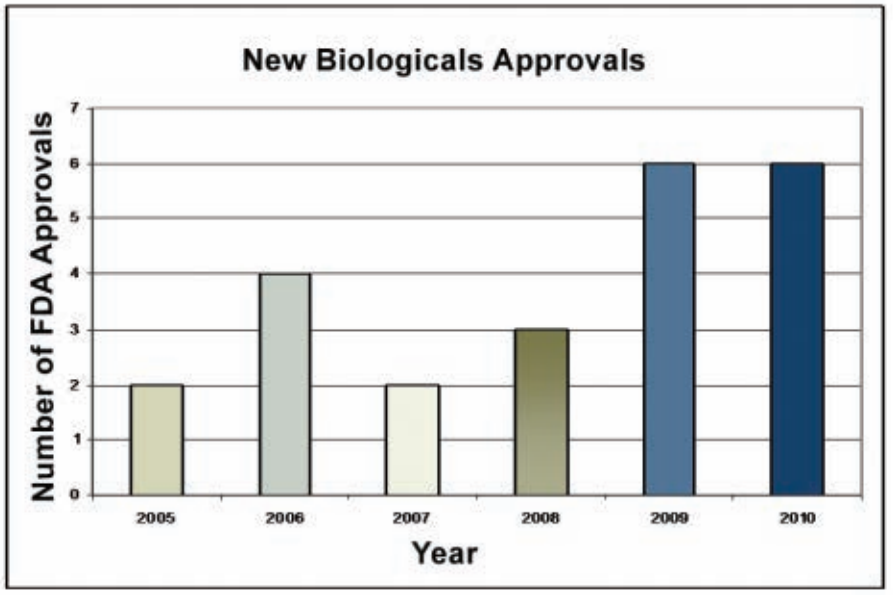
Development of novel delivery strategies and formulation techniques can be effectively leveraged by drug developers to carve a niche and gain an edge over others in the competitive biopharmaceuticals market. Some of the key players in this area include Aegis, Aileron Therapeutics, and Entrega Biosciences, which have developed innovative peptide delivery platforms. Entrega Biosciences has developed a platform technology for oral delivery of proteins and peptide drugs, while Aegis, OptiNose, and Baxter BioPharma are into intranasal, pulmonary, and oral formulations.

Transdermal delivery is convenient and overcomes some of the side effects of systemic administration. Several companies have developed microneedle transdermal patches, laser-based systems, and electroporation techniques that can successfully deliver biopharmaceuticals via the transdermal route. Altea Therapeutics, Flugen, Zosano Pharma, TransDermal Technologies Inc, and Pantec Solutions have developed a number of innovative transdermal delivery solutions.

In addition to developing new routes of administration, research is also targeted at developing formulation strategies to improve the PK/PD profiles of the drugs. A notable development in this field is Flamel Technologies' Medusa, a polymer hydrogel for delivering proteins and vaccines. Their platform has been utilized in a number of biologics and vaccines by big pharma companies like Baxter, Pfizer, Merck Serono, and several others. Aileron's Peptide stapling technology to improve drug performance has been well received, and Roche entered into a collaborative agreement to leverage this platform.

With further developments in delivery systems and an increase in funding and partnerships within this segment of the industry, biopharmaceutical companies will find opportunities to boost their pipeline with respect to efficacy, reduction of side effects, possible decrease in cost, and most importantly, improved patient compliance.

FIGURE 3



DEVELOPING A TARGETED APPROACH: A KEY FOR ONCOLOGY TREATMENT

Personalized medicine (PM), focused on developing tailor made designer therapies for patients, has been the buzzword for the past few years and is emerging as one of the most sought after concepts. High costs linked to treatment of certain diseases like cancer and drug-related side effects has fuelled developments in PM - to stratify patient populations according to their individual genetic and molecular signatures, and accordingly design therapies. Biopharmaceuticals in general focus on specific pathways and diseases, offering a more targeted form of therapy when compared to small molecules. More recently, use of these drugs in conjunction with companion diagnostics has paved the way for customized treatment options, which can help improve clinical outcomes, reduce treatment costs, and avoid unnecessary side effects.

Immunotherapy for cancer treatment can greatly benefit with this custom design approach. A good example is Biovest International Inc.'s late-stage non-Hodgkin's lymphoma cancer vaccine candidate BiovaxID, which recently demonstrated positive results in Phase III trials. Signe Biopharma Inc. is another company developing targeted therapies for breast cancer based on immunology and molecular biology-based diagnostics. In spite of the potential of personalized therapeutics, there are still a few hurdles (regulatory, high initial costs, etc.) to overcome before it can achieve full fledged clinical utility - once this is well accepted, PM will turn out to be a viable shift for cancer treatment.

PRODUCTION STRATEGIES: DEVELOPMENT OF NOVEL EXPRESSION SYSTEMS

Manufacturing biologics is more complex and expensive compared to small molecules. Many biopharmaceutical developers are actively seeking newer production strategies that can bring down costs, simplify the process, and improve drug characteristics. While simple biologics like insulin and hormones can be easily manufactured by companies, monoclonal antibodies, vaccines, and gene therapy products require more fine tuned design of manufacture to obtain optimally functioning products. New expression systems are being developed to allow production of proteins on a large-scale and cost-efficient manner. Conventional bacterial, yeast-based systems are cheap, deliver high yields, and are still employed for a number of biopharma products. Many biopharmaceutical companies are switching to novel plant and mammalian expression platforms for production of safer and more efficacious drugs. A number of companies in the US and Europe have utilized mammalian and plant cell lines for biopharma production, but countries like China, Singapore, and India are still heavily reliant on bacterial (E. coli) and yeast-based systems.

Glycosylation patterns have been recognized as an important determinant of overall drug performance and safety. Using glycoengineering tools for existing biologics can provide patenting strategies for development of biobetters. Development of fully human glycosylated proteins also improves the safety profile and PK/PD, which can ensure quicker and easier time to market. There are several companies in Europe specializing in contract manufacturing for biologics. Glycotope Gmbh, Probiogen, and Roche-Glycart are some of the innovative mammalian expression system developers that have actively collaborated with many top pharmaceutical companies and also have their own candidates. Similarly, there are a number of companies like Greenovation Gmbh, Biolex, and iBio that have introduced novel plant-based platforms for low cost, highly scalable biopharmaceutical manufacture. Downstream process for extraction and purification of the desired biopharmaceutical requires considerable attention in the design and operation of the separation units. Choice of cell lines also plays a role in streamlining these processes. Better purification strategies to retain proper folding and conformation to provide functionality are highly desirable.

Considering the current scenario, companies working on innovative production platforms are likely to be attractive licensing or acquisition targets for big biopharmaceutical companies. With the market competition getting stiffer, companies that leverage newer platform technologies for optimized and cost-effective protein production are quite certain to benefit.

EMERGING COUNTRIES AS POTENTIAL R&D HUBS

While the mature markets of the US and Europe will continue to lead the biopharmaceutical market, emerging economies in Asia Pacific are being looked at as potential R&D hubs for biopharmaceutical research and not just for outsourcing activities. India has been known for its capabilities in generics manufacturing, but the scene is changing with increased funding for new drug

discovery programs. Companies like Dr. Reddy's, Ranbaxy, and Nicolas Piramal are R&D focused and have a number of programs dedicated to the discovery of biologicals.

Intellectual property (IP) protection should be more actively sought after by companies from Asia to gain a global footfold. Currently, India and China have very few US patent holdings for biopharma products in spite of having a number of innovative moieties and technologies in the portfolio. Harmonization of regulatory processes is essential for companies to achieve a global presence.

CHANGING INDUSTRY DYNAMICS

The biopharmaceutical industry involves long-term, high-capital investments (R&D infrastructure, resources, etc.), which has made companies recognize the need to switch to alternative, sustainable business models to attain long-term growth. More than 70% of the biotech companies existing today do not have products in the market. They are developers of platforms or have candidates across different stages of clinical development. The high risks involved with discovery and development of a new biological entity (NBE) and the extensive R&D required is not a viable option for many biotech companies.

While a few firms are working single-handedly on development of blockbuster drugs, there are several others developing allied technology platforms (high throughput screening, delivery, expression platforms, formulations, etc.), biosimilars manufacture, and drug development via collaborative R&D and licensing agreements. Leveraging individual strengths to improve product portfolio and minimize risks is a general trend observed in this industry. Many biotech start-ups and medium-size companies are developing technology platforms (genomics/proteomics, bioinformatics, production systems) that are utilized by bigger biopharmaceutical companies via licensing agreements. Such platforms involve low investment and lower risks compared to new drug development. Partnerships vary across geographies. While US and European biotech companies mostly function via licensing and joint development collaboration with bigger pharma companies, countries like India and China heavily rely on partnering with the government for furthering their biotech research. The scene is slowly changing with global pharma giants expressing interest in companies in India and China. Many companies in emerging economies are working on incremental innovations, which involve shorter and less-risky timelines.

Partnerships occur primarily at two levels, platform technologies and well-developed product candidates. Platform technologies offer a wide array of opportunities for utilization across diseases and can be a source of multiple partnership opportunities for developers. On the other hand, candidates in mid phases of development (Phase IIa/IIb) are excellent targets for in-licensing and acquisition by bigger pharmaceutical companies as they offer high probability of returns. This type of partnering is also beneficial for smaller companies that do not have resources to take the drug through the entire process of clinical development and regulatory approval, marketing, distribution, etc.

Another noticeable activity in this industry is the increasing number of M&As. These are steadily increasing with 2010 to 2011 witnessing more than 10 major M&A deals. Some of the noteworthy partnerships and acquisitions between pharma and biotech companies in the past 2 to 3 years are Roche-Genentech, Sanofi-Genzyme, and Teva-Cephalon. The recent acquisition of Cephalon by Teva for $6.8 billion was the biggest deal in 2011. The acquisitions of Inspire Pharmaceuticals (by Merck), Prism Pharma (by Baxter), and Bergamo (by Amgen) are some of the other major deals of 2011. A number of licensing and collaborative agreements between medium-size biotech companies (Inovio Pharma, MedImmune, etc.) and global giants like Abbott, Merck, Johnson & Johnson, Sanofi, and others have taken place in 2011. ◆

BIOGRAPHY

Ruplekha Choudhurie is a Research Analyst for Frost & Sullivan's Technical Insights practice. She maintains industry expertise in genetics, bioprocess engineering, drug discovery, and bioinformatics. When Ms. Choudhurie began at Frost & Sullivan in 2010, she brought technical expertise and in-depth understanding of the biotechnology sector to the team, including knowledge of genetics, biopharmaceuticals, and molecular biology. Her functional experience includes technical intelligence as well as competitive benchmarking. Ms. Choudhurie also tracks and roadmaps emerging technology trends in the life sciences and biotech sectors that are primed for growth. She has worked with ABL Biotechnologies and with mitochondrial assays in the genetics laboratory at the Children's Hospital of Philadelphia (CHOP). Ms. Choudhurie earned her MS in Biotechnology, specializing in Biopharmaceuticals/ Bioengineering, from the University of Pennsylvania in Philadelphia.

Leading Technologies in Drug Delivery

By: Ipshita Chakraborty, MS, Industry Analyst, Technical Insights, Frost & Sullivan

INTRODUCTION

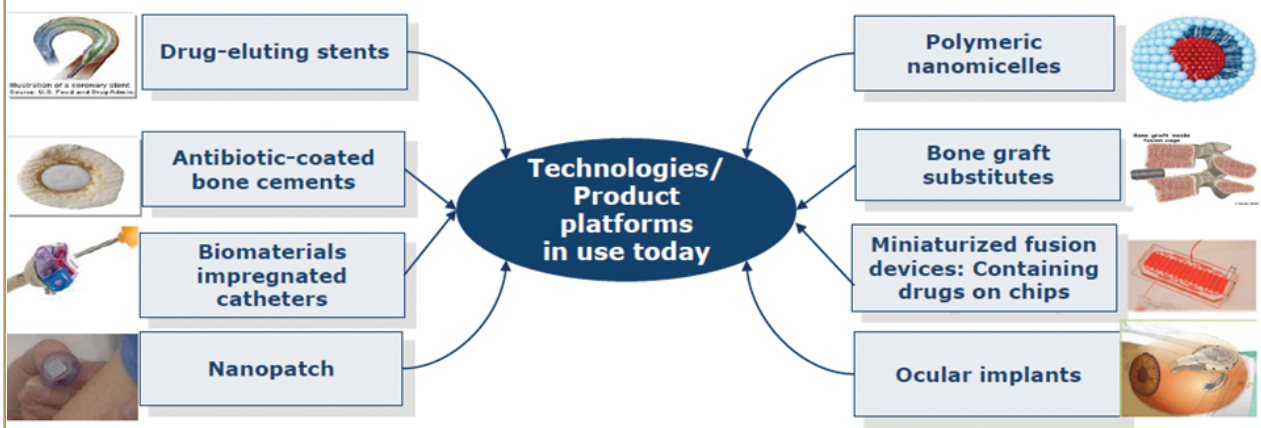
The topic of 2010 in vaccine delivery was the needle-free, painless vaccine delivery system called Nanopatch™ that is smaller than a postage stamp and uses microneedles to achieve delivery directly to the key intradermal areas. This development has been hailed as "vaccine utopia" and can be the answer to the paradox faced in developing countries - providing an adequate supply of vaccines to meet the rising demands of immunization programs. This development is just an example of a number of other developments that have changed the face of drug delivery as an industrial sector - not only in terms of technology but also in the way pharmaceutical and biotech business models have changed to align themselves with it.

The advent of novel drug formulations, such as peptide drugs, nucleic acid aptamers, and RNA interference, as well as new vaccine technologies, have augured the need for delivery technologies that can optimize the efficacy of these drugs and ensure that the cellular uptake is adequate. The most upcoming technology platforms in use today to develop such delivery devices are summarized in Figure 1. These include drug-eluting stents, antibody-coated bone cements, biomaterials-impregnated catheters, nanopatches, polymeric nanomicelles, bone graft substitutes, miniaturized fusion devices (including drug-on-a-chip), and ocular implants.

Drug delivery is a phrase synonymous with a "system" approach and every system must have its key components. The components of a standard drug delivery system have been summarized in Figure 2 with explanations of each.

The design of a drug delivery system has two main foci - the carrier and the administration route. While the carriers are addressed by the technology platforms, the administration routes have also diversified and are driven by a number of factors, including patient acceptability, the properties of the drug (solubility and vaporization), access to a disease location, or effectiveness in dealing with the specific disease. The oral route remains the most preferred, followed by pulmonary and transdermal delivery points. Parenteral delivery routes, including intravenous, intramuscular, and subcutaneous routes, have regained prominence with the emergence of novel carriers, such as liposomes and other nanoscale particles or

FIGURE 1



Emerging Technology Platforms for Drug Delivery

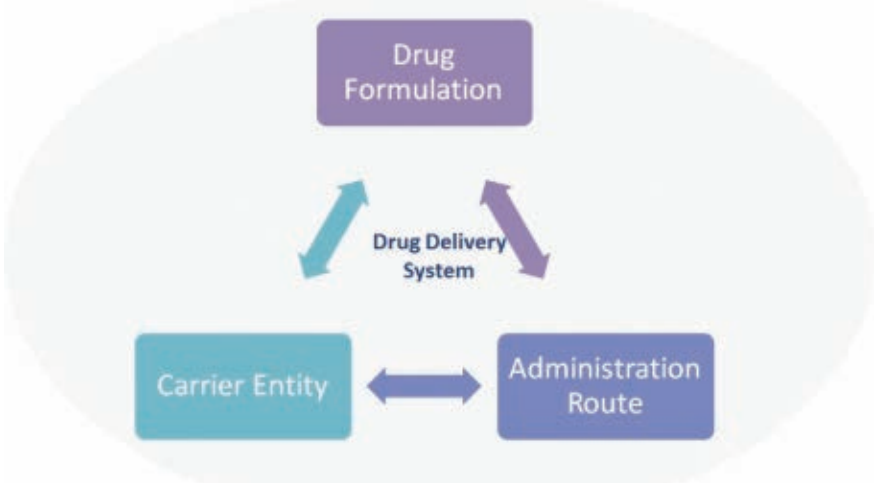
conjugates. Finally, trans-tissue and local delivery systems that pertain to only resected tissues during surgery also exist. Trans-tissue systems include drug-loaded gelatinous gels, which are formed in situ and adhere to resected tissues; releasing drugs; proteins or gene-encoding adenoviruses; antibody-fixed gelatinous gels (cytokine barrier) that form a barrier, which, on a target tissue could prevent the permeation of cytokines into that tissue; cell-based delivery, which involves a gene-transduced oral mucosal epithelial cell (OMEC)-implanted sheet; and device-directed delivery - a rechargeable drug infusion device that can be attached to the resected site.

Drug delivery systems have evolved and continue to evolve in response to three major objectives - to ease availability of the drug in particular regions (especially in the case of vaccines), to enable delivery of a particular drug formulation, or to enhance the delivery of an already existing drug.

HOT TECHNOLOGIES - NANOPARTICLES IN DRUG DELIVERY

Nanoparticles have emerged in the past 5 years as the most focused upon platform in drug delivery technologies due to their ability to achieve controlled drug release. The advent of nanotechnology applied to medicine has given birth to a new discipline named nanomedicine. This discipline deals with the current engineering efforts to apply the nanotechnology to improve treatments and therapeutic initiatives in the current healthcare industry. Nanoparticles can be polymer-based, can take the form of nonpolar nanoscale coatings, can be allied with smart materials (such as bioreceptors), and can also have magnetic properties. Nanoparticles are being employed to achieve targeted delivery and ensure maximum cellular uptake for drugs aimed at a number of types of cancers, from solid tumors to metastatic melanomas. They have actually come a long way from their niche focus of small molecules and expanded their applicability to fill the delivery gaps for

FIGURE 2



Components of a Complete Drug Delivery System

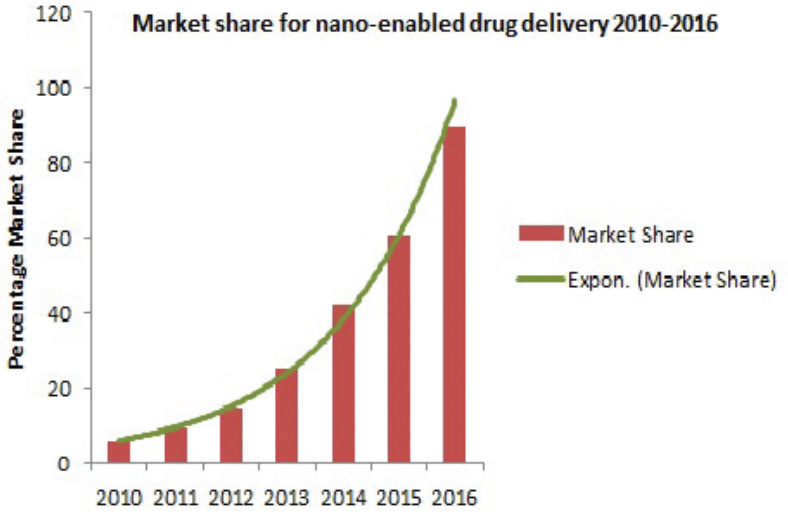
emerging biologics, such as ribonucleic acid/RNA therapeutics like small-interfering RNA (siRNA) and MicroRNA (miRNA). This is a field in which there are still a number of simple and complex challenges to overcome from the delivery perspective, such as protecting the small RNAs from systemic degradation by RNAase activity or escorting them across cellular membranes to the appropriate intracellular site. Leonardo Biosystems Inc., headquartered in Pasadena, CA, has been actively involved in building a nanoparticle-based multistage delivery approach. This multistage drug delivery approach, designed by the firm's founders, Mauro Ferrari and his colleagues, provides an opportunity to load not only therapeutics, but also imaging agents.

One of the other recently explored novel applications of nanomedicine is based on the utilization of carbon nanotubes to expand the contact surface of drug delivery systems in order to improve the dosage during a therapeutic initiative. Some of the main applications of drug delivery systems based in nanosystems are hip replacements to vascular stents with drug-seeded coating to prevent infection, control clotting, or decrease inflammation. Delivery of drugs locally from an implant surface, rather than systemically, can reduce unnecessary side effects and the amount of drug required to reach the same goal. Scientists at the Department of Bioengineering and Therapeutic Sciences at the University of California, San Francisco, CA, headed by Tejal Desai, are studying the implications of this novel concept of drug-eluting devices using nanostructured titanium dioxide (TiO_2) as a candidate for a drug-eluting implant coating.

Neurological diseases are an area that has immense potential with regard to nanoparticle-based therapy as they require highly targeted delivery. Delpor, headquartered in San Francisco, CA, and headed by Frank Martin, has been extensively involved in the investigation of a subcutaneous drug delivery system based on nanostructured membrane jointly with a mechanical-free components pump. The implant is a cylindrical device of approximately 4 mm in diameter and 4 cm in length and enables zero-order release of certain drugs and biopharmaceuticals. The technology provides an alternative to the therapies based on frequent injections for the delivery of bioactive agents, such as proteins and peptides, amongst others. Such a mechanism will be useful in the treatment of schizophrenia that requires extensively targeted dosage and also has new recombinant drug candidates being developed for it.

Nano-enabled drug delivery is gradually capturing market share and is here to stay. Market estimates indicate that by 2016, it will have a massive market share of 90% in the drug delivery space. As trends like personalized medicine and targeted drug delivery gain prominence, this forecast looks

FIGURE 3



Market Share Forecast for Nano-Enabled Drug Delivery Devices (2010-2016)

poised to transform into the real picture in a decade. The market share forecast for nano-enabled drug delivery from 2010-2016 is depicted in Figure 3. It reflects the projected exponential rise of nanoparticles in the drug delivery space.

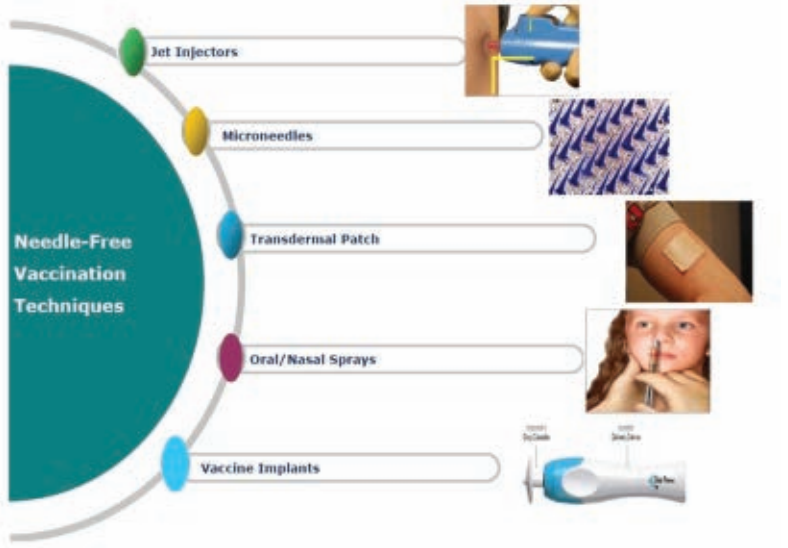
HOT TECHNOLOGIES - DRUG DELIVERY IN THE VACCINE SPACE

One domain in which delivery has been the driving factor for development and even sustainability is vaccines. The global vaccines market has witnessed above average growth throughout the past decade and is expected to continue its growth moving forward. Although Europe is currently leading the vaccine industry in production with 90% of the total global output, the US has taken a lead in developing both novel vaccine technologies as well as ingenious methods for their delivery. A prime example of this is Inovio Pharmaceuticals, a vaccine product development and delivery technology company that has pioneered the use of in vivo electroporation for vaccine delivery. Taking advantage of the already established electroporation technology that uses electrical pulses to create pores in skin and muscle cells for intracellular DNA delivery, Inovio has made itself the pioneer of in vivo electroporation - the application of this technology to animals and humans. In addition, Inovio has also developed the proprietary SynCon® DNA vaccine platform to facilitate the design of next-generation vaccines and synthetic consensus immunogens to maximum immunological response from the body.

This trend points to a key paradigm shift in the vaccine business model. The most viable option from a strategic perspective, for a vaccine company, is to develop vaccine candidates and the delivery technology in parallel. The shift is obvious as vaccine developers are in the best position to identify the carrier and administration route that will elicit optimal functionality from their vaccines with minimum to zero side-effects. However, the number of companies that have made this transition are still few. The majority of vaccines companies still develop vaccines independently and then use in-licensing to acquire the appropriate delivery technology. All vaccines are currently trying to move to needle-free delivery technologies as they are safer, less invasive, and easier to provide in developing economies where there can be a lack of skilled personnel to administer vaccine injections. The upcoming technologies in needle-free vaccine delivery have been summarized in Figure 4.

Companies concentrate on a particular technology platform and develop delivery devices in the same. Unique vaccine formulations are then developed with novel carriers, such as nanoemulsions, lypophilized vaccines, or novel adjuvants to reduce vaccine dosage and break the cold storage supply chain. The vaccine product and delivery platform are then ready to undergo regulatory testing in a combined state. Optinose, based out of Wiltshire, UK, and Mystic Pharmaceuticals of Austin, TX, are examples of companies working in the muscosal (oral/nasal) delivery space. Optimist, the product from Optinose, is an exhalation-actuated device, which delivers the intranasal vaccine to the nasal cavity

FIGURE 4



Types of Needle-Free Vaccine Delivery Technologies

without lung deposition of the aerosol. The VeriDoser and VRx2 systems from Mystic Pharmaceuticals are single disposable and dual-chambered units, respectively. While VeriDoser provides precise aseptic delivery in the form of an optimized plume, VRx2 maintains the sterile freeze-dried vaccine and diluent solution in different chambers, to mix upon activation. Companies to follow in the jet injector space include Eurojet, Valeritas, Bioject Medical Technologies Ltd., Antares Pharma, and Nanopass Technologies Ltd.

Transdermal delivery is the platform that has received a great deal of attention of late, particularly with the development of Nanopatch and the PassPort™ system from Altea Therapeutics. The PassPort system has been developed with a broad spectrum approach in mind to be applicable for easing delivery of both drugs and vaccines. It has been successfully tested for the delivery of transdermal delivery of insulin. It has also been tested in pilot studies for the successful delivery of the hepatitis B antigen. This is the R&D model that most companies in the drug delivery sector have been following for the past 5 to 6 years. The platform technology is developed to enhance the delivery of an existing drug, or specially formulated drugs are developed subsequent to the development of the delivery platform. This model is also on the verge of experiencing some transitions that are discussed in the following section.

THE CHANGING DRUG DELIVERY BUSINESS MODEL

What is the future of the drug delivery sector? How has the business model changed with new biological and drug formulations being developed so rapidly? In order to answer these questions, it is necessary to understand the trends that are shaping R&D in the drug delivery sector. In the past 5 years, drug delivery technologies have experienced a decline in public and investor support. Drug delivery has traditionally been viewed as an accessory segment for pharmaceuticals and biologics rather than an independent sector in itself. According to several leading players in the industry, one of the deterrents against drug delivery enjoying abundant funding and regulatory support is that several of these companies have ventured into re-branding themselves as specialty pharmaceutical companies. The intensity of innovation in drug delivery has decreased. A hindrance in drug delivery products enjoying exclusive market share has been their regulatory route, 505(b)(2), a method that relies on the FDA's findings for a previously approved drug to obtain approval for the current New Drug Application (NDA). Despite the fact that this method saves companies both cost and time, it also precludes the delivery platform from enjoying more than 3 years of market exclusivity after which suitable generics can be manufactured and introduced. This is not adequate time for any company to follow a risk-adjusted cost plan, keep a minimal profit margin of 20%, and recover its investment costs. More than 3 years are required to just break even.

In addition, there are several other factors related to the drug delivery technology that indicate that it should be treated as a separate sector and undergo standardized regulatory procedures. Drug delivery methods have been shown to have a directly proportional relationship with patient compliance, indicating that less-invasive, particularly needle-free delivery methods, will replace a significant portion of injectable drugs. The keyword for drug delivery companies today and for the future is collaboration. Close-knit collaborations with pharmaceutical and biotechnology companies will bring about greater synergy in developing delivery technology platforms that are the most optimized for that particular drug. Drug delivery methods for chronic diseases, such as diabetes, hyperlipidemia, and arthritis, are domains that require more developmental work. The drug and the delivery method are interrelated - the business sectors must remain independently defined, but the technologies have to work hand in hand. ◆

BIOGRAPHY

Ipshita Chakraborty is an Industry Analyst for Frost & Sullivan's Technical Insights practice. Her research focuses on genetic technology, drug discovery, medical devices, medical diagnostics, and imaging. Ms. Chakraborty maintains engineering and consulting expertise, which includes tracking emerging technologies and trends, research and analysis for R&D portfolio and investment, and technology roadmap predictions. Prior to joining Frost & Sullivan in 2010, she led numerous projects and consulted for several leading firms, including National Instruments. She also has working experience in the test, measurement, and automation spaces with leading companies in government, public, and private sectors, such as GE, Department of Defense, and Raytheon. She earned her MS in Biomedical Engineering and an MS in Computer Engineering from Vanderbilt University in Nashville, TN.

THERAPEUTICS MARKET

Therapeutic Areas - Will This Area See Future Growth?

By: Cecilia E. Van Cauwenberghe, Senior Research Analyst, Life Sciences & Biotech, Technical Insights, Frost & Sullivan

INTRODUCTION

An old citation authored by Armand Trousseau, a French internist who performed his activities during the 19th century, says:

"Every science touches art at some points, every art has its scientific side; the worst man of science is he who is never an artist, and the worst artist is he who is never a man of science. In early times, medicine was an art, which took its place at the side of poetry and painting; today they try to make a science of it, placing it beside mathematics, astronomy, and physics."

Nowadays, almost a century and a half later, physicians continue to let the day-by-day practice of medicine affect their judgment and intuition. Moreover, unfortunately, biophysics and biochemical sciences have followed separate routes over the pace of time. While physicians of the last generation had limited access to information, enormous advances in molecular biology were significantly influencing clinical medicine. In current times, overcoming the barrier of limited access, impressive volumes of information have been generated, both in biophysics and biochemistry fields, where omics revolution has taken place. Indeed, a large number of clinical studies containing substantial information regarding different patient's stratification wait to be analyzed and discussed promoting the development of clinically supported individualized therapies. Thus, in view of the overflowing amount of information, conscious strategies to discriminate the relevant advances from the overall information are crucially needed.

Addressing this concern, the following is dedicated to integrating different areas of clinical medicine, comprehending the latest advances in life sciences and biotechnology toward the most targeted therapies.

GENERAL BACKGROUND

The incorporation of genetic screening, prevention, diagnosis, therapy, and monitoring to medical practices derives the common term, integrative healthcare systems. The pace of molecular diagnostics, as well as genetics- and genome-based medicines, developments points toward such merging disciplines. In accomplishing this integration, several factors should be combined, including screening for a certain disease, early diagnostics, as well as prevention and monitoring techniques.

The individualization of therapy comes from some cell therapies, including recombinant human proteins, therapeutic monoclonal antibodies, autologous tissue and cell transplantation, gene therapy, stem cells advances, among many others.

Indeed, as it is stated in Frost & Sullivan's re-titled Recombinant and Designer Therapeutics, the advent of the biotechnology industry and the development of the first recombinant therapeutic three decades ago have been of an increasing focus around the development of advanced and superior biomedical improvements. The translation of such enhanced solutions into medical practice has derived relevant targeted therapeutics, gene and cell delivery, among others, to treat a wide variety of diseases. As far as the drug development and therapeutic industry is concerned, the revolution in recombinant DNA technology brought about a fundamental paradigm shift in the manner in which diseases were being approached and treated. From the first instance of drug discovery to the development of therapeutic vehicles for delivery, the focus has shifted from targeting the symptom to targeting the cause.

Currently, therapeutic proteins based

on recombinant molecules approved for clinical use and undergoing preclinical studies and clinical trials in humans are significantly increasing. Moreover, computer-driven prediction tests, followed by in vitro and in vivo testing of any potentially immunogenic epitopes, are also being developed to help avoid or minimize immune responses to therapeutic proteins and thus prevent potentially serious side effects by immunogenicity.

On the other hand, compared with small-molecule drugs and usual recombinant therapies, antibodies (Abs) are very specific and are less likely to cause toxicity based on factors other than the mechanism of action. Hepatotoxic, along with other cytotoxic effects involving drug-drug interactions, are the most frequently observed. From the point of view of a clean safety profile, antibodies are extremely attractive due to their ability to be designed to be very specific with high affinity for the target.

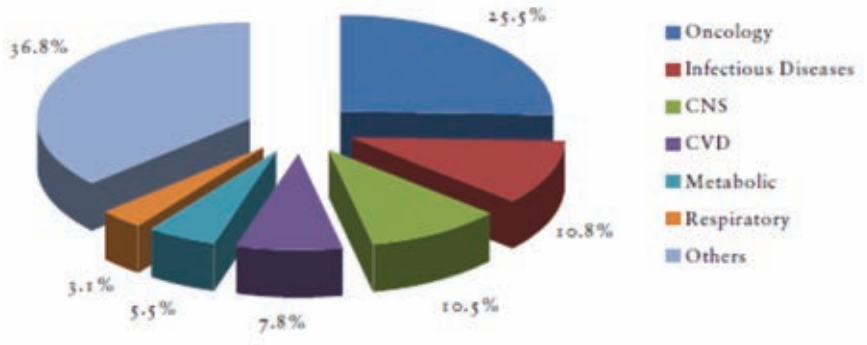
Particularly useful in the development of novel approaches to medicine are the monoclonal antibodies (MAbs) for molecular targeting therapies, especially in cancer treatment. In this regard, a variety of clinical trials based on MAbs, both as a single and as a chemotherapy - or immuno-conjugates-combined agent - still hold a promising performance in the treatment of specific diseases. Certainly, a deeper understanding of their action mechanisms is expected to improve such a therapeutic approach.

In this regard, gene therapy, defined as the transfer of a given genetic material to specific target cells to treat a particular disease, involves the identification of the mutated gene to be replaced by a healthy copy. Gene therapy also serves as the vector to deliver the healthy gene to a patient's cells, using additional DNA elements to properly activate this healthy gene. Undoubtedly, the approach from gene therapy to personalized medicine cannot be neglected.

In the past decade, novel advances in the field of research of cell therapies have gained special attention in replacing, repairing, or enhancing the function of damaged tissues or organs. Cell therapy alludes to the administration of properly treated cells into the human body. Cell lines, as well as cell and tissue transplantation, belong to this technology. Cell transplantation, as with organ transplantation, needs immunosuppressive therapy in order to avoid rejection.

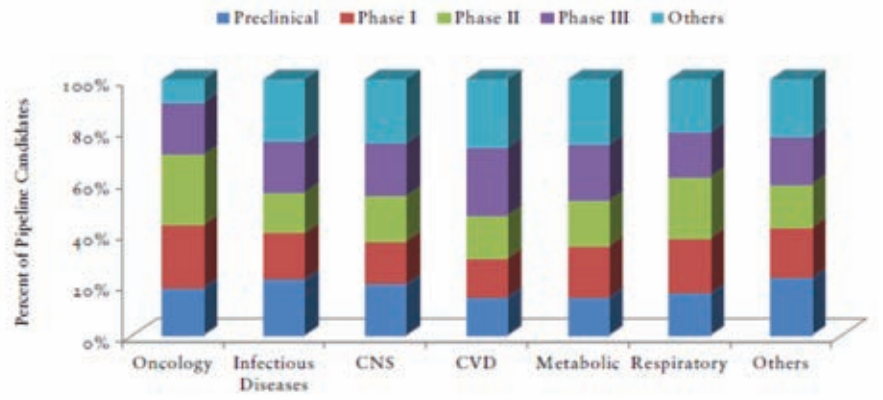
On the other hand, stem cells are those cells that retain the capability of differentiating into many other cell types. Embryonic stem cells (ESCs) are continuously growing cell lines of embryonic origin derived from the pluripotent cells of the inner cell mass, or epiblast, of the mammalian embryo. They may give rise to any cell type but not to an independent organism.

FIGURE 1



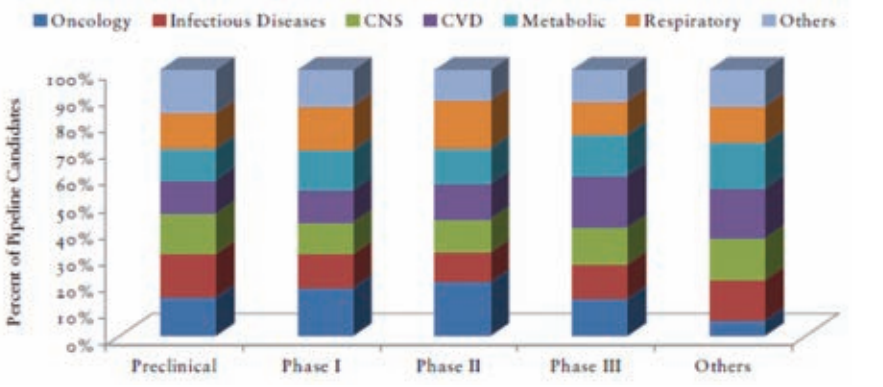
R&D Clinical Trial Pipeline by Therapeutic Area (Source: Frost & Sullivan)

FIGURE 2



Percent of Clinical Trials in the R&D Pipeline by Therapeutic Area (Source: Frost & Sullivan)

FIGURE 3



Percent of Clinical Trials in the R&D Pipeline by Phase (Source: Frost & Sullivan)

Furthermore, stem cells are starting to be used for drug testing and discovery, allowing the evaluation of different responses to certain agents, as well as their metabolizing capacity. Mesenchymal stem cells (MSCs) can be isolated and expanded for their in vitro study, enabling not only the assessment of their sensitivity and response to various drugs, but also serving as a useful parameter for adjusting dose regimens and optimizing treatment plans.

Antisense therapy is also emerging as a novel technology able to mirror specific mRNA sequences and block protein production by means of antisense drugs. Antisense therapeutics used to be considered a form of gene therapy due to its ability to modulate gene function for therapeutic purposes, indeed, the definition of gene therapies. Nevertheless, oligonucleotides presenting antisense properties differ from standard gene therapies under the conception of such molecules that have the ability to only block the expression of existing genes, but oligonucleotides are not able to give place to a new gene expression.

One of the most promising features of antisense technology relies on technology that leads to an innate form of customization in comparison with a variety of drugs. This characteristic makes antisense therapy a real-world candidate for cancer treatment design as it has already been demonstrated in clinical practice.

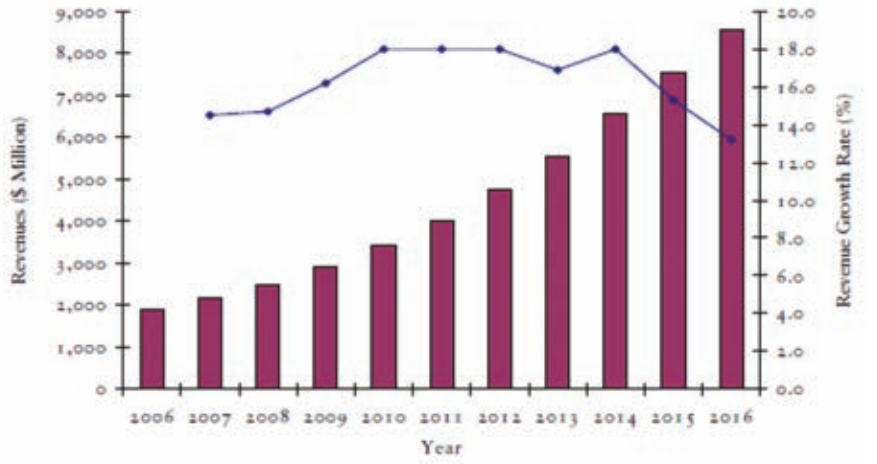
Addressing this technology, detailed research about a specific version of antisense therapy, RNA interference (RNAi), was published by Frost & Sullivan last year. RNAi is a system by which living cells control the activity of a gene. RNAs are direct products of genes. Small RNAs, such as microRNA (miRNA) and small interfering RNA (siRNA), can bind to other specific RNAs to increase or decrease their activity. This mechanism naturally helps in defending cells against parasitic genes, and plays a crucial role in personalized therapies.

Regarding some technological aspects, gene silencing involves the use of a double-stranded RNA (dsRNA), which enters the cell and is processed into approximately 20 nucleotides dsRNAs, known as small interfering RNAs (siRNAs). Such nucleotides are able to recognize and destroy complementary RNAs for therapeutic purposes, such as cancer treatment, by controlling tumor cell growth. This modality also gives place to another novel approach known as allele-specific inhibition (ASI), which precisely involves the development of siRNAs as a therapeutic approach for genotype-specific inhibition of tumor growth. ASI is expected to be a promising approach to cancer treatment. In addition, sequence-specific targeting of a gene might open the possibility of the allele-specific inhibition of genes involved in dominant genetic diseases. At this respect, even though only a few siRNAs are today enrolled in clinical trials, the role of RNAi in the development of personalized medicine constitutes an essential interest.

On the other hand, polymorphisms in the miRNA pathway are emerging as powerful tools to procure a better understanding of the biology associated with a certain disease for both prognosis and diagnosis. The detection of miRSNPs or MiR-polymorphisms, which have been defined as polymorphisms present at or near a microRNA binding site of functional genes, thus affecting the gene expression by interfering with a miRNA function, holds promise in the field of miRNA pharmacogenomics, molecular epidemiology, and for individualized medicine.

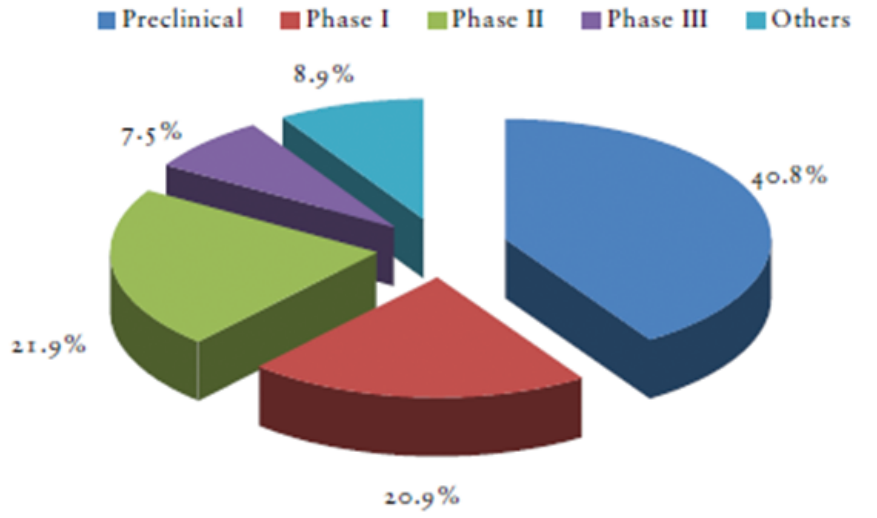
According to recent studies, advances in miRNA research indicate the clear involvement of miRNAs and genetic variations

FIGURE 4



Oncology Revenue Forecasts (US), 2006-2016 (Source: Frost & Sullivan)

FIGURE 5



Percent of Oncology Clinical Trials by Phase. (Source: Frost & Sullivan)

in the progression and prognosis of diseases via miRNA pathways, including not only cancer, but also other chronic inflammation-related disease, such as hypertension, coronary and peripherical cardiovascular disease, diabetes, Alzheimer's disease and related neurological disorders, muscular hypertrophy, etc.

TOP THERAPEUTIC AREAS

For the purpose of exposing the top therapeutic areas, the current market can be divided into the following major segments:

- Oncology
- Infectious Diseases
- Central Nervous System (CNS) Disorders
- Cardiovascular (CVD) Disorders
- Metabolic Disorders
- Respiratory & Allergy Disorders
- Other therapeutic markets include immune, renal, hepatic, gastrointestinal, musculoskeletal, pain management, respiratory, dermatological, and genitourinary, amongst other diseases.

The top five therapeutic markets account for 63.2 percent (approximately two-thirds) of the total development pipeline, while the other segments account for the rest (approximately one-third).

The choice of the top therapeutic areas is based on individual growth rates, future course of the market, individual weightage in development pipelines as well as potential for global impact and expansion of trials. A key aspect of therapeutic segmentation is the ability to look at vertical markets (versus segmentation by phase, which is horizontal) and identify potential growth areas.

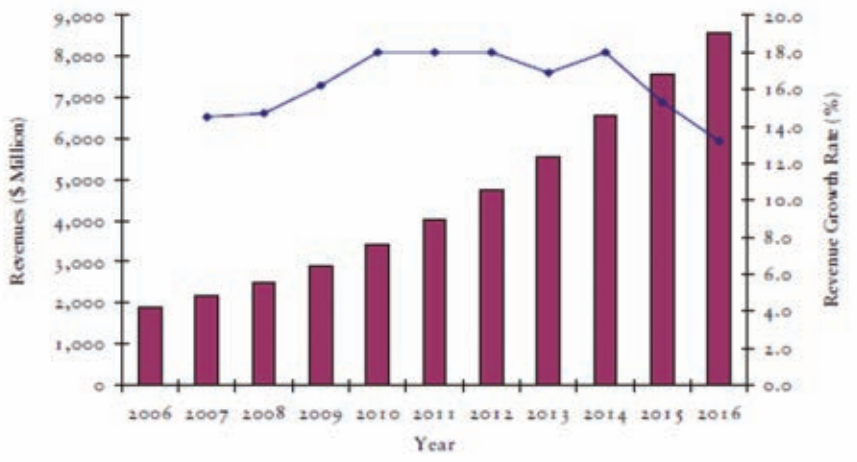
Regarding the marketing point of view, amongst the therapeutic areas, oncology is the largest with 25.5 percent share of the clinical pipeline. Infectious diseases, CNS, and CVD account for 10.8 percent, 10.5 percent, and 7.8 percent of the clinical pipeline, respectively. Amongst these therapeutic areas, revenues from outsourced oncology trials are projected to grow the fastest at a compound annual growth rate (CAGR) of 16.7 percent. Metabolic diseases, infectious diseases, and respiratory and allergy are projected to grow at 14 percent, 13.8 percent, and 13.3 percent, respectively.

ONCOLOGY

Even with the advent of genomics and related omics technologies, cancer disease treatment and management have had a negative balance in the past decades. In addressing this concern, great expectations rely on the deeper understanding of this disease at the molecular level. The extensive analysis of gene expression profiles, as well as novel developments regarding protein studies, have successfully thrown out clinically relevant results, both for the classification of tumors and response prediction according to individual treatment.

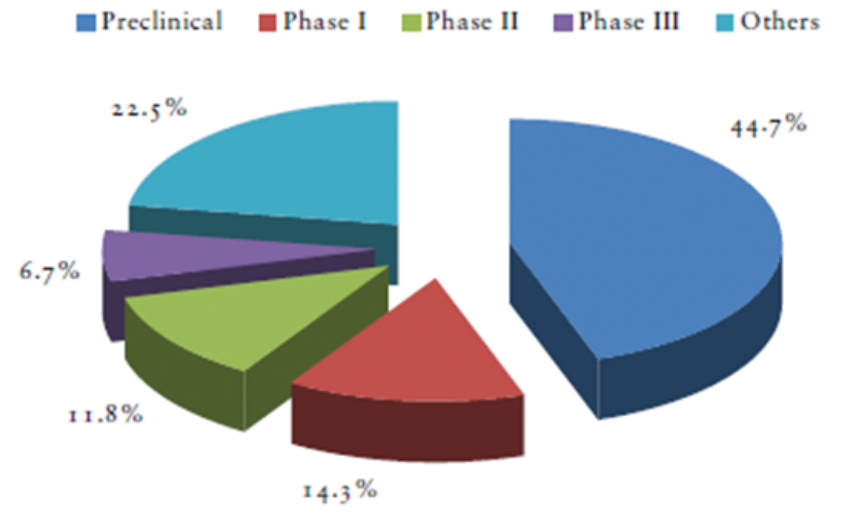
In this regard, molecular diagnosis, already mentioned as one of the most relevant foundations of personalized medicine, has a significant impact over the proper management of cancer, taking into account its heterogeneities. Indeed, molecular diagnosis enables the classification of cancer based on molecular profiles, while it allows the prediction of drug response and prognosis.

FIGURE 6



Infectious Diseases Revenue Forecasts (US), 2006-2016 (Source: Frost & Sullivan)

FIGURE 7



Percent of Infectious Diseases Clinical Trials by Phase (Source: Frost & Sullivan)

Tumoral formations arise as a consequence of the ability of cancer cells to turn a variety of genes on and off, making any form of internal control unsuccessful. Furthermore, when cells alter large portions of their chromosomes, such a formation could be significantly severe.

In the past few years, on the base of these chromosome alterations, a series of methods have been reported. These developments represent a great improvement in the genomics field of research by enabling new techniques to tailor better individualized cancer treatments.

By considering the technical instruments helping to carry out such improvements, robotically printed DNA microarrays offer great advantages in measuring the expression of tens of thousands of genes at a time, leading to the creation of a molecular profile of the RNA in a tumor sample. Additional analysis tools encompass these procedures, including pattern recognition algorithms to identify subgroups of tumors that have related gene-expression profiles, statistical methods to relate gene-expression data and clinical data, and bioinformatic tools to evaluate expression levels.

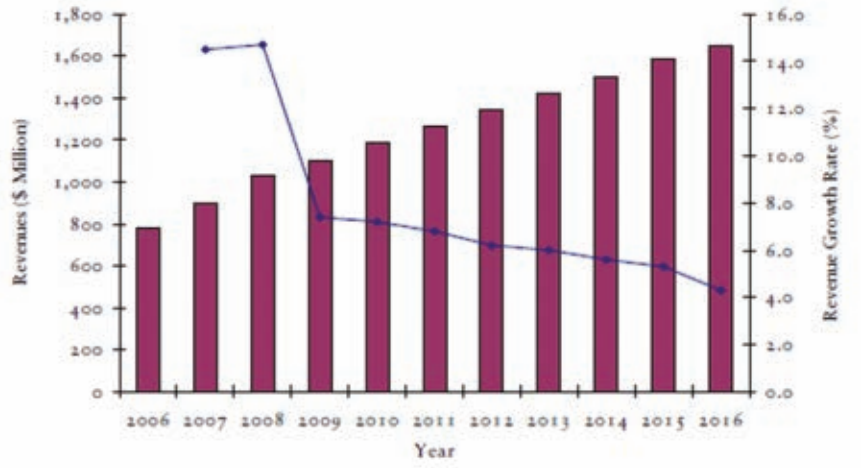
Successful results have been obtained by using gene expression microarray technology in bladder carcinoma and breast cancer, among others. Nevertheless, the most promising applications of these advances are associated with the discovery and development of different cancer therapies. Thus, molecular biomarker identification, as well as pharmacodynamic (PD) endpoints and prognostic biomarkers, represent good examples.

In order to detect the loss of hetegozygosity (LOH), or the loss of normal function of one allele of a gene in which the other allele was already inactivated, microarrays need to be enhanced in many cancer cells. In this manner, these customized tag-array systems focus on suspect regions of chromosomes for signs of deleted genetic material known to play a role in cancer, rather than covering the entire genome. Consequently, an improved parallel system for the assessment of multiple genomic alterations is obtained, helping clinicians to adequately identify the risk level that the disease evidences.

In spite of these advances in malignancies diagnostics, a large number of detailed investigations fail to reveal a primary site of origin for a subset of patients with metastatic cancer. This is often referred to as carcinoma of unknown primary origin (CUP), or occult primary malignancy. According to the American Cancer Society and the European Cancer Organization, CUP accounts for approximately 3 percent of all malignant neoplasms and is therefore one of the 10 most frequent cancer diagnoses in humans. Challenges for that problem rely on the early detection of the disease. In fact, the site of origin cannot be identified at the time of diagnosis, which derives in metastasis. A deeper understanding of the biomechanisms that govern CUP is crucially needed. In this regard, it is expected that a group of technologies related to pathology investigations, including molecular diagnosis, electron microscopy, and immunohistochemistry, along with current mapping technology such as CT, mammography, PET scan, etc., lead to an improvement in this arena.

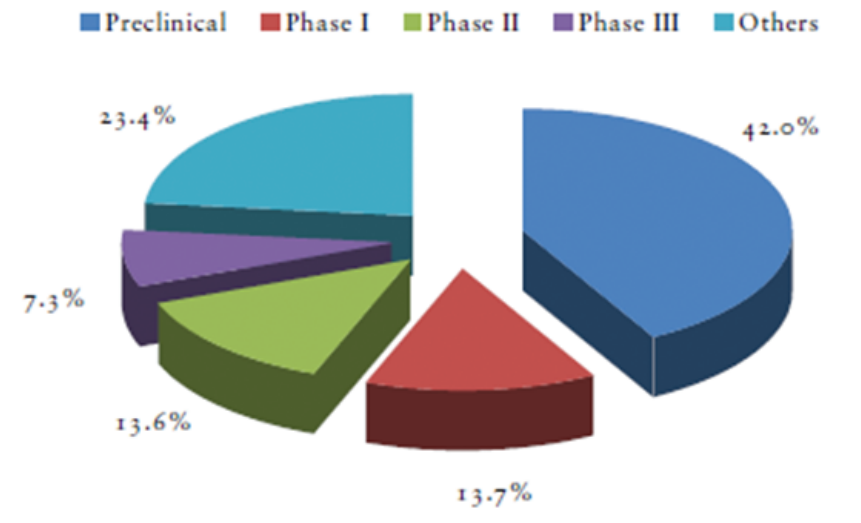
Another issue related to cancer therapies is the minimal residual disease (MRD), which represents the major cause of relapse in cancer and leukaemia. MRD is the name given to small numbers of leukaemic cells that remain in the patient during or after treatment when the patient is in remission without symptoms or signs of disease. The utilized technology is the reverse transcriptase polymerase chain

FIGURE 8



CNS Revenue Forecasts (US), 2006-2016 (Source: Frost & Sullivan)

FIGURE 9



Percent of CNS Clinical Trials by Phase (Source: Frost & Sullivan)

reaction (RT-PCR), which is able to detect BCR-ABL transcripts in chronic myeloid leukemia (CML) in a chronic phase.

Technologies, such as fluorescence in situ hybridization (FISH) are nowadays part of the routine medical practice regarding cancer treatment and monitoring to detect and localize the presence or absence of specific DNA sequences on chromosomes. According to the advances in personalized medicine approaches, FISH studies are expected to be even more frequently used, helping to define the spatial-temporal patterns of gene expression within cells and tissues. Indeed, lab-on-a-chip microfluidic devices have been developed incorporating networks of microchannels that can miniaturize, integrate and automate conventional analytical techniques onto chip-style platforms, including FISH studies.

In this regard, a crucial challenge toward the achievement of a new conception of medicine consists of the development of different technological platforms for routine clinical diagnosis on the base of gene expression profiling. Naturally, such platform developments are extremely important in performing clinical trials, which, facing the advent of novel technologies, definitely need to comprise genomic-scale gene expression profiling in order to characterize the genes involved in the response to the drugs under research. This methodology also improves the molecular diagnosis of the disease, allowing the employment of new treatment technologies working in the development of tailored therapies for molecularly defined diseases.

On the other hand, revenues generated from outsourced oncology clinical trials in North America have been estimated as $3.912 billion in 2011. Through 2016, this is forecasted to reach $8.555 billion by 2016 at a CAGR of 16.7 percent.

Oncology continues to remain the top therapeutic area within the North American market with a 26.5 percent share of market revenues. This is forecasted to increase to 37.4 percent by 2016. This significant growth in outsourced oncology clinical research is expected to be driven primarily by the biopharmaceutical industry.

Due to the emergence of new cases of cancer and increasing survival rates, the outlook for newer therapies looks bright. Companies are continuously looking to improve as well as expand label indications of current therapies. Increasing incidence of cancer in emerging markets is also prompting greater need for global trials, especially due to easier access to a wider pool of patients.

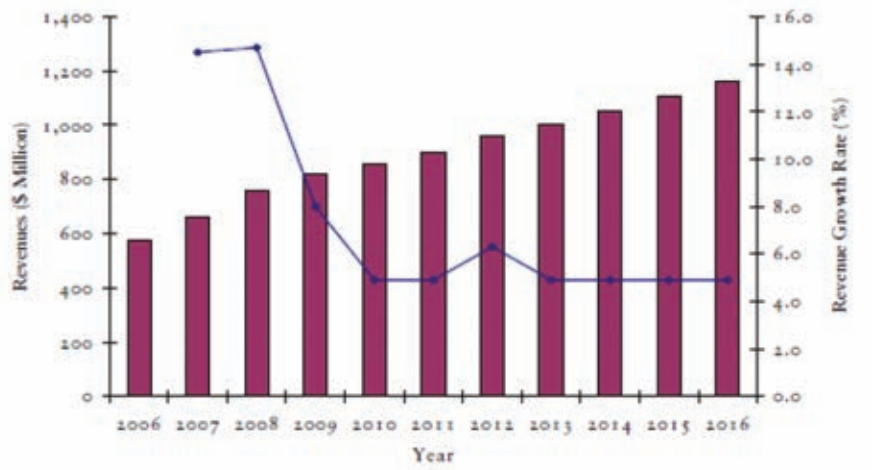
Infectious Diseases

A personalized approach to infectious diseases therapies relies on the genetic differential responses to infectious agents and the targeting drugs. The most used instances to describe the behavior of infectious diseases and need for a prompt solution are given by human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), tuberculosis (TB), and malaria.

In order to achieve a broad understanding of the immunological response to each individual facing infectious agents, research methodologies are focused on the study of the immune characteristics at the cellular-based level. Such studies include the chromosomal susceptibility to acquire a viral infection, and whole genome characterizations at this respect.

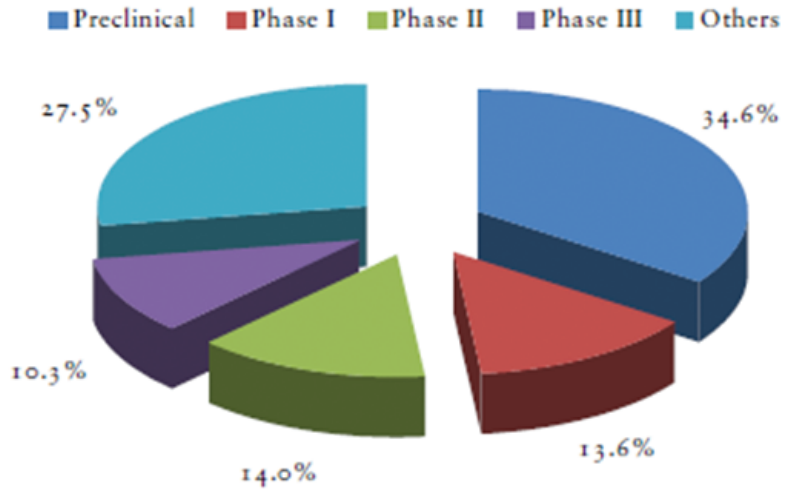
HIV: Regarding the current treatments, even though a large number of drugs for HIV working under different mechanisms are

FIGURE 10



CVD Revenue Forecasts (US), 2006-2016. (Source: Frost & Sullivan)

FIGURE 11



Percent of CVD Clinical Trials by Phase. (Source: Frost & Sullivan)

available, no significant variation in the response to antiretroviral therapies among individuals is observed in pharmacokinetics and cytotoxicity research. In this aspect, a wide range of analysis of genetic variation in mitochondrial genes, lipid metabolism, and transport genes to investigate the basis of metabolic and lipid disorders associated with the use of specific antiretroviral agents have been performed.

Currently, an increasing number of drugs associated with infectious diseases exist in the market, with a growing number of candidates under clinical development. In this regard, the development of entry inhibitors comes at an opportune time due to the appearance of virus strains presenting severe resistance to existing reverse transcriptase and protease inhibitors. Taking a more technical road, entry inhibitors target Env protein of HIV-1, which has demonstrated to be highly variable in its density, receptor expression levels, and differences in affinity and receptor presentation. In this way, entry inhibitors need to overcome this feature in order to be suitable for therapy applications.

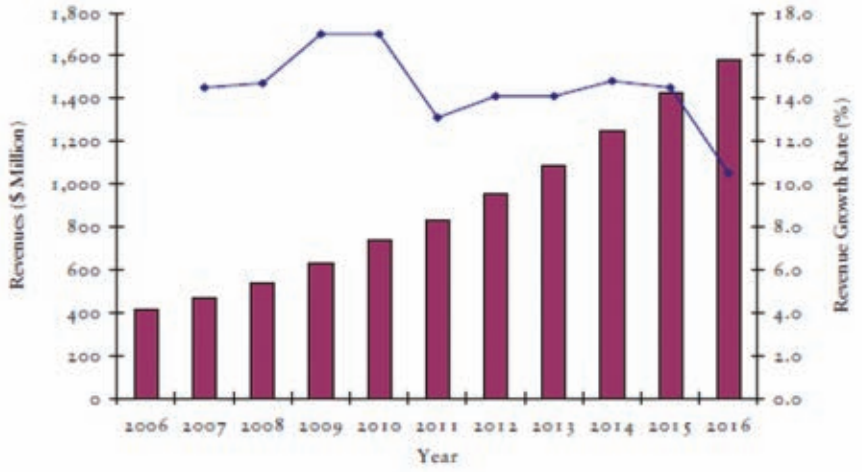
In the management of HIV in previous detection of HIV-infected individuals and posterior evaluation of their health conditions, a therapeutic regimen is established and periodically monitored. Following the procedure, the CD4+ viral load represents an indicator parameter for the prognosis of disease progression. As the disease advances, the most challenging aspects result in the management of the drug resistance, along with the prevention of adverse reactions to drugs and the treatment of other diseases, frequently present due to immunological affection issues.

Circulating CD4 T-cells drops significantly after the infection. Therefore, CD4 counts are dormant for the beginning of the treatment with the indication of an anti-retroviral drug. Such therapy used to result in satisfactory effectiveness in reducing viral replication. Nonetheless, a phenomenon known as multi-drug resistance (MDR) emerges, limiting or even eliminating the utility of the treatment. Indeed, MDR involves more than 100 individual mutations in the HIV genetic code so that a reactional and in-depth understanding of the mechanisms taking part is a critical challenge. Addressing this concern, genotyping has demonstrated important clinical utility.

The reason to monitor CD4 T-cells relies on one of the principal characteristics of the HIV-1, which infects cells by using a CD4 cell surface receptor, along with one of two co-receptors, that is CCR5 or CXCR4. As an additional interesting feature, scientists have found a more rapid disease progression when the CCR5 co-receptor is substituted by the CXCR4.

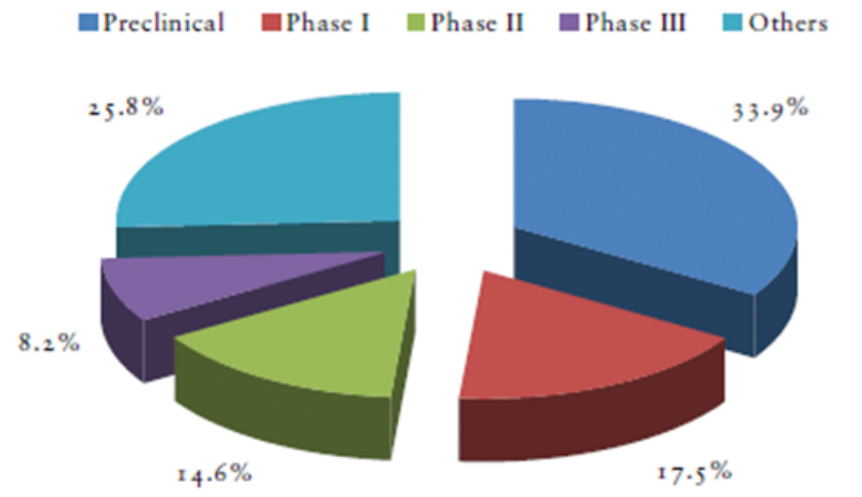
A personalized approach to HIV therapy should consider individual genetic and metabolic variations. A typical example is given by efavirenz, which shows different assimilation rates due to genetic mutations in certain groups of patients, leading to important adverse side effects in some of them, including neurological disorders. A good predictor for those variations is genotyping, which is becoming in itself an opportunity for personalized treatment. On its base, prospective clinical trials and cohort studies have associated a variety of genetic features with drug metabolism and toxicity. In this respect, in addition to efavirenz plasma levels and central nervous system side effects, other commonly used drugs, such as nevirapine, have shown hypersensitivity and hepatotoxicity. Moreover, indinavir and atazanavir have been associated with hyperbilirubinemia, hyperlipidaemia,

FIGURE 12



Metabolic Disorders Revenue Forecasts (US), 2006-2016. (Source: Frost & Sullivan)

FIGURE 13



Percent of Metabolic Disorders Clinical Trials by Phase. (Source: Frost & Sullivan)

lipodystrophy, peripheral neuropathy, and pancreatitis. Additionally, tenofovir has shown renal proximal tubulopathy as an adverse side effect.

These findings give place to pharmacogenetics in striving for the benefit in HIV therapeutics by considering the high prevalence of drug-related adverse events, as well as, the long-term nature and complexity of such a therapy. Pharmacogenetics is expected to play an important role in HIV treatment in the near future, focused not only on therapy efficiency, but also in avoiding adverse side effects, including metabolic-associated disorders and toxicity.

As a further challenge in HIV treatment, the recognition and depuration of viral reservoirs, or "sanctuaries," still continue to be the most intricate tasks. Therefore, with the advent of pharmacogenetics and nucleic acid technologies, more sophisticated and reservoir target viral genetic markers are expected, with the consequent inclusion into the clinical diagnostic routine.

Hepatitis B (HBV): Hepatitis B, caused by the hepatitis B virus (HBV), is the most common, serious liver infection in the world. The Food and Drug Administration (FDA) has approved several drugs in the U.S. to treat chronic HBV, including Intron A (Interferon Alpha), Pegasys (Pegylated Interferon), Epivir HBV (Lamivudine), Hepsera (Adefovir), Baraclude (Entecavir), Tyzeka (Telbivudine), and Viread (Tenofovir). Nonetheless, significant variations among the set of patients has been observed. The immunologic disposition of the host and genetic factors of the virus itself are probably the main determinants for the drug response. A more specific biomarker technology is expected to solve these controversies and help target better and more individualized therapies.

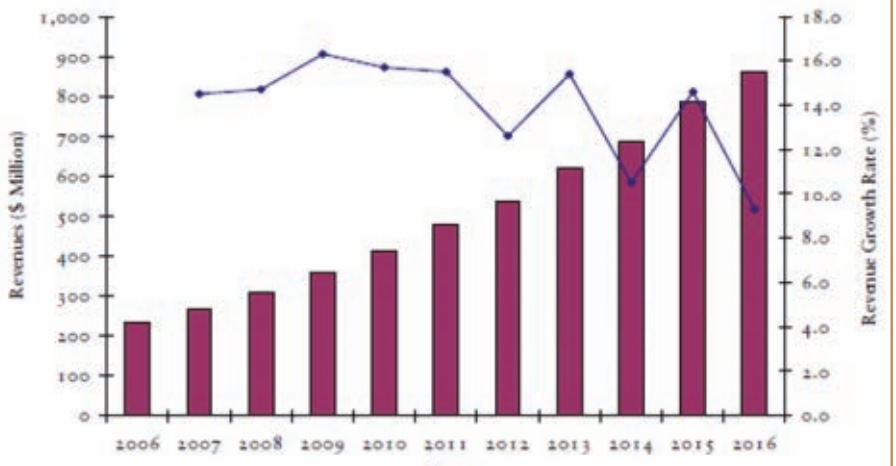
Hepatitis C: Co-infection with HIV and hepatitis C (HCV) complicates both diseases. HIV causes HCV to progress more quickly. An estimated 4 to 5 million people in the U.S. have been infected with HCV. Some of these people cleared the HCV virus and are no longer infected, so the number of people who are chronically infected is smaller, though precise figures for chronic HCV infection are difficult to obtain. More than 1 million people in the U.S. have HIV/AIDS, with 25 percent to 30 percent being co-infected with HCV.

Worldwide, about 4 to 5 million people are co-infected with HIV and HCV. Co-infection rates range from about 9 percent of HIV positive people in the U.K. to almost 50 percent in Spain and Italy. Co-infection rates as high as 60 percent to 70 percent have been found in groups of injection drug users (IDUs) in various countries, including the U.S., which has very high co-infection rates in some urban areas. Furthermore, the complications of chronic HCV, including cirrhosis and hepatocellular carcinoma, are expected to increase significantly worldwide throughout the next 10 to 20 years.

Globally, sexual transmission accounts for the majority of new HIV infections each year. However, injection drug use is driving the HIV epidemics in Eastern Europe and Central Asia. Co-infection with HCV and HIV is common among current and former IDUs, especially in countries where access to syringes and/or substitution treatment (methadone or buprenorphine, or heroin maintenance) is uneven, severely restricted, or nonexistent.

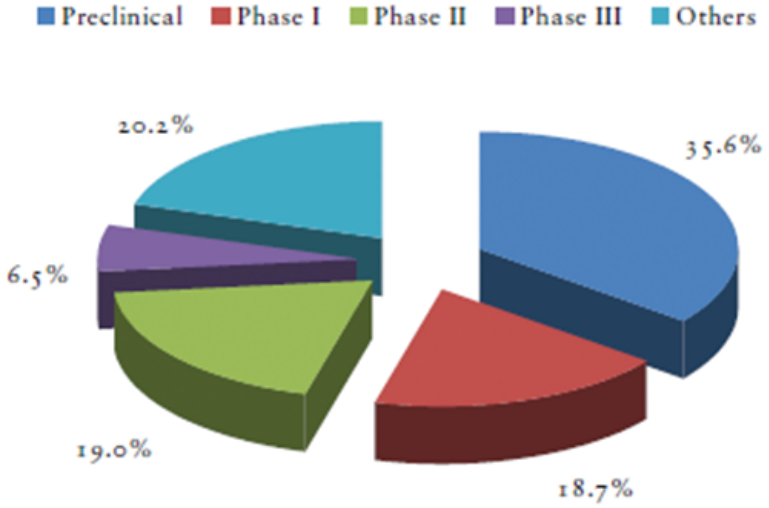
Toward more personalized approaches to treatment, genotyping along with viral RNA levels are the most relevant candidates as indicators of sustained virological response.

FIGURE 14



Respiratory & Allergy Revenue Forecasts (US), 2006-2016. (Source: Frost & Sullivan)

FIGURE 15



Percent of Respiratory & Allergy Clinical Trials by Phase. Source: (Frost & Sullivan)

Then, statistical-based tools, such as covariance network analysis, could be applicable to the RNA virus.

Tuberculosis (TB): According to the U.S. Centers for Disease Control and Prevention (CDC), TB is one of the deadliest diseases worldwide. One-third of the world's population is infected with TB. Each year, more than 9 million people around the world become sick with TB, and almost 2 million TB-related deaths are reported globally. Additionally, TB represents a leading killer of people who are HIV infected. According to World Health Organization (WHO) statistics, in total, 12,904 TB cases (a rate of 4.2 cases per 100,000 persons) were reported in the U.S. in 2008, which determines its classification as a pandemic disease.

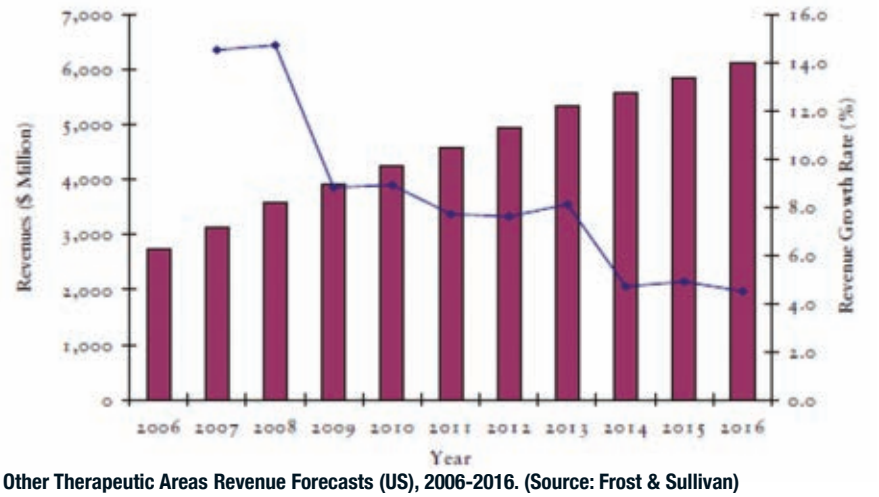
The medical therapy applied to TB for more than five decades has been based on a combination of drugs relying on simple probability. The standard regimen for TB is isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, then isoniazid and rifampicin alone for four additional months. The patient is considered cured at six months (although there is still a relapse rate of 2 percent to 3 percent). For latent tuberculosis, the standard treatment is six to nine months of isoniazid alone.

Concerning healthcare policies, statistics suggest that healthcare budgets in a wide range of developing countries are fully overwhelmed. In fact, in addition to TB treatment associated costs, the failure of such therapies represents a significant issue, as well as the evidenced multi-drug resistance (MDR) and extensively drug resistance (XDR). Furthermore, co-infection with HIV and other infectious diseases makes the eradication of TB very complex. In this matter, the opportunity for a personalized approach to the treatment of infectious disease relies on this complexity, including infection and co-infection. The aforementioned genotyping method and viral RNA levels, in addition to the development of novel biomarkers for diagnosis and monitoring, are considered quite promising technologies.

Malaria: According to WHO, malaria is a deadly mosquito-borne disease that affects millions each year in Africa and around the world. There are an estimated 250 million cases of malaria each year produced by Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, or Plasmodium malariae. Nearly 1 million people die from malaria each year, mostly children younger than 5 years old. Although the vast majority of malaria cases occur in sub-Saharan Africa, which result in a 90 percent malaria death rate, the disease is a public health problem in more than 109 countries in the world. Of these, 45 are in Africa, where approximately 3.3 billion people live in areas where malaria is a constant threat. In fact, Africa experiences malaria costs of an estimated $12 billion in lost productivity. Insecticides have demonstrated some efficiency in reducing malaria cases, but contamination and associated diseases, including different types of cancer, arise under these conditions.

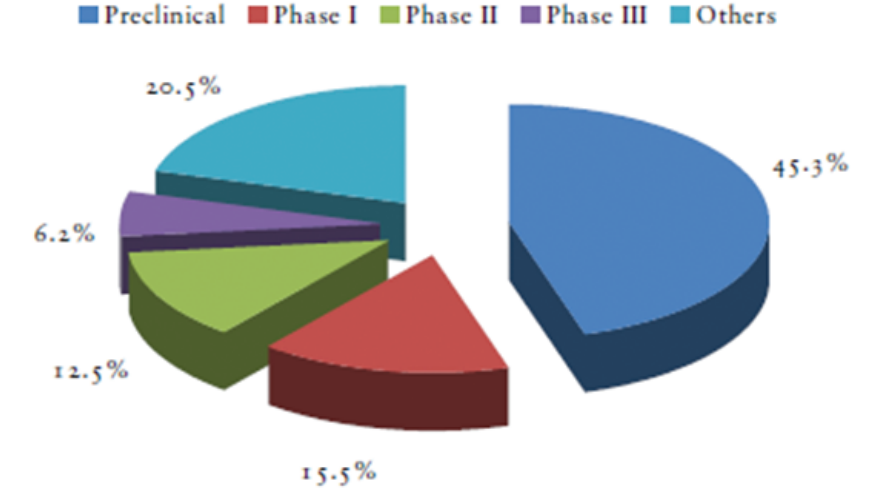
Regarding the current treatments, the development of resistance to this drug has limited its efficacy in most parts of the world. Indeed, there are few effective treatments available. In addressing this concern, scientists are focused on developing novel therapies based on genomic knowledge of the Plasmodium falciparum. DNA sequences of chromosomes 2, 3, 10, 11, and 14 are already determined with several others nearing completion regarding the malaria genome

FIGURE 16



Other Therapeutic Areas Revenue Forecasts (US), 2006-2016. (Source: Frost & Sullivan)

FIGURE 17



Percent of Other Therapeutic Areas Clinical Trials by Phase. (Source: Frost & Sullivan)

sequencing project (MGSP). The main goal of this project relies on getting a deeper understanding of the gene compositions and expression patterns of the parasite, building a comprehensive picture of the parasites' characteristics. From this point, the recently coined term of vaccinomics has emerged to describe the comprehensive, genomics-based effort to develop a working vaccine, in addition to new genetically based drug targets.

Regarding market positioning, infectious diseases are a leading therapeutic area within the North American market with 11 percent share of market revenues. This is forecasted to increase to 12.9 percent by 2016. The emergence and spread of a variety of infectious diseases and the increasing importance of vaccines as a part of the public health system in many Western and developing countries are driving the growth of this market segment.

Within the infectious diseases market, antivirals represent the biggest growth opportunity while the other segments, such as antifungals, cephalosporins, penicillins, and quinolones, are expected to shrink in revenues due to the influx of generics as well as the effect of lifecycle maturity on many legacy compounds.

On the other hand, vaccines account for a significant share of the infectious disease pipeline and, due to the increasing interest from Big Pharma companies, this segment is likely to witness sustained investments through the forecast period. Due to their global presence, large-scale trials are likely to be a key driving factor for increased outsourcing with significant global scale and capabilities.

Central Nervous System Disorders

Structural, biochemical, or electrical abnormalities in the brain or spinal cord, as well as in the associated nerves, can result in neurological disorders of varied severity. According to WHO, currently, more than 1 billion people suffer some form of neurological disorders or their sequelae worldwide.

Furthermore, the drug discovery and development process for neurological disorders faces important challenges. In fact, it is estimated that 90 percent of target drugs fail at gaining regulatory approval, especially those targeting the CNS, where inaccurate drug delivery and adverse side effects can lead to significantly serious outcomes. Therefore, great expectations rely on more personalized approaches that take into consideration a wide range of disciplines, including genomics developments.

In addressing this concern, novel technologies based on molecular imaging and associated disciplines have led to notable approaches to introduce imaging diagnostic techniques into the drug discovery and development process. Through this, significant reduction in the failure risk of drug molecules at each stage of development is expected to be achieved in the near future.

The market for drugs for CNS disorders is expected to contract during the forecast period between 2009 and 2016. Despite widespread occurrence of CNS disorders, such as depression and related ailments, the impact of generics is widespread, prompting a significant contraction of the market. The only segment within CNS disorders that is expected to have a positive growth rate during this period is anti-migraines.

Cardiovascular Diseases

According to WHO, cardiovascular diseases (CVD) are the world's largest killers, claiming 17.1 million lives a year. In addition, the American Heart Association (AHA) has defined a more generalized metabolic syndrome, which includes a variety of aspects, such as abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance or glucose intolerance, prothrombotic state, and proinflammatory state, among others. According to the AHA, more than 50 million people in the U.S. are diagnosed with metabolic syndrome.

Additionally, the risk of coronary artery disease (CAD) and other diseases related to plaque build-up in arterial walls, such as stroke and peripheral artery disease (PAD), are considerably increased in people suffering from a metabolic syndrome.

Attempting to address a more personalized approach for the management of this disease, some considerations should be concentrated first on diagnostic considerations. To date, there are no consensus criteria for diagnosing metabolic syndrome. The criteria proposed by the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), with minor modifications, are currently recommended and widely used. Nevertheless, a deeper understanding of the interaction of the broad spectrum of factors participating in this physiological disorder is crucially needed. Furthermore, the extended analysis of all of the information regarding these interpretations represents an important challenge. A more personalized criterion naturally claims an organized and formerly stratified appreciation of variations in genes and gene products, both at individual and regional levels. Such alterations in the associated proteins, as well as in the DNA and mRNA, can be studied by analyzing the pharmacokinetics and pharmacodynamics according to the metabolic cycles and the physiological variations of involved genes and proteins, without neglecting environmental aspects.

The market for CVD drugs is expected to contract significantly during the forecast period between 2010 and 2016. Despite being the most common disease category in North America with a patient incidence of more than 58 million, the impact of generics has been significant, causing the market to shrink. Although the overall market is expected to contract, there are high-growth segments within the market, such as anti-arrhythmics and vasodilators, which are likely to grow at above-market average growth rates.

Metabolic Diseases

The market for metabolic disease drugs is one of the fastest growing therapeutic markets as it is considered a lifestyle disorder, which is a major concern in both Western and emerging markets. There is significant interest in this space from all tiers of competition, including Big Pharma, specialty pharma, and niche/emerging pharma. Diabetes is the biggest segment within this market and is

expected to drive growth quite significantly.

Respiratory & Allergy Diseases

Respiratory and allergy are one of the fastest growing therapeutic areas, with a 3.3 percent share of North American market revenues in 2011. This is forecasted to increase to 3.8 percent by 2016. Within the respiratory and allergy field, chronic oppressive pulmonary disorder (COPD) is expected to be the fastest growing segment with significant interest from all competitive tiers of the pharmaceutical and biotechnology industry.

Other Therapeutic Areas

The prevalence of kidney diseases is increasing significantly, and the cost of treating these chronic diseases represents a leading threat to healthcare resources worldwide. The frequency of chronic kidney disease (CKD) continues to increase globally as does the prevalence of end-stage renal disease (ESRD). The most common, but not the only, causes of CKD are hypertension and diabetes. The presence of CKD is associated with a large increase in cardiovascular (CV) risk. Moreover, CV risk increases proportionally as eGFR falls below 60 mL per minute. Deaths from CV causes are eight-fold higher in CKD, much higher than death from cancer. Consequently, the identification and reduction of CKD has become a vital public health priority.

The reported prevalence of CKD stages 1 to 4 in the most recent National Health and Nutrition Examination Survey (NHANES) between 1999 and 2006 was 26 million (13 percent) out of approximately 200 million U.S. residents aged 20 and older. Of these, 65.3 percent had CKD stage 3 or 4.

The most recent report of the US Renal Data System estimates that nearly 500,000 patients in the U.S. were treated for ESRD in 2004. The elderly are a growing segment of the population and at increased risk for renal disease. Additionally, males and African Americans with pre-existing hypertension or diabetes and CKD are also at a much higher risk for ESRD. These observations have also been confirmed throughout the developed world: Europe, Asia, Australia, as well as in developing regions, such as China, India, and Africa.

Increasingly individualized approaches to renal disease treatment have been conducted under the focus of pharmacogenomics. In this regard, some polymorphysms of the angiotensin-converting enzyme (ACE), which inhibitors are considered to preserve native kidney function better than other antihypertensive drugs, have demonstrated more effectiveness in reducing proteinuria. Nonetheless, such studies have not shown really useful results. Therefore, more appropriately designed program studies need to be performed. On the other hand, regarding the management of type I primary hyperoxaluria, better approaches have been obtained, especially in procuring an early diagnosis of the condition. In the near future, it is expected that a large number of factors intervening in overall renal failure were examined under omics technologies, leading to a more personalized approach to medicine.

THE THERAPEUTIC MARKET

The overall growth rate for this market is determined by the individual growth rates of these therapeutic areas, some of which are expected to contract. Hence, the overall growth rate for this segment is lower than the market average. The influx of generics is having a major impact on several therapeutic areas, prompting companies to move focus to other potentially lucrative therapeutic areas. With Big Pharma moving toward biotechnology, high-growth opportunities are moving toward oncology and other specialty areas for underserved markets.

Despite the challenges faced by the market, outsourcing of clinical trials is driven by strong fundamentals. Even within markets dominated by generics, opportunities for Phase IV post-marketing studies exist. While the top five therapeutic areas represented 63.2 percent of clinical trials, the other therapeutic areas represented 36.8 percent in 2010. ◆

BIOGRAPHY

Cecilia E. Van Cauwenberghe is a Senior Research Analyst for Frost & Sullivan's Technical Insights practice. She has more than a decade of professional expertise in chemical and biomedical engineering arenas, which include R&D activities in several well-renowned universities and multinational companies. Ms. Van Cauwenberghe has particular expertise in leading and executing projects related to life sciences and biotechnology, healthcare and biomedical devices, biomedical and clinical engineering, and energy and geophysics. Before joining the Frost & Sullivan team in 2010, Ms. Van Cauwenberghe worked with Dr. Rene G. Favaloro Foundation University, South National University, Comahue National University as well as YPF S.A., The Techint Group and the National Institute of Industrial Technology (INTI).

Sheraton San Diego Hotel and Marina

San Diego

2012 AAPS National Biotechnology Conference

Advancing Health Through Innovations in Biotherapeutics

Call for Papers

May 21~23, 2012

CONTRIBUTED PAPERS SUBMISSION DEADLINE: JANUARY 25, 2012

www.aaps.org/nationalbiotech

CONTRACT SERVICES TRENDS

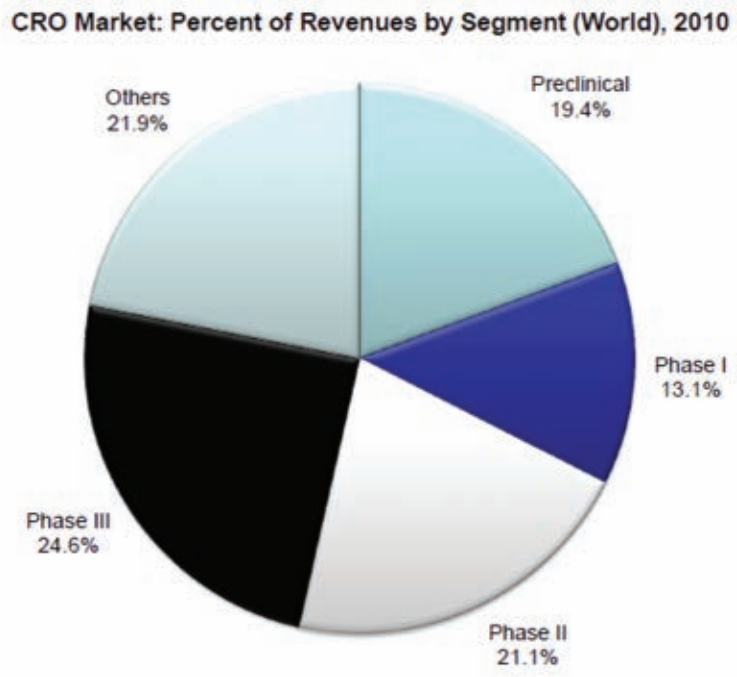
Contract Services: A Stronghold in Drug Development & Clinical Trials for Pharma & Biotech

By: Ipshita Chakraborty, MS, Industry Analyst, Technical Insights, Frost & Sullivan

INTRODUCTION

The biopharmaceutical industry, including both pharmaceutical entities and biotechnology products, has been experiencing diminishing R&D productivity. The situation has been almost paradoxical as R&D investment more than doubled throughout the past decade, while the number of approvals for new drug applications reduced significantly. This situation has made it challenging for companies to recover even their cost of capital for a typical biopharmaceutical portfolio. The response of the industry to such an occurrence has been visible in the form of a number of unique initiatives, in particular, outsourcing more R&D to increase the number of drug projects in the pipeline and thus enhancing the chances of getting a major new product to market. A quick observation of the numbers reveals that more than half of the late-stage clinical compounds are currently externally sourced. This has given rise to the strong role of contract services in drug development, particularly during the clinical development stages. Contract manufacturing organizations (CMOs) and contract research organizations (CROs) have become strongholds in drug development and clinical trials for pharma and biotech companies alike.

FIGURE 1



Global Distribution of CRO Revenues by Development Phase

How has the trend shifted toward a business model that works in collaboration with research services? A number of major changes in the drug discovery and development sector have led to the rise of contract services. The foremost reason is the aforementioned financial risk structure involved in drug development that has led pharmaceutical and biotech firms to restructure their portfolio investment options and externalize the clinical part of drug development to CROs. This trend picked up the most in 2007 when R&D spending in most companies was high and ranged between 7% to 8%. The economic crisis of 2009 has led to almost a cessation in R&D spending and growth, an

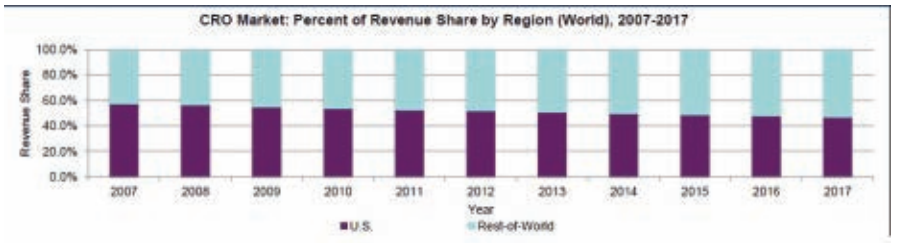
occurrence that has had a deep impact on contract services. Factors responsible for these spending cutbacks include large-scale M&A activities, company restructuring, and an ever-increasing rush to get closer to the market by concentrating on late-stage products. While this has been a boon in disguise for some CROs and CMOs, for those engaging in contract services during early development, such as preclinical and Phase I trials, it has been a sizeable setback. Figure 1 shows the percentage of revenue for CROs from each developmental phase on a global basis in 2010. Phase III takes the highest share at 24.6% as these are the candidates with the least time to market. Preclinical has the lowest share at 19.4% as it is the most preliminary stage.

Where then are the rising trends in the CRO and CMO businesses? In order to answer that question, it is first essential to understand the upcoming molecular entities that require CMOs for manufacturing or CROs to perform clinical research. The biotechnology sector has traditionally been one of the key base drivers of R&D and CRO business growth in the pharmaceutical industry. However, the economic downturn has affected it significantly, reducing funding from venture capitalists, credit, and partnering.

CONTRACT RESEARCH TRENDS

Contract research services have undergone some major changes in the past 10 years with the emergence of rapidly developing economies in Asia, where such organizations have sprung in high numbers. Outsourcing contract research services pertaining to clinical development or high-volume manufacture has been steadily shifting to countries like India and China. The associated overhead costs are much less in these countries, and clinical trials, particularly for infectious disease vaccines, are frequently carried out in these regions. Hence, it is more convenient to have a local CRO in charge of the clinical research procedures, such as manufacturing by cGMP standards, recruiting subjects for clinical trials, and collecting and interpreting data. Figure 2 illustrates this fact. It shows the revenue sharing among CROs in the US and the rest of the world. While CROs in the US had a higher share of the revenue in 2007, by 2017, this proportion will get reversed with the rest of the world contributing to a higher share in revenues compared to the US. The outsourcing model for Asian countries like India and China will gradually gain prominence, while others like Indonesia and Vietnam will also join this group.

FIGURE 2



Revenue Share of CROs in the US and the Rest of the World

A second vital factor that has witnessed some shifting trends is the development phase at which work is taken up by a CRO. Preclinical work was traditionally not something that was outsourced to a CRO as a number of drugs were made in collaboration with biotechnology companies or universities who could perform the required preclinical research. However, with the emergence of new molecular entities, such as peptide-based drugs, biosimilars, newer protein formulations, and nucleic acid-based drugs, it has become imperative to ensure safe pharmacological and toxicological profiles at earlier stages instead of waiting for the first phase of clinical trials to assess the safety profile of an active pharmaceutical ingredient (API). Therefore, another trend that has been predicted in this regard is that earlier phases of development, such as preclinical and Phase I, will also gradually move to the contract research domain. The chart in Figure 3 depicts this situation with preclinical occupying the lowest share of CRO revenues by development phase in 2007 at approximately $2 billion, but crosses the $5 billion mark by 2017. This corroborates the fact mentioned earlier that CROs will soon be engaged at an earlier stage of clinical research, particularly in developing and emerging economies.

In addition, there are also certain sectors in which contract research has completely shifted to particular regions; one such example is proteomics. Proteomics is the comprehensive analysis of the proteins in a cell, tissue, or organism, or more simply, a system. Exemplifying the practical term of system, proteomics is used in both narrow and broad senses. It is used with great precision to study specific pathways within a cell, or broadly, with the example of the Human Liver Proteome Project centered in China, to map every protein involved in the operation of the second most complex organ in the human body.

The growing interest in analyzing protein systems in a high level of detail has led to a focus on post translational modifications (PTMs), such as phosphorylation and redox changes of thiol groups. These PTMs allow a number of new categories of protein activities to be targeted with exquisite selectivity. The techniques being developed also have another tremendous benefit; they provide a new suite of tools for the rapidly emerging biosimilars market by allowing for a precision approach to quality control (QC). This rapidly growing market is forecasted to be $77 billion by 2012. Biosimilars, also termed as biogenerics or follow-on biologics, include monoclonal antibody type drugs and novel medications like insulin, beta interferon, G-CSF, and coagulation factors.

FIGURE 3

CRO Revenues by Development Phase from 2007-2017

CONTRACT MANUFACTURING PROMINENCE IN SOME SECTORS

A growing role for CROs in the protein analysis sector is to offer complete and independent molecular characterization. This ranges from verification of amino acid sequence to disulphide bridging and ratifying of PEGylation sites. Many techniques remain in their infancy in traditional analytical labs, whilst accredited facilities to test the feasibility of such techniques are extremely rare. Regulatory agencies, such as the FDA, are starting to realize the power of this new application of proteomics and are pressing for reliable mass spectrometry-based data. Regional testing authorities, such as the National Association of Testing Authorities of Australia and Asia Pacific Laboratory Accreditation Cooperation, are responding to this requirement, and it is probable that ISO/IEC 17025 laboratory standards will become an essential QC requirement for advanced proteomics facilities. The broadening interest in proteins as therapeutic and agri-biochemical targets, or as diagnostic markers, implies that projects are abundant in this space, and so are techniques for pursuing these projects. Although the collaboration type will display some novel features and there will be several trials and errors before the right balance is found, the engagement of researchers with contract service providers will ultimately ensure a faster path to the discovery of new proteins.

Contract research services for clinical research assistance have been a mainstay in the pharma industry. However, in recent years, the value chain model has changed with the focus shifting from just clinical development to an organization providing a comprehensive range of services from drug development to commercial manufacture. The use of contract services has therefore transitioned toward contract manufacturing and has undergone shifts in two aspects - novel molecular entities and high-volume research services. One sector that uses contract manufacturing heavily and advantageously is peptide therapeutics. A number of collaborating pharma companies have displayed a growing interest in peptide drugs and are working a great deal with peptide discovery companies. Consequently, the peptide ingredient market is also growing rapidly, and drug developers are asking custom manufacturers to make the newest generation of peptide drug candidates. Although these peptides are longer and more complex than earlier ones, technical improvements and economies of scale have made production faster and more cost effective. By harnessing multiple synthetic and recombinant techniques, contract manufacturers are helping turn peptides into affordable and effective drugs. According to Rodney Lax, the Senior Director of Business Development in North America at the PolyPeptide Group, which has operations in the US, Europe, and India, peptide manufacturing is substantially more expensive than manufacturing small molecules; however, it is still often less expensive than using recombinant procedures for quantities under 50 kg to 100 kg. Making a peptide for clinical trials using recombinant methods can be more expensive compared to synthesizing it using chemical synthesis.

A second sector in which contract manufacturing has become an ongoing trend is vaccine production. The vaccine industry is dominated by a number of interconnected factors, including global need, international alliances, cold storage chains, and vaccine technology used. A factor that has caused this shift of manufacturing trends in the vaccine industry is the participation of several pharmaceutical and biotechnology companies in this domain. Vaccines are being recognized as powerful tools in the defense of human health, with the human vaccines market projected at $100 billion by 2024. As these growth drivers continue to aid the growth of the vaccine market, more vaccine products (prophylactic and therapeutic) are under development now than for any other class of biological medicine. This brings up the natural question - what is the most reliable and cost-effective vaccine manufacturing method? An evaluation of all possible approaches seems to point to one optimized solution - outsource contract manufacturing.

Vaccines are possibly the most disparate of all biological medicines, and there are only a limited number of platform manufacturing methods applicable to distinct vaccines. In addition, there is not a sole expression system suitable for numerous vaccine candidates, and vaccine types range from relatively simple polypeptides to entire cells. It is essential that an expression system produces a product of consistent safety and quality, and that the yield of the production method is fully optimized, as cost-of-goods for vaccines is critically important, particularly for use in developing nations. The complexity of vaccines creates a unique set of challenges during process and product development. In this context, CMOs

may hold a key to economic production, although a developer has to be highly selective in choosing such an organization. Within a portfolio of vaccines, there may be a wide range of products, each requiring different production technologies, such as viral, microbial, and mammalian. Very few CMOs have the expertise and facilities required for all these technologies. This implies that vaccine developers must manage multiple vendors, relationships, and locations to progress development of their vaccine portfolio. In the development of monoclonal antibodies, stakeholders have the mutual confidence that a small-scale, in-house developed process can be transferred to a number of diverse CMOs for scaling up production. In contrast, vaccine developers will typically engage with CMOs earlier in development to negate the possibility of transfer issues at a later stage. In addition to specific manufacturing capabilities, it is necessary to find a CMO that can provide expertise in a range of ancillary functions, such as characterization and formulation, as described earlier. Outsourced inventory management of vaccines can also be challenging, as very few contract service providers have the capability to formulate and fill live bacterial or viral vaccines.

However, effective outsourced vaccine development is achievable as long as the right partners are chosen and the relationship is managed carefully. To take complete advantage of new technological advances and innovative strategic approaches that are now creating entry opportunity for small- and medium-size companies, vaccine developers must carefully evaluate CMOs and select only those who can provide expertise across a range of functions. Ideally, the CMO will be able to manage a wide range of products and different technologies, such as viral, microbial, and mammalian production, and also have the manufacturing facilities required for managing a diverse vaccine portfolio.

SUMMARY

Contract research and contract manufacturing services have both become mainstays of the life sciences industry. They form an essential part of the value chain for almost all drug sectors and are also making their way into diagnostics and research tools such as assays. Although major names in contract research in the US and Europe, such as ICON and Parexel, will still contribute to global CRO revenue shares, the market is already witnessing a shift as CROs and BioPharma firms in the Asia-Pacific region are headed for an exciting phase of growth in the coming decade. The outlook for the Asia-Pacific clinical and contract research outsourcing industry is optimistic, with R&D spending expected to post consistent growth throughout the next years to 2015. The Asia-Pacific CRO market for clinical services (excluding drug discovery) has been forecasted to grow at a compound annual growth rate (CAGR) of 20% to reach close to $2.5 billion by 2015.

In terms of development phase, preclinical toxicology will lead volume growth within the preclinical outsourcing market while pricing pressures are driving down actual profitability and revenue percentage growth. This can only be addressed with improved platform technologies that can reduce the development time. Specialty pharma and biotech sectors will lead the demand for contract services leading to improved capital market funding. Companies in these sectors typically lack the infrastructural ability or the production know-how to conduct Phase I trials or to manufacture their product according to cGMP practices. In addition, investors for these firms also look at any mitigating factors that can decrease their level of risk - contract research and manufacturing services provide that buffer. To conclude, contract services are here to stay and to grow further, albeit with certain paradigm shifts. ◆

BIOGRAPHY

Ipshita Chakraborty is an Industry Analyst for Frost & Sullivan's Technical Insights practice. Her research focuses on genetic technology, drug discovery, medical devices, medical diagnostics, and imaging. Ms. Chakraborty maintains engineering and consulting expertise, which includes tracking emerging technologies and trends, research and analysis for R&D portfolio and investment, and technology roadmap predictions. Prior to joining Frost & Sullivan in 2010, she led numerous projects and consulted for several leading firms, including National Instruments. She also has working experience in the test, measurement, and automation spaces with leading companies in government, public, and private sectors, such as GE, Department of Defense, Raytheon. She earned her MS in Biomedical Engineering and an MS in Computer Engineering from Vanderbilt University in Nashville, TN.

Advanced Drug Delivery Technologies: Enabling Drug Reformulations & New Administration Routes

By: Hermann AM Mucke, PhD, H.M. Pharma Consultancy

INTRODUCTION

Exciting developments are occurring in the field of alternative drug delivery - a phrase that describes the reformulation of drugs to enable lower doses, more convenient delivery routes, and treatment for additional therapeutic indications.

The pharmaceutical industry is in a long-lasting structural crisis that manifests as the collective corporate inability to close - or even narrow - the earnings gap that results from the aging of top revenue-generating drugs that lose patent protection. The industry's traditional business model, which relies on new molecular entities to feed the development pipeline and push a constant stream of new drug products into pharmaceutical markets that enthusiastically receive such improved products, is no longer working to a degree that could compensate for these losses. The estimated $49.4 billion that the US pharmaceutical industry alone invested in research in 2010 is generating insufficient returns.[1]

The numerous synergizing reasons for this critical development have been under scrutiny and discussion for years, but no obvious solution has emerged. Indeed, no easy solution for the "pharmaceutical productivity crisis" can be reasonably expected, because it actually is a crisis of the entire business environment and the way the industry responds to the scientific, regulatory, and political challenges of the changes in this environment. A new holistic business model is needed to drive the pharmaceutical industry's revenue, as well as medical progress, in the 21st century; however, its design and implementation is a continuous and integrated process, not a single dramatic event.

While this process is slowly beginning to take shape, the industry has turned its attention to aspects of innovation and business development that it has always employed on occasion, but not systematically exploited before. These involve finding new uses for known active ingredients, either by repurposing them to entirely new therapeutic fields, or by leveraging modern formulation technology to significantly improve their properties - sometimes to a point that could not be achieved by new chemical entities.

WHAT IS ALTERNATIVE DRUG DELIVERY?

The classical view held it to be an essential point that no form of drug delivery, however advanced, would involve chemical modifications to the active ingredients.

With the advent of newer technologies, this strict definition has meanwhile blurred considerably. While chemical modifications of the active ingredient molecular scaffold are still considered to transgress the realm of drug delivery, covalently attaching the molecules to much larger inactive structures (solid micro- and nanoparticles, dendrimers, or chemically activated liposomes) is now considered standard in drug delivery.

What then makes a drug delivery technology alternative? There are no unexploited, fundamental alternatives to the classical delivery routes (oral, injection/infusion, and transdermal). Alternative drug delivery is not so much about fundamentally different roads into the unknown that have not been taken before, but rather about new dimensions of the known routes that have been created by

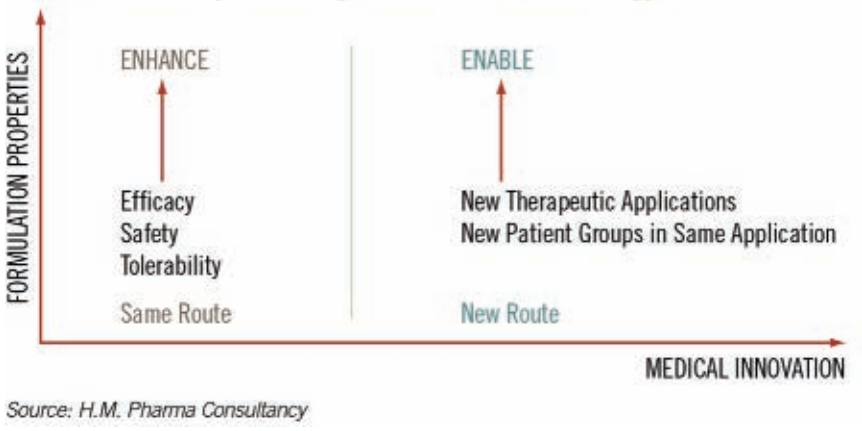
clever technical advancements. This does not imply these advances are merely incremental; disruptive innovation is possible and has already been achieved.

Progress in drug delivery technology happens in two dimensions: one that is specific to each known delivery route; and one in which new modalities overarch these known routes. From the medical application perspective, there are two classes: enhancing technologies (those that improve efficacy, safety, tolerability, and convenience/compliance) and enabling technologies (those that improve previously unacceptable drug parameters, such as solubility and bioavailability, to the point at which the use of a compound as a drug becomes feasible at all, or enable an extension of the treatable patient groups or even a new therapeutic application).

These dimensions are by no means mutually exclusive. Among the best examples for technologies that are both overarching and enhancing, as well as potentially enabling, are those that impart new physical properties to drugs by either scaling down particle size to the nanometer scale and/or by using nanostructures that are not simply grains or rods. This can achieve effects that cannot be accomplished by any other means. An example of a set of approaches that is more enhancing than enabling is the broad range of drug-targeting technologies.

FIGURE 1

Figure 1.1. Enhancement of Drug Properties vs. Enablement of New Routes and Therapies through Formulation Technology



Enhancement of Drug Properties Versus Enablement of New Routes & Therapies Through Formulation Technology (Source: H.M. Pharma Consultancy)

THE MARRIAGE OF DRUGS & DEVICES: REINVIGORATING OLD TECHNOLOGIES

Medical devices play an enabling role in drug delivery technology. The integration of drugs with advanced delivery devices has produced modalities of delivery that would be simply impossible with formulation technology alone. This sets the stage for the newest and most exciting drug delivery technologies to be applied within the drug-device combination framework.

For example, transdermal delivery technology is seeing an amazing resurgence. Active transdermal drug delivery systems that "push" their drug payload through the skin via various means, including microscopic needles, iontophoresis, ultrasound, or even suction, have become a topic of intense research and development. Medicated clothing is a peculiar emerging concept of advanced transdermal drug delivery, which calls for drug formulations that are retained in, on, or between the fibers of textiles that are used to tailor tight-fitting garments.

Vaginal drug delivery is an interesting new segment of transmucosal delivery with some potential for systemic delivery; a surprising amount of drug delivery technology investigation is taking place in this niche field.

NANOSCALE DRUG VEHICLES: REDEFINING DRUG DELIVERY TECHNOLOGY

The overarching importance of nanotechnology in all segments of drug delivery is hard to overestimate. Nanoparticles have such peculiar properties that they can almost be considered another state of matter. Nanomedicine is a hybrid discipline born from a combination of biology, medicine, and the science of nanomaterials, which includes applications, such as drug delivery but also those of materials sciences, which today are already impacting the development of medical devices. In 2008, the entire US demand for nanomedicine was forecast to expand 17% annually to $43 billion in 2012.

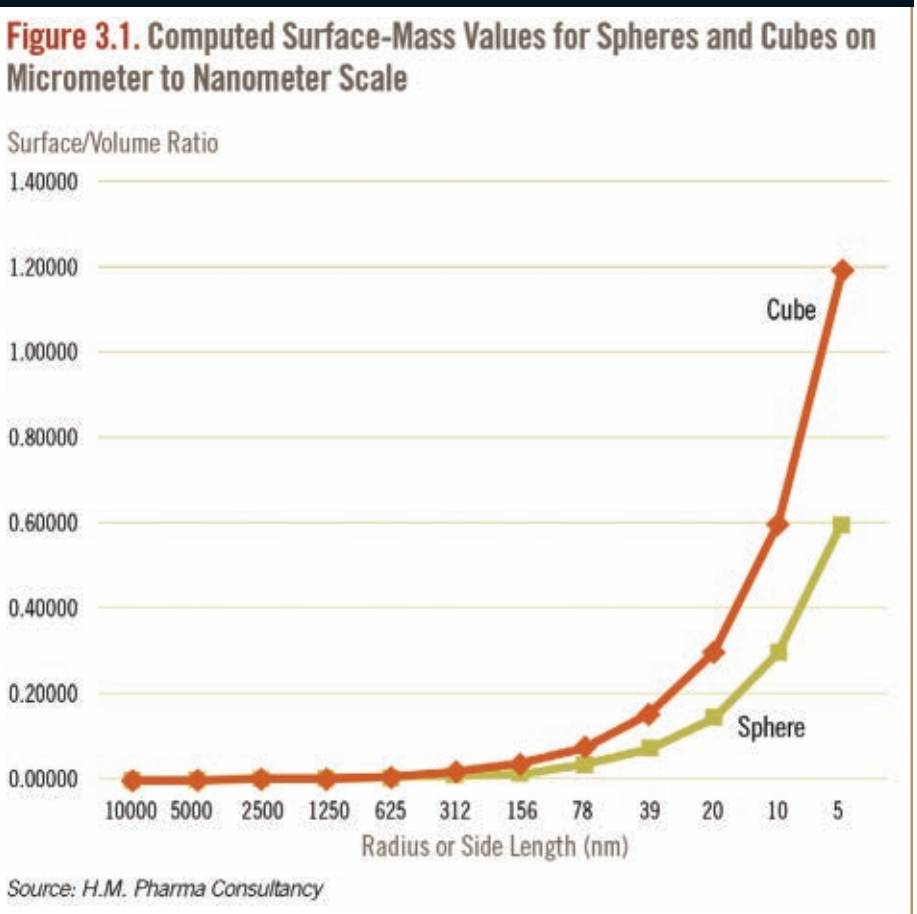
In contrast to the semi-intelligent "nanomachines" that are so often mentioned in popular writing, the drug-coated nanoparticles, the drug-encapsulating liposomes and nanotubes, and the tree-like dendrimers are already very much a medical reality. When combined with the appropriate targeting moieties, they enable organ and tissue targeting, most notably to malignant tumors.

These passive nanoscale structures are designed to exploit physical and chemical effects in the context of drugs and medical devices that become relevant only at the sub-micrometer scale. While some of these effects are attributable to the particles' extremely small size as such, others result from the vastly increased ratio of surface area to volume present in nanoscale particles and charge effects. Others are dependent on specific nanoscale shapes. Most importantly, nanostructures can be functionalized to act as vehicles that carry and deliver pharmaceutical cargos, their biological capabilities resulting from a combination of these peculiar physical properties.

ROLE OF ADVANCED DRUG DELIVERY IN ORGAN & TISSUE TARGETING

Actual anatomical barriers, which tend to exclude drugs from the space they enclose and protect, exist between the peripheral circulation and the brain and the retina as well as between

FIGURE 2



Computed Surface-Mass Values for Spheres & Cubes on Micrometer to Nanometer Scale (Source: H.M. Pharma Consultancy)

the outer environment and the eye; these barriers can be tricked into allowing entrance to properly formulated active ingredients that would normally be excluded. Several companies specialize in such barrier-penetration technologies. Even more important are the functional barriers that make it difficult for drugs to reach the bulk of tumor tissues. The prevention of growth of residual bacteria and accelerated healing of periodontal pockets is an interesting niche field of localized drug delivery.

Ongoing developments in targeted drug delivery illustrate the huge potential that alternative drug delivery carries for highly innovative, specialty pharmaceutical companies. Especially nanotechnology is an enabling tool that gives the term "value-enhanced generics" an entirely new meaning. It allows cancer chemotherapy drugs to achieve therapeutically effective concentrations at the tumor site, at doses that reduce the therapy-limiting side effects. The same is true for local antimicrobial therapy of periodontal disease, which cannot, of course, be compared to cancer, but is so extremely prevalent (and contributes to cardiovascular disease) that it is considered a huge disease burden nevertheless. Pharmacological therapy of sight-destroying retinal disease would be all but impossible without local drug delivery, although most of the drugs that are delivered this way are long-established generics. Drug delivery systems that advance the therapeutic utility of generics also offer elegant options for the original developers of an active ingredient to recoup more of their investment.

TECHNOLOGIES FOR PROTEIN & NUCLEIC ACID DELIVERY

Alternative delivery modalities for biotechnology-derived drugs are a particularly fascinating subject. The emerging market for biosimilars has added momentum to the drive for protein drugs that can be given non-invasively. Peptides, proteins, and antibodies were formerly administered solely by injection, but today, solutions for inhaled, transdermal, and even oral delivery are available or under investigation for most established products. While inhalable insulins have met rough conditions in their development (as well as [in a single case] on the market), promising developments are underway for vaccines and many other biotech products. Even in cases in which these maintain the injection delivery route, the actives have been massively improved in terms of shelf-life, biological half-life, and reduced immunogenicity.

Clearly, a non-parenteral route of administration will provide significant added value to a biogeneric and may allow the developer to price its products higher than the original…in other words, to make its version of the product into one that is analogous to a value-added small-molecule generic and that is sometimes called "biobetter" or "biosuperior."

Nucleic acid delivery technologies are not actually "alternative" but rather initially enabling for their novel cargoes, because unprotected or untargeted delivery of gene therapies or interfering RNAs is inconceivable. The full armamentarium of nanotechnology is unleashed in this emerging field, which mostly attends to cancer at present but has almost universal applicability.

ADVANCED DRUG DELIVERY & THE PRODUCT LIFECYCLE

Between 2012 and 2014, patent expiries will cause an estimated $140 billion in pharmaceutical sales to evaporate because original drugs will be rapidly replaced by corresponding generics, which are sold extensively and at much lower prices. Many industry indicators support the much-discussed notion that pharmaceutical innovation, as measured in new chemical entities that reach the market (and remain there long enough to recoup the investments made to get them there), is getting increasingly scarce. Definitely, new approaches are required to keep the pharmaceutical business model attractive.

Obviously the "better way" will have to consist of a mix of strategies, one of which is

to achieve higher return on investment on existing drug assets. Advanced drug delivery technologies can be leveraged to change the way known active ingredients are administered so that new therapeutic applications can be realized. Even if this is not possible, the market for a developed API can be expanded with new routes of administration that either increase its utility in existing therapeutic settings, or boost patient acceptance or compliance. Given the fact that a shift of a few percent in market share upward or downward could translate into hundreds of millions of dollars over an active ingredient's lifecycle, paying attention to innovative alternate drug delivery formats should be a very lucrative proposition for mature products.

Cleverly applied technologies can reinvigorate drugs that have already lost patent protection or that have not fully exploited their potential. Such efforts make sense only if patents can be obtained for the new products, which (though a specialist task) is neither as trivial nor as impossible as is frequently believed. Reformulation and new delivery paths for known compounds constitute a very significant fraction of all drug-related patenting. If a patent is obtained, and if a drug is marketed on this basis, the exclusivity for the drug franchise will effectively be extended to the new patent term even if the patents for the active ingredient itself and/or its use in the particular medical condition have expired, and the lifecycle will be longer.

SUMMARY & PERSPECTIVES

The Preprogrammed Rise of Alternative Drug Delivery seems an unavoidable development, driven by the fact that lifecycle management and recouping of value from existing resources will continue to rule the pharmaceutical industry's business throughout the 2010s. Given the fact that launching a new formulation of a marketed drug currently returns more than twice as much for each invested dollar as does a new chemical entity, it is unlikely that innovation in newly designed or discovered molecular entities, or the exploitation of new drug targets, could turn the tables on this situation within the present decade.

Using advanced drug delivery technology to intelligently reformulate marketed active ingredients is true innovation, but just as repurposing a drug for new therapeutic fields (a move that often requires reformulation), it is a different kind of innovation than the one which pharma has become accustomed to. As long as new chemical entity development was sufficiently rewarding from the global perspective, despite its high risk and long timelines, companies could focus on comparatively simple delivery modalities and on obvious applications and leave much of the remaining potential unexploited, and even unexplored.

Today, this is no longer an option. Drug repurposing and reformulation technologies can recoup such value from earlier investments in drug discovery and development, and reformulation can create entire new markets if the "old" active ingredient is now delivered in a way that addresses new patient strata. In the present environment for the industry, applying alternative delivery is essential to medical progress as well as to the economic sustainability of the pharmaceutical business model throughout the long period of restructuring that it will need in the years to come. Once an almost languishing field called "galenics," drug formulation is today a resurging and exciting field that will occupy more of our attention in the future. A recent report on advanced drug delivery technologies describes the options that new technologies in formulation have created (and continue to create), and explores the medical and commercial perspectives.[2] ◆

REFERENCES

1. Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2011 (Washington, DC: PhRMA, April 2011). Copyright © 2011 by the Pharmaceutical Research and Manufacturers of America.
2. Mucke, HAM. Advanced Drug Delivery Technologies: Enabling Drug Reformulations and Administration Routes (Needham, MA: Insight Pharma Reports, January 2011). Copyright © 2011 by Cambridge Healthtech Institute (CHI).

BIOGRAPHY

Dr. Hermann AM Mucke spent 17 years in academia and industry before he founded H.M. Pharma Consultancy (www.hmpharmacon.com) in 2000 to become an independent pharmaceutical consultant, analyst, and science author. His last industry position was Vice President R&D in a European pharmaceutical company, which he helped to take public on the Frankfurt Stock Exchange in 1999. Since then, Dr. Mucke, who earned his PhD in Biochemistry from the University of Vienna (Austria), has become a consultant and advisory board member for several European and American pharmaceutical companies and a regular reviewer of drugs and patents for Thomson Reuters Scientific and the Future Science Group. Dr. Mucke is based in Vienna.

16TH ANNUAL

DRUG DELIVERY PARTNERSHIPS™

Visionaries meet. Challenges are overcome. Innovation happens.

HEALTHCARE

Mark McClellan
Former CMS Administrator and Commissioner, US FDA

GLOBALIZATION

G. Steven Burrill
CEO, Burill & Company

INNOVATION

Marc Koska
Inventor and Philanthropist

Hear from Prominent Innovators and First Time DDP Speakers

New Value Proposition for Drug Development

John Baldoni
SVP, Platform Technology & Science, GSK PHARMACEUTICALS

R&D Budget Cuts and the Effect on Drug Delivery Partnering

David Nicholson, PhD
SVP and Head, Worldwide Licensing & Knowledge Management, MERCK

Uncover Emerging Market Opportunities

Chris Jones
VP and Global Head, Pharmaceutical Development, ASTRAZENECA

Overcome Barriers to Commercialize Products Overseas

Christopher Seaton
SVP, Global Licensing, BAYER PHARMACEUTICALS

Drug Delivery Devices as a Growth Mechanism

Beth Hill, PhD
Global Development Director, JANSSEN PHARMACEUTICALS

Bring Formulation into the Delivery Partnership Strategy

Michael Kaufman
VP, Pharmaceutical Sciences, MILLENNIUM PHARMACEUTICALS

The largest global drug delivery event accelerating drugs to market and lengthening lifecycles through:

NEW drug delivery technologies

NEW formulation strategies

NEW partners

Be a Part of the **NEW** Drug Delivery Partnerships Experience

- **10+ Hours of Networking** with **500+ Industry Professionals** before, during and after the conference with our expanded partnering tool and at the conference in the DDP Hall
- **6 NEW Symposia**, featuring **Three Full Day Events** including, "Manage Macromolecule Challenges to Deliver a Robust Biologic Product" and "Maximize the Potential of your Drug Delivery System through Drug Delivery Device Combination Products
- **80+ Speakers** including **40 NEW** DDP speakers
- **40+ Technology Presenters** with the latest drug delivery technology innovations

25% off the standard rate
That's up to $798 off!
Please register with VIP Code
XP1778DDD

JANUARY 25-27, 2012
CAESARS PALACE , LAS VEGAS, NV
www.drugdeliverypartnerships.com

AAIPHARMA SERVICES

Your project. Our passion.

OVERVIEW OF SERVICES

aaipharma.com
services@aaipharma.com
1.800.575.4224

DRUG DEVELOPMENT

Analytical Chemistry

Assuring robust methods that can be transferred throughout the world

- Analytics for Small Molecules
- Assay of Biopharmaceuticals/Biotechnology Products
- Physical Chemistry and Material Characterization
- Stability Storage and Analysis
- Compendial Raw Materials Testing

Formulation Services

Proven know-how and timeliness for every development project

- More than 300 compounds formulated over 30-plus years have gone to clinical trial
- Solid Oral Dosage Form Development
- Injectable (both Liquid and Lyophilized) Formulation Development
- Proprietary Oral Drug Delivery Technologies

Highlights:

- Formulations to improve pharmacokinetics
- Meeting or beating development timelines by as much as 10%; lowering costs by as much as 20%
- Online Services system for compendial raw materials testing, with release in 10 business days or less
- 5,000 square foot stability testing facility with full ICH and custom conditions
- Strong compliance record and excellent audit history

MANUFACTURING & PACKAGING

Manufacturing Services

cGMP facilities for solid dose and sterile drug products

SOLID DOSE:

- Capsules and Tablets in Batch Sizes from 200g of API to Large-scale 650Kg
- Potent Compound Manufacturing and Difficult-to-make Products
- Dry Blends, Roller Compaction, Wet Granulation (Low/High Shear and Spray), Film Coating, Tablet and Capsule Manufacturing
- Flex Suites for Novel Manufacturing Processes

PARENTERAL:

- Sterile Products for Small Molecules and Biologics, including Proteins, Peptides, Monoclonal Antibodies, and Other Large Molecules
- Batch Sizes from 200mL up to 340L
- Terminal Sterilization, Lyophilization and Aseptic Manufacturing/Filling

Highlights:

- MHRA to EMA compliant facilities
- More than 670 clinical/commercial solid dose batches and 384 sterile fills produced in the last four years
- Powder-in-Capsule using Xcelodose® 600S and powder in bottle using Autodose™
- Monthly parenteral manufacturing of more than 50,000 units in mixed sizes
- DEA compliant for controlled substances
- Distribution to clinical trials anywhere in the world

Packaging Services

Automated packaging lines for clinical and commercial; manual for custom configurations. Manual packaging for custom configurations

- Custom Packaging, Labeling and Kitting for Clinical Trial Supplies
- Special Packaging Needs – square bottles, blisters, cartons, vials, ancillary supplies, concomitant medications, cases and cachets
- Temperature and Humidity controlled Storage
- Temperature Monitoring and Validated Shipment Configurations

SUPPORT SERVICES

Our in-house expertise in Regulatory Affairs and Quality Assurance can support your projects, inspections and filings

- Quality Assurance
- Regulatory Affairs
- Stability Management

Aveva Drug Delivery Systems, Inc.
3250 Commerce Parkway
Miramar, FL 33025
T: (954) 430-3340 F: (954) 430-3390
Website: www.avevadds.com
Contact email: Robert.bloder@avevadds.com

Aveva Drug Delivery Systems, a Nitto Denko company with revenues in excess of $6.4 billion, is one of the world's largest manufacturers of, and a pioneer in, transdermal drug delivery systems. Nitto Denko has a 40-year history of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs or are high-quality, low-cost brand equivalents. Leveraging this experience, Aveva offers a full range of research, development, and manufacturing capabilities using a number of sophisticated technologies to produce proprietary and generic transdermal drug delivery systems.

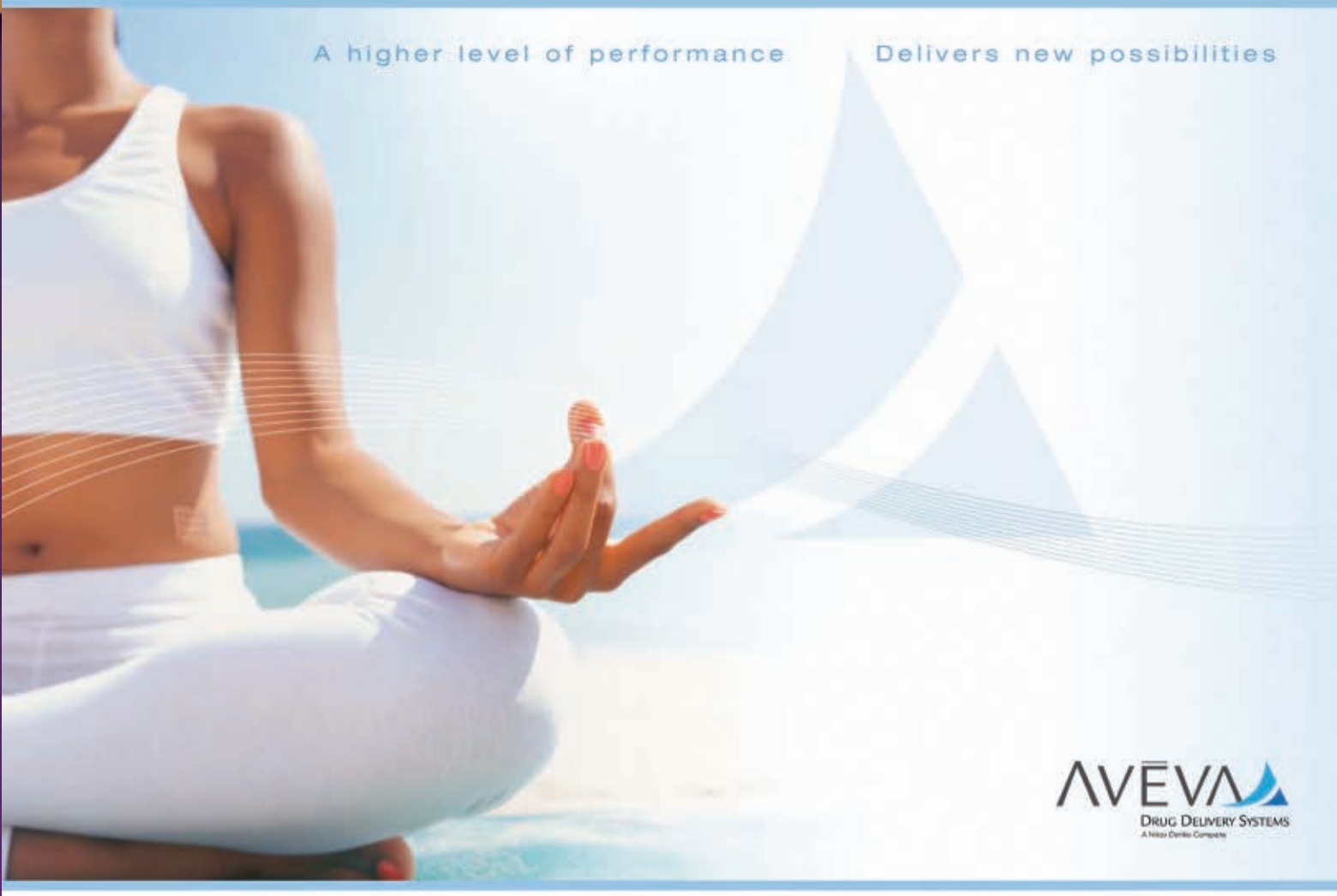
Aveva offers:
- Global licenses for Aveva's approved products and development pipeline
- Transdermal candidate assessments of APIs in as little as 4 weeks
- Extensive expertise in polymer synthesis and adhesive formulation technologies
- A full range of research, development, and manufacturing capabilities
- Creative solutions & sophisticated technologies to overcome formulation challenges

Proprietary Gel Matrix Adhesive Technology

Aveva DDS and Nitto Denko have produced the first and only marketed transdermal patch using a revolutionary Gel Matrix adhesive system for an unequaled balance of adhesion reliability and gentleness. Because the Gel Matrix adhesive minimizes the disruption of the stratum corneum (skin) during removal, these patches can be removed and reapplied with minimal skin irritation, resulting in a desirable patient experience. This technology also contributes to increased patient compliance and enhanced persistency, which are critical for patients with chronic conditions.

NITTO DENKO

TRANSDERMAL TRANSCENDENCE



That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

As one of the world's largest manufacturers of transdermal patches offering a full range of research, development and manufacturing capabilities, Aveva transcends traditional limitations of patch technology and business partnerships to achieve new levels of product and corporate performance.

- Customizing solutions to the unique characteristics of each drug
- Masterfully balancing the patch properties of adhesion reliability and gentleness that lead to an enhanced patient experience.
- Managing a higher drug concentration in a smaller patch

A flexible, customer-oriented business philosophy that adds value to projects and exceeds customer expectations.

To license a product or to see how we can add value to your project, call Robert J. Bloder, Vice President Business Development, at **954.624.1374** or visit **www.AvevaDDS.com**

NITTO DENKO GROUP

Company Profile

Baxter Healthcare Corporation
25212 W. Illinois Route 120
Round Lake, IL 60073
US: 1-800-4-BAXTER International: 1-847-948-4779
F: 1-847-948-4770 E: biopharmasolutions@baxter.com
Website: www.baxterbiopharmasolutions.com

BioPharma Solutions

The Promise of Science Realized

BioPharma Solutions, a business unit of Baxter, partners with pharmaceutical companies to support your commercialization objectives by providing scientific expertise, sterile manufacturing solutions, parenteral delivery systems, and customized support services needed to meet the unique challenges that parenteral products face.

Experience Makes the Difference. With 80 years of parenteral expertise, we can help to navigate the pathway of success for your molecule. Our long-standing history puts unique expertise at your fingertips.

We Understand Parenterals. As a parenterals specialist, BioPharma Solutions offers unique delivery systems and a wide variety of manufacturing solutions to meet complex and traditional sterile manufacturing challenges. In addition, we offer a broad spectrum of support services including formulation and development to help solve the high-stakes challenges in today's complex parenteral marketplace. Our areas of expertise include:





Parenteral Delivery Systems
- -Powder Filled Vials
- -Sterile Crystallization
- -Prefilled Syringes
- -Liquid Vials
- -Lyophilized Vials
- -Cartridges
- -Frozen Premix Systems
- -Liquid Premix Systems
- -BIO-SET Luer System
- -Diluents for Reconstitution
- -Ampoules

Drug Categories
- -Small Molecules
- -Biologics; including Monoclonal Antibodies & Therapeutic Proteins
- -Vaccines; both Adjuvant & Conjugate
- -Cytotoxics
- -Antibody-Drug Conjugates (ADCs)
- -Highly Potent Compounds
- -Cephalosporins/Penicillins

Extensive Network. With more than 50 manufacturing facilities across six continents, Baxter's global presence provides opportunities for unique manufacturing collaborations to provide the most value for our partners. The power of an extensive global network lies in the coordination of, and efficiencies resulting from, a systemic approach to cGMP manufacturing.

We Take Partnering Seriously. As a partner to over 60 pharmaceutical clients, we realize that successful alliances are critical in this extremely competitive environment. BioPharma Solutions has developed strong organizational capabilities to ensure our partnership provides the value you deserve and expect. Because of this we have been honored with various global distinctions by the industry including "Best Contract Manufacturing Organization" at the Vaccine Industry Excellence Awards and European Outsourcing Award winner for Most Effective Scale-up/Technical Transfer, to name a few.

Ultimately, our goal is to make you feel confident and secure choosing BioPharmaSolutions as a partner - helping you to avoid the unexpected and guiding you through marketplace complexities so you can achieve the full potential of your molecule.

BioPharma Solutions provides our clients with confidence of delivery, service, and integrity - we know the work we do is ultimately vital to the patients you serve.

Baxter

BioPharma Solutions

The Promise of Science Formulated

Experience Makes the Difference

With 80 years of parenteral expertise, we can help to navigate the pathway of success for your molecule. We can help you overcome technical challenges, including process and formulation development, technology transfer, and analytical methods development. Our scientific teams are skilled in the development of solutions, suspensions, and freeze-dried dosage forms to help optimize product quality throughout manufacturing. BioPharma Solutions provides our clients with confidence of delivery, service, and integrity—we know the work we do is ultimately **vital to the patients you serve.**

For more information, visit
baxterbiopharmasolutions.com
or email us at
biopharmasolutions@baxter.com

Baxter

About Cambridge Healthtech Institute

www.chicorporate.com

Cambridge Healthtech Institute (CHI) is the preeminent life science network for leading researchers and business experts from top pharmaceutical, biotech and academic organizations. CHI's portfolio of products includes Cambridge Healthtech Institute Conferences, Insight Pharma Reports, Cambridge Marketing Consultants, Barnett Educational Services, Cambridge Meeting Planners and Cambridge Healthtech's Media Group, which includes numerous e-newsletters as well as Bio-IT World magazine.

Founded in 1992, Cambridge Healthtech Institute strives to develop quality information sources that provide valuable new insights and competing points of view while offering balanced coverage of the latest developments. Basic research related to commercial implications is covered, with heavy emphasis placed on end-user insights into new products and technology as well as coverage on the strategy behind the business.

About Insight Pharma Reports

www.insightpharmareports.com

CHI's Insight Pharma Reports are written by experts who collaborate with CHI to provide a series of reports that evaluate the salient trends in pharmaceutical technology, business, and therapy markets. Insight Pharma Reports are used by senior decision makers at life sciences companies to keep abreast of the latest advances in pharmaceutical R&D, their potential applications and business impacts. Our clients include the top 50 pharmaceutical companies, top 100 biotechnology companies, and top 100 vendors of life science products and services. Typical purchasers are managers, directors, and VPs in business development, discovery research, clinical development, strategic planning, portfolio management, new product planning, and marketing.

Cambridge Healthtech Media Group

www.chimediagroup.com

Cambridge Healthtech Media Group's suite of published resources include: Bio-IT World Magazine — CHI's flagship publication, three topic-specific eNewsletters, and three web sites focusing on the life sciences industry. These media offerings provide advertisers like you, an additional means to reach a core audience from pharmaceutical, biotechnology, academic, and niche provider organizations involved in early discovery techniques to clinical trials through personalized medicine. With over 100 conferences held throughout the U.S. each year, a leading publication aimed at the life sciences industry, online opportunities including web advertising and topic-specific eNewsletters, as well as list rental and broadcast services, CHI is poised to be the number one multi-media resource to reach your buying audience.

About Barnett International

www.barnettinternational.com

Founded in 1979, Barnett International is widely recognized for its superior consulting services and its targeted education and training programs. Barnett helps clients get the most out of their research and development dollars by managing change effectively, improving organizational performance, and enhancing staff knowledge. The Barnett approach is a unique combination of strategy development and practical, hands-on implementation. The "Barnett Difference" is evident in our deep understanding of the clinical research process and in the rapid and tangible performance improvements we deliver.

We help pharmaceutical, biotechnology and medical device companies maximize the speed and quality of their product development efforts. With an international presence and many staff members working from the client site for increased benefits, Barnett is able to apply a global expertise to its projects. Barnett International was acquired by Cambridge Healthtech Institute in April of 2008.

About Cambridge Healthtech Associates and the Drug Safety Executive Council

www.chacorporate.com

CHA is the leading organizer of consortia in life sciences. CHA reduces the costs of R&D by bringing companies together to work cooperatively. The Technology Evaluation Consortium determines the scientific utility of predictive safety technologies by leveraging the expertise of biopharmaceutical companies. CHA also manages DSEC, an online, peer membership of over 2,000 drug safety leaders. Learn more at www.chacorporate.com and www.drugsafetycouncil.org. CHA is a wholly owned by Cambridge Healthtech Institute (CHI).

Life Science Reports You Can Rely On

An Essential Collection of Timely & Concise Reports Analyzing the Technologies, Markets, and Strategic Issues Driving R&D Productivity

For more info & to order: InsightPharmaReports.com

Insight Pharma Reports *a division of Cambridge Healthtech Institute*
250 First Ave., Suite 300, Needham, MA 02494
T: 781-972-5400 Toll-free in the U.S. 888-999-6288 F: 781-972-5425

Catalent Pharma Solutions
14 Schoolhouse Road
Somerset, NJ 08873
T: (866) 720-3148
Email: info@catalent.com

Catalyst + Talent. Our name combines these ideas. From drug and biologic development services to delivery technologies to supply solutions, we are the catalyst for your success. With over 75 years of experience, we have the deepest expertise, the broadest offerings, and the most innovative technologies to help you get more molecules to market faster, enhance product performance, and provide superior, reliable manufacturing and packaging results.

We serve thousands of innovators, large and small, in over 100 markets, including 44 of the top 50 biotech companies and 90 of the top 100 pharmaceutical companies. Our team of over 1,000 talented scientists supports 40% of recent new drug approvals, and our 20+ global sites make or package over 100 billion units annually. Our significant intellectual property includes over 1,200 patents and patent applications.

Whether you are looking for a single, tailored solution or multiple answers throughout your product's lifecycle, we can improve the total value of your treatments - from discovery to market and beyond.

Catalent. More products. Better treatments. Reliably supplied.™

Development

With our broad range of expert services - including analytical, biologics, preformulation, and formulation - we drive faster, more efficient development timelines and produce better products. Our robust GPEx® mammalian cell line engineering technology accelerates large molecule drugs from discovery to clinic, and our unique Optiform™ technology ensures maximum API optimization. With our deep expertise and our extensive formulation capabilities in oral dose forms, controlled release, inhaled dose forms, and softgel technologies, we can solve even the most complex bioavailability, solubility, and permeability challenges.

Delivery

We are a world leader in drug delivery solutions with a proven track record of helping our customers create better treatments by boosting bioavailability, solubility, and permeability; improving ease and route of administration; and increasing patient compliance. Our unique delivery technologies - including softgel solutions, Liqui-Gels® capsules and Vegicaps® capsules, Zydis® and Lyopan® fast-dissolve, controlled release, including OSDrC® Optidose™ optimized dose delivery, and inhaled dose forms - improve how products work in and for patients.

Supply

As a seamless extension of your supply chain, we have the technology and expertise to offer global, integrated manufacturing and packaging solutions to take your product from design, to clinical trial, to plant, and to pharmacy. We manufacture oral, sterile, and inhaled dose forms, produce biologics for preclinical and clinical studies, and are the recognized leader in both biotechnology product packaging and the design and development of proprietary innovations, such as the RxBarrier+™ compliance package and DelPouch® technology. As the largest provider of packaging services to the pharmaceutical industry, we are globally positioned to serve all your commercial packaging needs.

Catalent®

CATALENT TO BECOME #2 GLOBAL CLINICAL SUPPLY LEADER WITH PENDING APTUIT CTS ACQUISITION

more products to market faster.

We have the advanced technologies and broad drug development expertise to solve even the most complex challenges, and drive faster timelines with lower risk.

OPTIMAL API SCREENING

With our proven Optiform™ technology, we can help you find optimal solid forms and solve your bioavailability and delivery challenges.

BROADER DEVELOPMENT EXPERTISE

Our broad range of services, including formulation, analytical, and regulatory expertise, helps ensure better product filing and in-market success.

IDEAL DOSE FORM CREATION

With dose forms from oral and parenterals to biologic and inhalation, we provide optimal delivery and route of administration selection, feasibility, development, scale up, and supply.

ADVANCED BIOLOGIC SOLUTIONS

Our proprietary GPEx® technology creates stable, high-yielding mammalian cell lines with high speed and efficiency to take you from gene to clinic in one-third the time of traditional approaches.

Every molecule has a challenge.
We have a solution.

Call: + 1 888 SOLUTION
Email: solutions@catalent.com
Visit: www.catalent.com

DEVELOPMENT DELIVERY SUPPLY

The Conference Forum
445 Park Avenue, 9th floor
New York, NY 10022
Tel: 646-350-2580
Fax: 917-463-1047
Email: service@theconference.org
www.theconferenceforum.org

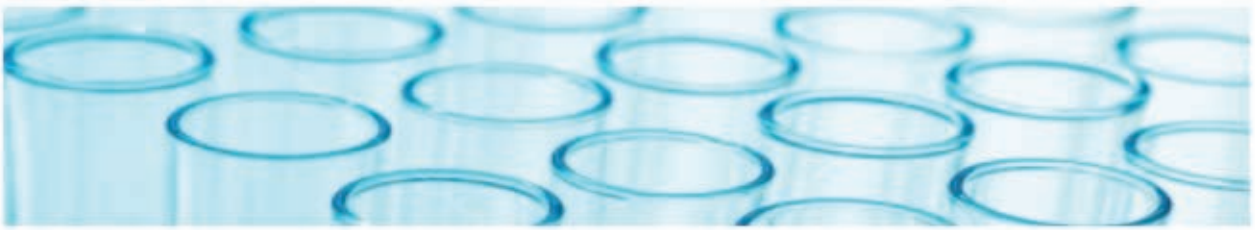
Setting new standards in information exchange for the pharmaceutical, biotech & drug delivery industry

The Conference Forum has a very specific focus - developing specialized events for professionals in the life science industry. Our mission is to create the best content in an ideal forum for the exchange of ideas among peers and networking for pharmaceutical and biotech professionals.

This new standard in information exchange is based on the quality of our research and our exceptional service. Our research team concentrates fully on in-depth market analysis to uncover the most relevant issues in the industry. Led by our Conference Research Director with more than 17 years of experience, our research team combines its detailed findings with penetrative insight from our Advisory Boards to create events that surpass industry expectations.

Quality research and information are the result of our commitment to providing outstanding service to our customers. Our job is to make you more successful in advancing drug development to enhance health and economic outcomes. We listen very carefully to the market, attendees, speakers and sponsors to ensure we continually improve our customer, networking and format experiences.

To suggest new topic areas or educational formats you would like to see us cover, please email us at Customer Service or call 646-350-2580.



VISIT WWW.THECONFERENCEFORUM.ORG OR CALL 646-350-2580

New Paradigms to Fund & Manage Product Development for Biotech, Drug Delivery & Small Pharma

New Models for New Times

January 13 - 14, 2011 San Francisco, CA

Co-Sponsors: CHI California Healthcare Institute; BAYBIO

Organized by: THEconferenceFORUM

Media Partner: Drug Delivery Technology

2011 Speaking Faculty as of 10/20/10

Co-Chair

Sandra Garrett, PhD, Executive Chair, **Global Research Services**

Co-Chair

Peter Milner, MD, FACC, Co-Founder, **CV Therapeutics, ARYx Therapeutics, and Optivia Biotechnology**

Speakers

Larry Atkins, Executive Director, US Public Policy, **Merck**

Safi Bahcall, PhD, Co-Founder & CEO, **Synta**

Karen Bernstein, PhD, Editor in Chief, **BioCentury**

George W Bickerstaff, Managing Director, **CRT Investment Banking**

Hans Bishop, Executive Vice President and COO, **Dendreon**

Rikki Bouchard, President, **RH Bouchard & Associates**

Gavin Choy, Vice President, Clinical Operations, **Supergen**

Xiangmin (Min) Cui, PhD, Bay City Capital

Rajeev Dadoo, PhD, Partner, **SR One**

Barbara Dalton, PhD, Vice President of Venture Capital, **Pfizer**

Kurt von Emster, CFA, Partner, **venBio LLC**

David Flores, CEO, **BioCentury**

Christopher Gallen, MD, PhD, Executive Vice President, R&D, **Zalicus**

Alan Garber, MD, PhD, Henry J. Kaiser Jr. Professor, **Stanford University**

David Gollaher, PhD, President and CEO, **California Healthcare Institute**

Yong Huang, PhD, Founder, President & CEO, **Optivia Biotechnology**

Barclay Kamb, Partner, **Cooley Godward Kronish LLP**

Frank Karbe, CFO, **Exelixis**

M. Ken Kengatharan, PhD, President and Chief Scientific Officer, **Altheos, Inc**

Lori Kunkel, MD, Principal, **Clinical Consultant**

Tracy Lefteroff, Global Managing Partner, **PWC**

John Lewis, Vice President, Public Policy, **ACRO**

James Li, MD, Kleiner Perkins

Bill Lis, CEO, **Portola Pharmaceuticals, Inc.**

Doug Malinowski, PhD, VP and Chief Scientific Officer, **BD Diagnostics TriPath**

Sean Na, former CEO, **NSpine**

Howard Palefsky, Partner, **Montreux**

Stephen Parker, PhD, Partner, **Celtic Pharma Holdings**

Rich Pascoe, President and CEO, **Somaxon Pharmaceuticals**

Doug Peddicord, PhD, Executive Director, **ACRO**

Dennis Purcell, Senior Managing Partner, **Aisling Capital**

Lori Rafield, PhD, LFR Advisors, former Partner, **APAX**

Greg Rossi, Vice President Global Pricing and Payer Strategy, **Genentech**

Greg Scott, Founder, **China Bio Investor**

David Shlaes, MD, PhD, President, **Anti-Infectives Consulting, LLC**

Daniel Spiegelman, previously CFO, **CV Therapeutics**

Bob Temple, MD, Director of the Office of Medical Policy, **CDER, FDA** (invited)

Bernice Welles, MD, CEO, **Alquest Therapeutics**

Travis Wilson, Morningside Group and CEO, **Stealth Peptides, Inc**

Fred Zheng, PhD, Research Scientist, Clinical Biomarker Group, Oncology Early Development, **AstraZeneca**

Wei Zhou, PhD, JD, President and CEO, **Centrillion**

Zhenping Zhu, MD, PhD, EVP, Global Biologics R&D, **Kadmon Pharmaceuticals,** President & CEO, **Kadmon China**

TO REGISTER, VISIT WWW.THECONFERENCEFORUM.ORG OR CALL 646-350-2580

25% Discount for Drug Delivery Technology Readers with Code DDTNP

Dow Pharmaceutical Sciences
Our Focus - Your Success
Since 1977

Dow Pharmaceutical Sciences
1330 Redwood Way
Petaluma, CA 94954-7121
T: (707) 793-2600 F: (707) 793-0145
E: vwaters@dowpharmsci.com
Website: www.dowpharmsci.com

Vital Statistics
Year founded: 1977
Number of Employees: 140

Who We Are
Our Focus - Your Success. Topical product development has been Dow Pharmaceutical Sciences' successful focus for more than 33 years. Dow helps clients with early feasibility studies through proof-of-concept in man and on to NDA. Over one third of all topical prescription dermatological products approved by the FDA from 2005 to 2010 were developed by Dow.

Dow provides a full range of product development services for pharmaceutical and biotechnology clients in the dermatologic, ophthalmic, women's health, topical pain, and topical anti-infectives arenas. Services include formulation development, in vitro tissue penetration studies, analytical services, regulatory strategy and submissions, and GMP clinical manufacturing and labeling.

Major Markets
Dow Pharmaceutical Sciences provides contract development services and clinical manufacturing, both sterile and non-sterile, to the pharmaceutical and biotechnology industries. We develop topical products for a wide variety of clients from around the world, from large multinational pharmaceutical companies to a "three men and a molecule" biotech start-up. Of the 30 topical product NDAs approved by the FDA in from 2005 to 2010, Dow developed the formulations for 11. By working with Dow, you gain access to this expertise, and increase your chance of success.

Services Offered
- Topical Product Consulting
- Topical Formulation Development
- In Vitro Drug Permeation & Penetration Testing
- Analytical Services
- Clinical Manufacturing (sterile & non-sterile)
- Clinical Supplies & Non-Clinical Supplies
- Clinical Labeling, Packaging & Worldwide Distribution
- Regulatory & Clinical Affairs
- e-Publishing Services
- Non-Clinical Services

Dow Pharmaceutical Sciences

Our Focus—Your Success

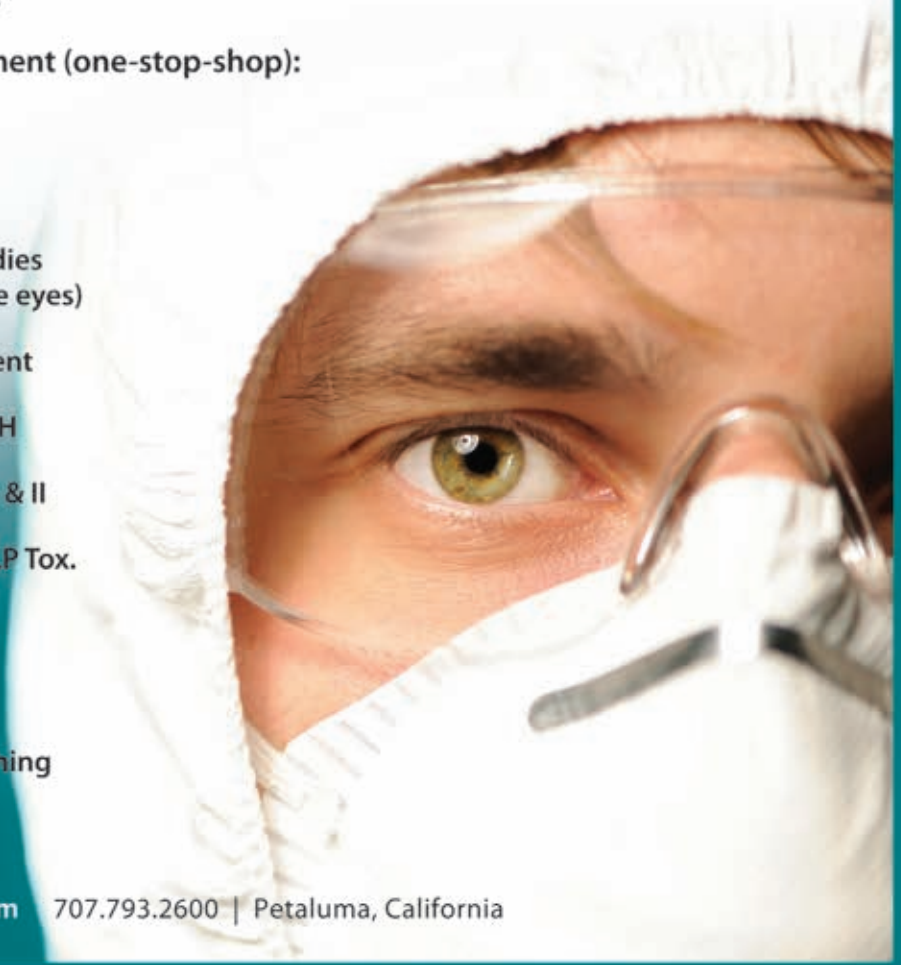
Since 1977

NEW Sterile Services!

Our Focus Your Success

Dow can offer you the following services for the production of sterile products

- Vials, and bottle filling; aseptic and terminally sterilized
- Solutions, suspensions, emulsions, ointments & gels
- Drug device combinations that may require aseptic assembly and filling
- Scale-up to pilot scale
- Tech transfer to CMO of choice
- Ophthalmic product development (one-stop-shop):
  - Pre-formulation
  - Formulation development
  - *In vitro* ocular penetration studies (using pristine newborn bovine eyes)
  - Analytical method mevelopment
  - Stability testing/studies per ICH
  - Clinical supplies – Mfg. Phase I & II
  - Non-clinical supplies – Mfg. GLP Tox.
  - Clinical labeling, packaging & global distribution
  - Regulatory affairs, nonclinical services & e-publishing



www.dowpharmsci.com 707.793.2600 | Petaluma, California

Company Profile

DPT Laboratories
318 McCullough Ave.
San Antonio, TX 78215
T: (210) 476-8100 F: (210) 829-8733
Web Site: www.dptlabs.com

Company Background: Date Founded: 1938
Number of Employees: 1,000

Company Description: With a specialized focus on semi-solids and liquids, DPT offers pharmaceutical companies the broadest range of capabilities in the industry. From R&D formulation to commercial-scale manufacturing, small batches to large, liquids to emulsions, cans to pumps, sterile or non-sterile, we offer clients of all sizes the most effective resources for meeting challenges.

And since semi-solids and liquids are the only thing we do, we have an unmatched level of scientific and engineering expertise - particularly when it comes to tackling unique projects and overcoming development and manufacturing challenges - and a good track record with the FDA. We also have a very stable employee base, giving us a wealth of institutional knowledge and the ability to be responsive to client requirements.

Whether you're a start-up operation or Big Pharma, we can take your project all the way from lab to production.

Just as important, we continue to invest heavily in our capabilities, including centers specializing in semi-solid and liquid manufacturing, aseptic manufacturing and R&D.

Our focused approach and extensive experience makes our operations extremely efficient, and gives us the foresight to plan effectively for each project's needs.

Services & Capabilities

Development

- Formulation Services
- Analytical Services
- Packaging
- Process Development
- Stability Studies
- Microbiology
- Clinical Trial Materials
- Regulatory Submission
- Inhalation Product Testing

Manufacturing

- Semi-solids & Liguids
- Sterile Products
- Aerosol Foams & Sprays
- Metered-Dose Inhalers (pMDIs)
- Site and Technical Transfers

Facilities

Each of DPT's three Centers of Excellence is staffed with experts who provide pharmaceutical development and manufacturing services dedicated to its respective specialty:

The Center of Excellence for Research and Development offers comprehensive development services and customized solutions for sterile and non-sterile semi-solid and liquid dosage forms.

The Center of Excellence for Semi-Solids and Liquids provides solutions for both clinical and commercial-scale manufacturing according to current Good Manufacturing Practice (cGMP) guidelines. This center also includes a dedicated aerosol and pressurized Metered-Dose Inhaler (pMDI) manufacturing facility.

The Center of Excellence for Sterile and Specialty Products specializes in the development and aseptic manufacturing of clinical trial materials and commercial-scale products that meet the most stringent sterile pharmaceutical requirements.

With DPT,
development and manufacturing piece together seamlessly.

DPT is the contract development and manufacturing organization (CDMO) that specializes in sterile and non-sterile semi-solid and liquid dosage forms. With unmatched technical expertise and fully integrated drug development and manufacturing services, we can help you successfully develop and commercialize your next product. Partnering with DPT gives you a seamless transition from pre-formulation to clinical supplies to commercial supply. After all, keeping it all together is what sets us apart. To get started, visit us at www.dptlabs.com or call 1.866.CALL.DPT.

DPT®

SOURCE WITH CONFIDENCE®

SEMI-SOLIDS • LIQUIDS • NASAL SPRAYS • PRESSURIZED METERED-DOSE INHALATION • AEROSOL FORMULATIONS • STERILE DOSE FORMS

1.866.CALL.DPT • WWW.DPTLABS.COM • SAN ANTONIO, TX • LAKEWOOD, NJ

Evonik Company Profile

Evonik Degussa Corporation
Pharma Polymers
2 Turner Place
Piscataway, NJ 08855
USA

TEL +1 732 981-5383
EMAIL eudragit-usa@evonik.com
www.eudragit.com
www.evonik.com

Evonik Industries AG
Pharma Polymers
Kirschenallee
64293 Darmstadt
Germany

TEL +49 6151 18-4019
EMAIL eudragit.germany@evonik.com
www.eudragit.com
www.evonik.com

With its Pharma Polymers product line, Evonik is a leading provider of functional pharmaceutical excipients and advanced formulation solutions. Providing a broad range of polymer products, combined with high quality pharmaceutical services we are a strategic resource for the health care industry for the design and development of pharmaceutical formulations and medical devices. Using us as a source for your drug developments can both reduce risks and increase speed to market.

Based on our well-known EUDRAGIT® product portfolio, we develop coatings and matrix systems that provide reliable and targeted controlled release of active pharmaceutical ingredients from oral dosage forms. Main functionalities are delayed and extended release as well as moisture protection, taste masking and solubility enhancement.

In March 2011 our oral drug delivery platform was complemented by the addition of the RESOMER® polymers which are used for depot formulations and bioresorbable implants as well as in medical devices. Their high level of purity and their excellent mechanical properties provide a comprehensive basis for innovative and patient friendly applications.

We support your development projects all over the world with 50+ formulations experts in our state-of-the-art equipped laboratories located in Germany, USA, India, China, Japan and Argentina. Our development services include all steps from early feasibility studies to large scale production transfer, including clinical supply manufacturing and scale-up support. To support your quality and development processes, as well as your regulatory submission processes, we provide comprehensive data packages as service for our customers.

Beyond that Evonik Pharma Polymers has developed proprietary technologies to enable superior therapeutic success. They include various technology platforms for bioavailability enhancement as well as customized polymer developments. All technologies offer high performance and attractive line extension options.

Formulation Development
- Matching desired release profiles
- Differentiating process technologies such as melt extrusion
- Clinical batch manufacturing
- Global lab network

Advanced Drug Delivery
- Joint development programs of enabling technologies (e.g. for bioavailability enhancement)
- Proprietary polymer design
- Portfolio of technology platforms

Pharma Polymers is a strategic resource to the health care industry for the design of drug and device functionality.

Eudragit®
- Oral delivery platform for SR, enteric, protective formulations
- Superior product quality and reliability of supply
- Technical and regulatory support

Resomer®
- Toolbox for parenteral depot formulations
- Toolbox for biocompatible medical device development
- Manufacturing of custom polymers
- Technical and regulatory support

EUDRAGIT® E PO ReadyMix

Taste masking has never been easier

Eudragit®

Achieve the best taste masking performance while saving time and money with EUDRAGIT® E PO ReadyMix. Matching your specific requirements, we prepare your customized coating formulation, including color matching. You receive the already mixed coating formulation and only need water and a conventional stirrer to prepare the spray suspension in short time. The spraying process will be the same as for the common EUDRAGIT® suspensions. At a glance: High performing taste masking coatings will be easy as pie. **For more information visit www.eudragit.com/readymix**

Evonik. Power to create.

EVONIK INDUSTRIES

Follow Us On

Frost & Sullivan, the Growth Partnership Company, enables clients to achieve best-in-class positions in growth, innovation and leadership. The company's Growth Partnership Service provides the CEO and the CEO's executive team with disciplined research and best practice models to drive the generation, evaluation and implementation of powerful growth strategies. Our mission is to research and analyze new market opportunities for corporate expansion. We are the world leader in growth consulting and the integrated areas of technology research, market research, economic research, corporate best practices, training, customer research, competitive intelligence and corporate strategy.

Exclusively Focused on Growth	Actively engaged in identifying new market opportunities, researching competitive strategies and developing implementation plans that enable clients to accelerate growth.
Industry Breadth	Cover the broadest spectrum of markets and technologies to provide clients with the ability to look outside the box and discover new and innovative ideas.
Global Perspective	Over 40 global offices ensure that clients receive global coverage and perspective based on local and regional expertise.
Continuous Monitoring	Continuously monitoring markets, technologies, careers and geographies for growth opportunities.
CEO's 360 Degree Perspective™	Disciplined research integrates all critical research methodologies to significantly enhance the accuracy of decision-making and lower the risk of implementing growth strategies.
Trusted Partner	Work closely with executive teams to leverage all of Frost & Sullivan's expertise to promote revenue-generating initiatives.

Gateway Analytical

Analytical Testing and Consulting Services

With expertise in product and process development, pharmaceutical forensics, and cGMP regulations, Gateway Analytical's services support many facets of the drug product lifecycle.

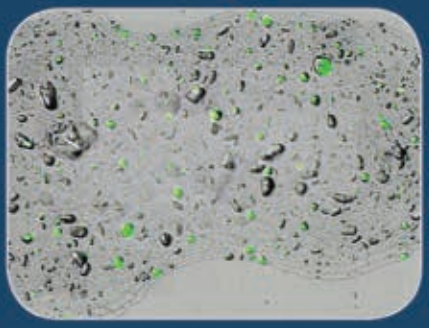
By pairing our expertise with innovative methods, we take a multi-analytical approach to scientific problem solving that relays more about a drug product's quality and performance.

Gateway ANALYTICAL

Pharmaceutical Forensics

- Foreign Particulate Matter Identification
- Nonconformance Issues
- OOS Investigations
- Particle Contamination Characterization
- Source Determination
- Failure Analysis

Product & Process Development



- Content and Blend Uniformity
- Polymorphs Characterization
- In Vitro Particle Characterization
- Layer Thickness Determination

Pharmaceutical Consulting

- Intellectual Property Support
- Legal Consult
- Technology Transfer

You Tube Watch us on YouTube
Youtube.com/user/GatewayAnalytical

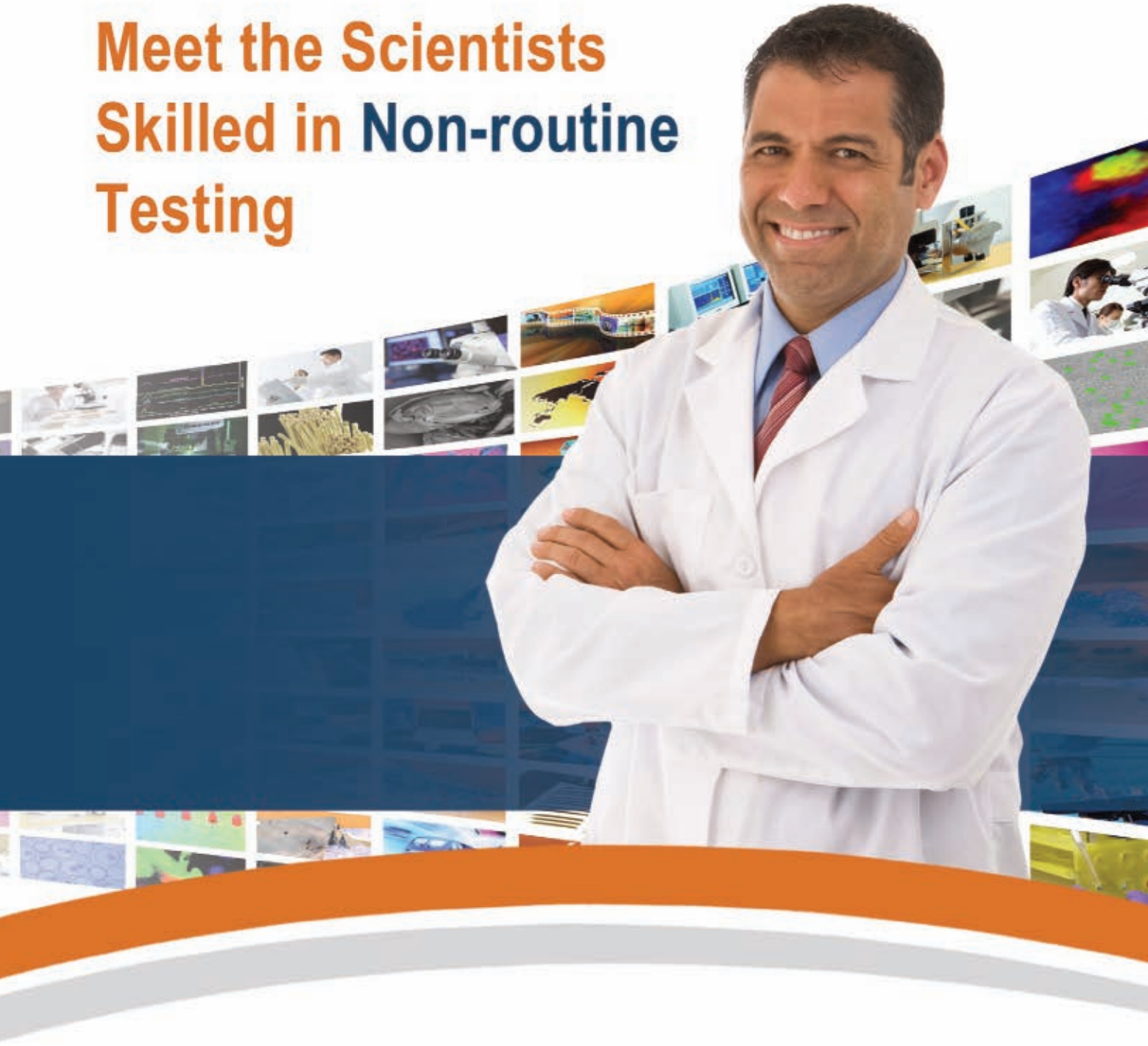
Follow us on Twitter
Twitter.com/GatewayTweets

E-Newsletter Sign Up
Ez.com/signup

Gateway ANALYTICAL

5316 William Flynn Highway
Gibsonia, PA 15044
Tel: +1 724-443-1900
www.gatewayanalytical.com

Meet the Scientists Skilled in Non-routine Testing



Your Non-routine Issue is Our Everyday

Whether it's addressing nonconformance issues or determining where a foreign particulate entered a manufacturing process, our scientists have the diverse industry expertise and the technical know-how to meet your unique needs quickly and efficiently.

Trust our more than 15 years of experience in novel analytical techniques, source determination and quality management to be an extension of your own capabilities.

Company Profile

Gattefossé USA
115 West Century Road, Suite 340
Paramus, NJ 07652
T: (201) 265-4800
Website: www.gattefosse.com

Gattefossé is a leading provider of multi-functional excipients and formulation solutions to health industries, worldwide.

Established in 1880 by pioneering scientists in France, Gattefossé today possesses core competencies in a number of areas, notably in lipid chemistry and the manufacture of unique excipients for the pharmaceutical industry.

Gattefossé remains loyal to its founders' aspirations in maintaining an innovative edge by investing in education and research, and instilling professional and social links that aim to serve the global village.

Formulation Solutions

Bioavailability enhancers, tablet lubricants, melt-granulation aids, sustained-release matrices, solubilizers, and taste-masking agents are among the diverse range of applications in many dosage forms (tablets, capsules, suppositories, creams, ointments, liquids, powders). Preparation techniques are equally diverse and include hot-melt coating; adsorption onto solids; melt extrusion or granulation; spray cooling; homogenization; emulsification; nano-lipid carriers, and solid lipid nanoparticles.

Gattefossé products and technologies are widely applied in currently marketed medicines.

Going the extra mile…

Further to product functionality, Gattefossé focuses on product safety, quality, and compliance with American, European, and Asian regulatory agencies. Assistance in drug filings of our customers includes sharing of full dossiers on safety/tox data, manufacturing, and quality systems for each product.

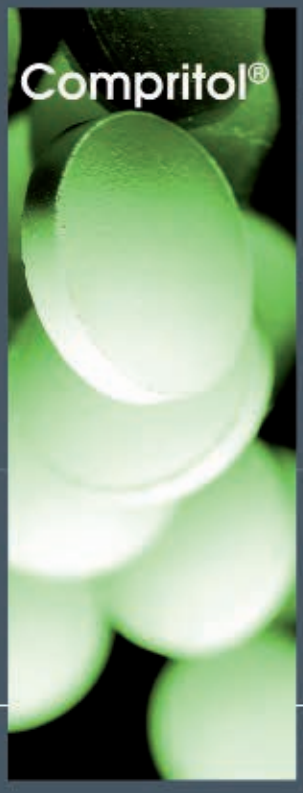
Gattefossé also offers lipid seminars and proof-of-concept studies for its customers. Our expert chemists also host training seminars for customers worldwide.

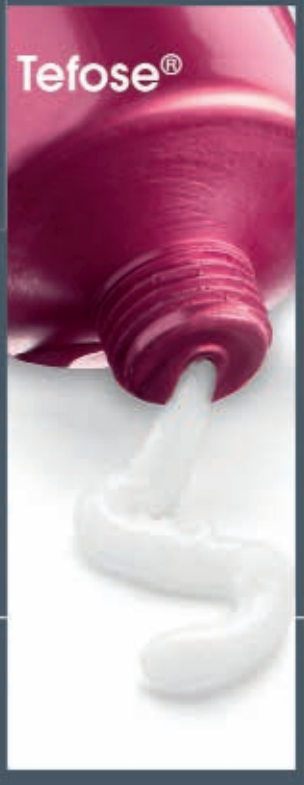
Just a call away…

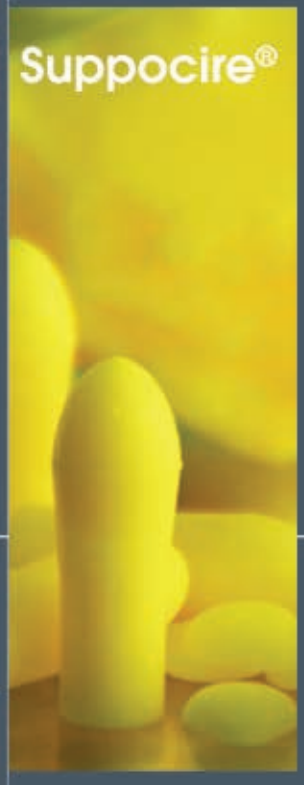
Our friendly professionals are a phone call away. Gattefossé has an extended network of affiliates and distributors in more than 60 countries. To find your local representative, simply visit www.gattefosse.com.

From United States and Americas, simply dial (201)-265-4800 or email hmbosly@gattefossecorp.com.

OUR FUNCTIONAL EXCIPIENTS ...YOUR DRUG DELIVERY SOLUTIONS







Gattefossé USA
Plaza I, 115 West Century Rd., Suite 340, Paramus, NJ 07652
Tel: 201-265-4800
www.gattefosse.com

GATTEFOSSÉ

INNERCAP Technologies, Inc.
9216 Palm River Road, Suite 203
Tampa, FL 33619
T: (813) 837-0796 E: busdevelopment@innercap.com
Website: www.innercap.com

INNERCAP Technologies, Inc. offers NOVACAPS™, a multi-phase, multi-compartment single pill solution for difficult combination drugs. The proprietary NOVACAPS™ delivery system accommodates otherwise incompatible pharmaceutical agents, solid or liquid, in a single-dosage, combination product. The delivery system also provides the option of working with multiple release profiles for the actives administered in the delivery system. Surging worldwide interest in such combination formats is evidenced by the FDA's initiative to advance the development of single-dosage forms for delivery of multiple HIV/AIDS drugs.

With the INNERCAP delivery system, therapeutic entities that have never been combined previously can now be administered together, via an oral, implanted, or a suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This approach maximizes bioavailability and, at the same time, addresses patient compliance issues that often plague multi-drug regimens.

The NOVACAPS™ delivery system can be used for all therapeutic classes, such as immunologic, cardiovascular, neurologic, psychiatric, oncologic, and pain management.

The INNERCAP delivery system also provides a solution to overcome the difficult development issues related to bi-layer tablets. This will provide companies with a quicker and efficient solution to transition innovations smoothly from development, through the clinical phase, and into commercialization — ultimately reaping the financial fruits of their labor.

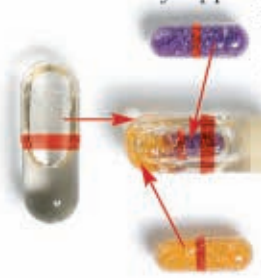
NOVACAPS™ offers a significant first-to-market advantage by minimizing valuable time in R&D when the product could be in clinical trials determining the patient response to a new combination product.

Companies interested in a novel solution for life-cycle management issues, patent protection, increased compliance, combination drugs, reduced counterfeiting, increased stability, multiple release profiles, increased bioavailability, barriers to entry, higher perceived value, and branding opportunities with difficult formulation issues can contact INNERCAP Technologies.

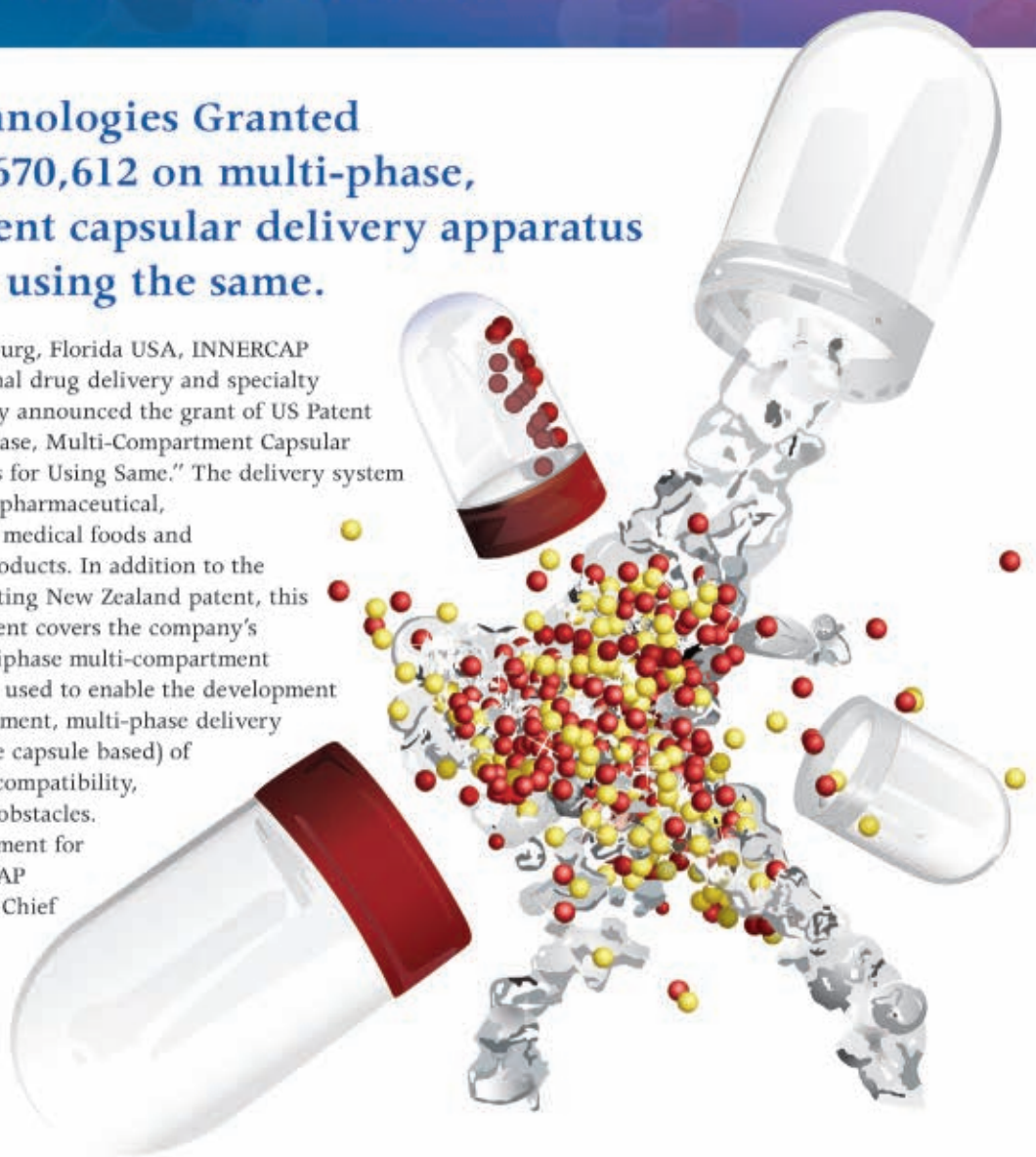
THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical, pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the company's multiphase multi-compartment delivery system used to enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.



"This is a significant development for INNERCAP Technologies NOVACAP technology," said Fred H. Miller, Chief Executive Officer at INNERCAP. "The continued growth of our patent portfolio establishes INNERCAP as one of the leading companies in this space."

The delivery system and combinations covered by the patent have the ability to deliver therapeutic entities that have never been combined previously and now can be administered together, via an oral, implanted, or suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This technology can therefore be used to enable capsule administration of compounds that are not normally administered as a combination product. The efficacy, safety, and side-effect profiles of drugs can be substantially improved using this delivery technology. It will also provide very significant quality-of-life improvements for patients and substantial economic savings for hard-pressed healthcare systems.

"INNERCAP's multi-phase, multi-compartment technology has been commercially manufactured and validated in several products, demonstrating that INNERCAP's delivery system creates real value to consumers and branded manufacturers," added Mr. Miller.

INNERCAP was represented by Cliff Davidson, Esq. of the patent firm Davidson, Davidson & Kappel, LLC (www.ddkpatent.com) based in New York City.

For more information contact us at the telephone number and email address below:

INNERCAP® TECHNOLOGIES, INC

United States Patent No. 7,670,612
US and International Patents Pending

9216 Palm River Road, Suite 203 • Tampa, FL 33619 USA • (813) 837-0796 • www.innercap.com • busdevelopment@innercap.com

LIGAND PHARMACEUTICALS, INC.
11085 North Torrey Pines Road, Suite 300
La Jolla, CA 92037
T: (858) 550-7500
Website: www.ligand.com

Founded in 1987 as a cutting-edge drug discovery biotech in La Jolla, California, Ligand Pharmaceuticals has built a rich 24-year heritage of drug discovery, development innovation and partnering.

Today, Ligand is a specialty biotech company based on a business model of developing or acquiring technology and royalty revenue generating assets that are coupled to a lean corporate cost structure. Ligand's goal is to produce a bottom line that supports a sustainably profitable business.

In comparison to its peers, we believe Ligand has assembled one of the largest and most diversified asset portfolios in the industry with the potential to generate revenue in the future. These therapies address the unmet medical needs of patients for a broad spectrum of diseases including hepatitis, muscle wasting, Alzheimer's disease, dyslipidemia, diabetes, anemia, COPD, asthma, rheumatoid arthritis and osteoporosis.

In 2011, Ligand acquired CyDex Pharmaceuticals, Inc. along with its drug formulation technology, Captisol®. Captisol is a patent protected, chemically modified cyclodextrin with a structure designed to optimize the solubility, stability, bioavailability, safety and dosing of active pharmaceutical ingredients.

Ligand has established multiple alliances with the world's leading pharmaceutical companies including GlaxoSmithKline, Merck, Pfizer, Baxter International, Bristol-Myers Squibb, Celgene, Onyx Pharmaceuticals, Lundbeck Inc. and The Medicines Company. Please visit www.captisol.com for more information on Captisol. For more information on Ligand, please visit www.ligand.com.

In addition to licensing our Captisol technology to other companies, Ligand also performs formulation development activities with a variety of existing APIs as well as NCEs that exhibit poor solubility, inherent instability, or low bioavailability. Each project is tailored to meet the scientific needs and timeframes of our clients. Please call (877) 575-5593 for additional information.

Ligand maintains patents in the United States and worldwide for its Captisol drug formulation technology and Captisol-enabled products Ligand also manages cGMP supply of Captisol and maintains a comprehensive Drug Master File.

Visit us at captisol.com

CAPTISOL®

Creating clear solutions.
Enabling product development.

LIGAND®
ligand.com

PARTICLE SCIENCES, INC.
3894 Courtney Street
Bethlehem, PA 18017
T: (610) 861-4701
Website: www.particlesciences.com

For 20 years Particle Sciences has been developing innovative drug delivery solutions. We are a full service CRO providing complete formulation development, GMP/GLP analytic and bioanalytic methods development and testing and clinical trial material manufacturing in our sterile, non-sterile and high containment clean rooms. We are DEA and FDA registered and work with highly potent compounds. We specialize in formulating BCS II and biologics with a range of technologies including nanoparticulates, solid solutions, semisolids and drug/device combination products, all aimed at optimizing the delivery of your API. At Particle Sciences, We Deliver®, taking your API from concept to clinic.

Our Approach

Drug delivery has advanced beyond dosage form specialization. Most APIs under development today have issues ranging from solubility to stability. Technologies that address these challenges cross dosage form boundaries and Particle Sciences is the leader in this API-centric trend. We believe a fundamental understanding of your compound and delivery goals is the key to success. At Particle Sciences we use the most advance tools to insure an efficient process including DOSE™, our own solubility characterization paradigm, Design of Experiments and state-of-the art equipment. Our client's needs are thoroughly discussed and documented prior to initiating a project so that everything we do is on mission and makes most of our client's resources.

Technology

Our staff has extensive experience in drug delivery formats including micro- and nano-particulates, emulsions, suspensions, encapsulated APIs, and controlled-release dosage forms. Fine-particle and nanoscale systems have been a focus of Particle Sciences since its inception in 1991. We employ technologies ranging from milling to controlled precipitation to polymeric solid solutions. Particle Sciences has all the necessary instrumentation and in-house expertise to rapidly produce and characterize these systems. Additionally, we have the industry's leading dedicated drug/device combination-product team with full compounding, injection-molding and analytic capabilities.

Client-Focused

Clients' projects receive individualized attention. Particle Sciences takes a collaborative approach to ensure positive project outcomes and the highest levels of client satisfaction. Projects are overseen and coordinated by a dedicated project manager in conjunction with a cross-functional team.

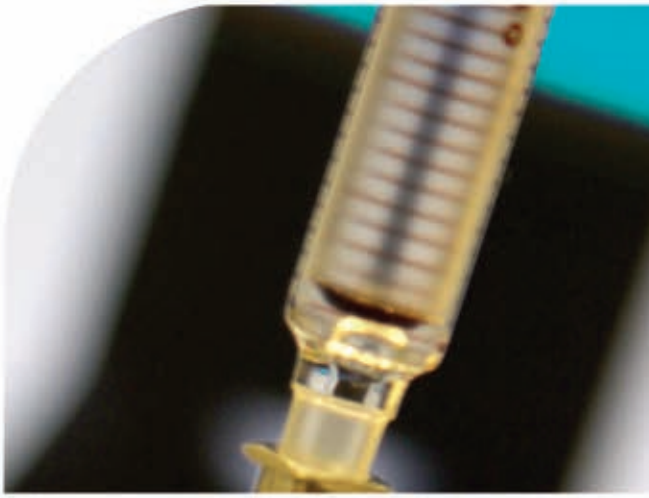
Integrated Process

Through a combination of preformulation, formulation, analytic, bioanalytic, and manufacturing services, Particle Sciences provides clients with a powerful, integrated solution to most efficiently take a drug from concept to clinic. With years of experience to draw from, Particle Sciences can confidently handle difficult APIs, complicated intellectual property terrains, and challenging delivery goals to arrive at the simplest, most efficient solution to meet your needs.

THE DRUG DELIVERY EXPERTS

Particle Sciences Inc. (PSI) is a fully-integrated analytic, formulation and clinical trial material manufacturing services provider. **PSI** offers a seamless drug development process that minimizes the time and risk going from discovery to the clinic. **PSI** brings unmatched experience in traditional and innovative approaches to drug product development. Expert in difficult-to-solubilize APIs, **PSI** works across a variety of dosage forms including: topical, mucosal, oral and parenteral and is a globally-recognized leader in the development of combination drug/device products. For more information, please visit www.particlesciences.com, email info@particlesciences.com or call (610) 861-4701.

AN INTERNATIONALLY RECOGNIZED LEADER



PARTICLE SCIENCES
DRUG DEVELOPMENT SERVICES

3894 Courtney Street | Bethlehem, Pennsylvania 18017
610·861·4701 ph | 610·861·4702 fax www.particlesciences.com

Patheon™
Performance the World Over

Patheon Inc.
4721 Emperor Blvd, Suite 200
Durham, NC 27703-8580
T: (866) Patheon F: (919) 474-2269
E: doingbusiness@patheon.com
Website: www.patheon.com

Patheon Inc. (TSX: PTI) is a leading global provider of contract development and manufacturing services to the global pharmaceutical industry. The company provides the highest quality products and services to approximately 300 of the world's leading pharmaceutical and biotechnology companies. Patheon's services range from preclinical development through commercial manufacturing of a full array of dosage forms, including parenteral, solid, semi-solid, and liquid forms.

The company uses many innovative technologies, including single-use disposables, liquid-filled hard and soft capsules, and a variety of modified-release technologies. Its comprehensive range of fully integrated Pharmaceutical Development Services includes preformulation, formulation, analytical development, clinical manufacturing, scale-up, and commercialization.

Patheon can take customers direct to clinic with global clinical packaging and distribution services and Patheon's Quick to Clinic™ programs can accelerate early phase development projects to clinical trials while minimizing the consumption of valuable API. The company's integrated development and manufacturing network of 10 facilities, 8 development centers, and 1 clinical trial packaging facility across North America and Europe ensures customer products can be launched with confidence anywhere in the world.

Choose Choice.

No other partner gives you more formulation options – royalty free.

Get access to the industry's widest range of complex formulation technologies for small molecules and biologics, and benefit from expertise forged over thousands of projects.

At Patheon, we're not tied to any technology. That means science alone drives the development of an optimal formulation, and you'll never pay us a royalty. Our commitment is to your success.

Choose choice – choose Patheon.

Call +1 866-PATHEON (+1 866-728-4366) or email doingbusiness@patheon.com

US Headquarters

Patheon Inc.
4721 Emperor Blvd, Suite 200
Durham, NC 27703-8580
USA
P: +1 919 226 3200
F: +1 919 474 2269
www.patheon.com

European Headquarters

Patheon UK Ltd.
Kingfisher Drive
Covingham, Swindon
Wiltshire SN3 5BZ
UK
P: +44 1793 524411
F: +44 1793 487053
www.patheon.com

Published 9/11 PATH0214R9

Patheon™
Performance the World Over

PHARMACIRCLE
Encinitas, CA 92024
T: (760) 436-1199 E: contact@pharmacircle.com
Website: www.pharmacircle.com

Pharmacircle™ is a best-in-class knowledge management company that provides a one-stop source for all information needs within the Pharmaceutical industry. PharmaCircle provides a detailed analysis of drug delivery technologies, marketed products/pipeline, deals, acquisitions, and venture capital. PharmaCircle also provides detailed company related information, such as employee numbers, R&D spending, product sales, product development costs, royalties, and more. The data within PharmaCircle is searchable and exportable into user-defined charts and graphs.

Why PharmaCircle?

- Comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc.) related information and analysis has utility for all segments of small and large companies.
- Facilitates product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts.
- Supplements internal efforts and costs at a fraction if performed internally.

PharmaCircle Content

- Unique and comprehensive content on Drug Delivery (DD), pharmaceutical, biotechnology, and related fields.
- Drug Delivery technologies, pipeline/products, deals, patents, etc. are organized using 180+ Drug Delivery categories, as well as therapeutic fields.
- Extensive information on physical, chemical, and pharmacokinetic properties of molecules.
- Searchable information on formulation, dosing, and administration for marketed and development products.
- Comprehensive Reviews and Compare & Contrast Tables for all major Drug Delivery technologies.
- Information updated daily is based on public sources and PharmaCircle's own analysis.
- Extensive search capabilities on almost every data entry.
- The data base structure and presentation are designed and supported by dedicated and skilled IT professionals.

putting together all the pieces at your fingertips

PharmaCircle™ is an innovative knowledge management company specializing in the drug delivery, pharmaceutical and biotechnology fields. With customers varying from world leaders to start up companies, our web of content and customer support gives you the cutting edge advantage.

"I can now hand the customers something when I thought we'd have to say we couldn't."
-Customer Feedback

- **Products & Pipeline**
- **Regulatory**
- **Formulation & Excipients**
- **Drug Delivery**
- **Clinical Trials**
- **Deals & Acquisitions**
- **Life Cycle Management**
- **Sales**
- **Veterinary**
- **Venture Capital**
- **Generics**
- **Paragraph IV**

PHARMACIRCLE™

Innovation in Pharmaceutical Knowledge Management

www.pharmacircle.com

760.436.1199
contact@pharmacircle.com

Company Profile

UPM Pharmaceuticals®, Inc.
6200 Seaforth St.
Baltimore, MD 21224
T: (410) 843-3738 F: (410) 633-4438
Website: www.upm-inc.com

UPM Pharmaceuticals®, Inc. is a Baltimore-based drug development and contract manufacturing company providing customized formulation development, manufacturing, and analytical services to pharmaceutical, biotechnology, and university clients. Fully appreciating that flexibility and time-to-market are critical; UPM is highly responsive to clients' program changes and specializes in developing creative solutions to unique challenges. UPM is characterized by the timeliness and thoroughness with which all projects are managed. Every step of the way, UPM Pharmaceuticals works to advance and optimize products through up-to-date resourceful approaches, while adhering to the highest quality standards. Through the years, our staff and systems have been consistently challenged by FDA, DEA, QP, and client audits, and we have passed these rigorous inspections repeatedly.

Scientific Expertise – Access to some of the industry's best formulation design specialists, manufacturing specialists, and analytical chemists, who are known for developing innovative solutions to difficult development challenges.

Rapid & Responsive Turnaround – Our scientists and senior managers utilize daily planning meetings and a master scheduling process that provides for timely and responsive project management.

Quality Assurance & Document Control – Our highly experienced quality assurance personnel implement complete cGMP quality and regulatory systems that support formulation development, clinical batch manufacturing, and analytical work-up.

Capital Investment – Recent equipment acquisitions have increased our capabilities for solid dose formulation development, including mini-scale R&D proof-of-concept manufacturing (BREVI-BATCH™), low solubility compound processing, uHPLC sample analysis, and bi-layer tableting.

Manufacturing Facilities – Additional expansion of the manufacturing facility, including a low-humidity/high-potency suite, direct API filling suites, and an expanded packaging line suite will allow UPM to continue to meet our clients' increased manufacturing demands.

Services Offered

- BREVI-BATCH™ mini-batch proof-of-concept studies
- Formulation Development
- Low Solubility Processing
- Wet Granulation
- Dry Granulation/Roller Compaction
- Particle Size Analysis
- Tableting
- Bi-layer Tableting
- Tablet & Particle Coating
- Direct API fill Into capsules for proof-of-concept studies
- Capsule Filling
- Feasibility to Small-Scale Commercial
- cGMP Manufacturing
- CTM Packaging
- Stability Testing
- Blinding of Clinical supplies
- Analytical Services

Company Profile

Xcelience
5415 West Laurel Street
Tampa, FL 33607
Corporate Phone: (813) 286-0404 Business Development Phone: (608) 643-4444
F: (813) 286-1105 E: Info@xcelience.com
Website: www.xcelience.com
Contact: Randall Guthrie, Vice President

Xcelience is a premier provider of formulation development and manufacturing solutions with a solid reputation for accelerating early phase development. Our outstanding quality record, drug development expertise, disciplined project management, and willingness to customize enables us to deliver real advantage to pharmaceutical innovators focused on small molecule development. Partnering with a specialist like Xcelience for early phase development can reduce product risk and accelerate development timelines. Since 1997, Xcelience has been renowned for reliably expediting drug development and reducing compound risk. Our scientists have considerable experience overcoming challenging physical and chemical properties in a manner that results in improved solubility and compound bioavailability.

XCELIENCE ADVANTAGE

- Three-phase facility expansion increases capacity and processing speed for formulation development, analytical, GMP manufacturing, and packaging.
- Expanded clinical trial supplies manufacturing capabilities increase overall capacity, improve production times, and expand upon existing capabilities for production, coating, and encapsulation.
- New fully automated packaging line for primary bottling of tablets and capsules enhances the speed for batch packaging, shortens timelines, and enables packaging of larger batches.
- Global access to four Xcelodose® precision powder microdosing systems, which enable clients to fill very small amounts of powder into capsule speeding time to first-in-human studies.
- Liquid-in-capsule services for overcoming the challenge of poor aqueous solubility and improving compound bioavailability.
- Small-scale batch production for companies facing the challenge of limited API.
- Comparator product blinding.

SERVICES & CAPABILITIES

Preformulation
- Salt Screens
- Polymorph Screens
- Drug Substance Characterization
- Excipient Compatibility
- Accelerated Stability
- Chiral Stability

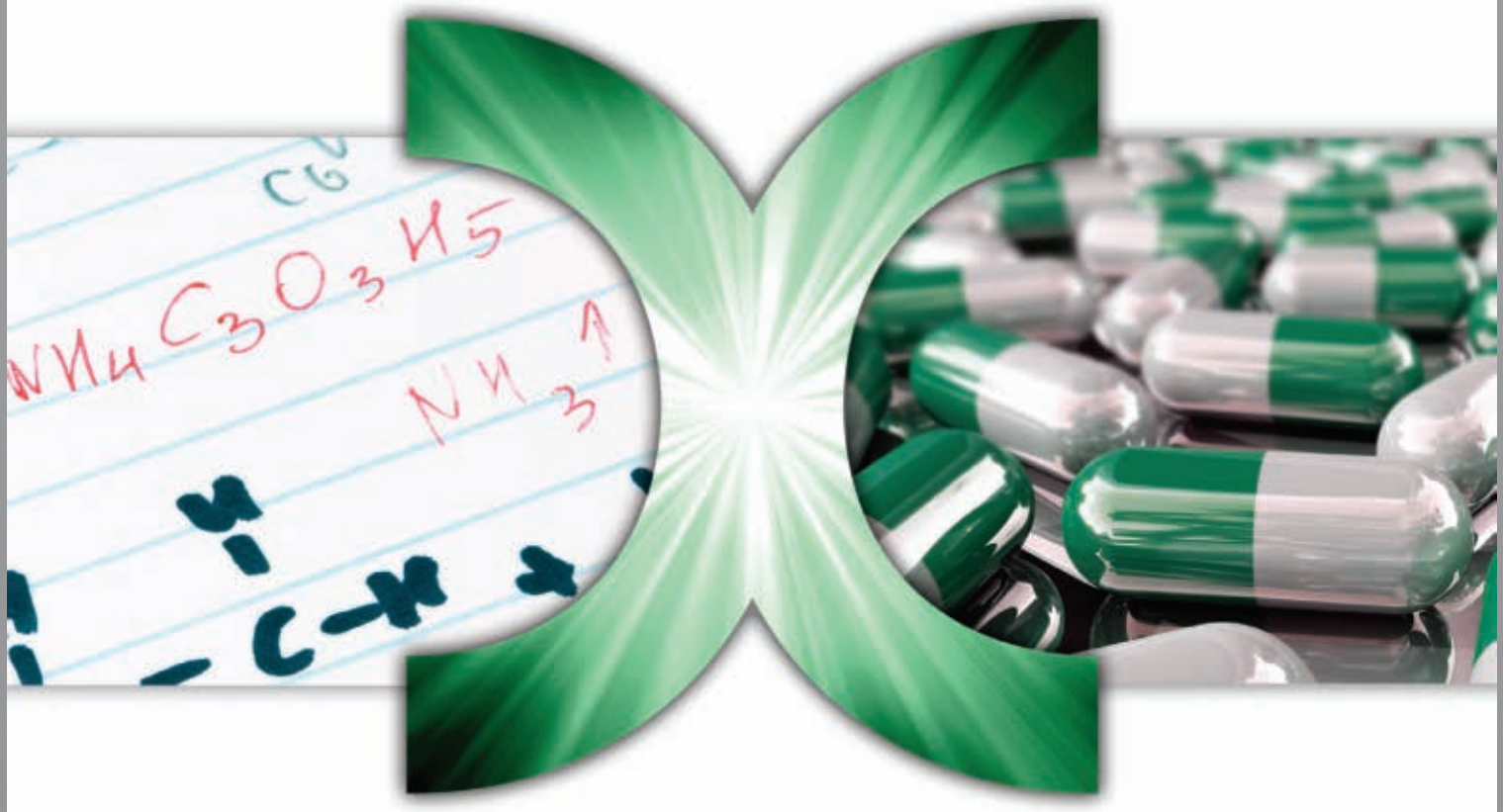
Analytical Services
- Method Development
- Qualification & Validation
- Raw Material Testing
- Stability Sample Analysis
- Dissolution Testing
- Residual Solvent Analysis
- Chiral Determination
- Cleaning Evaluations
- Technical Packages for Drug Substances

Formulation Development
- Solids (tablets, gelatin or HPMC capsules, sustained release, and coatings)
- Semi-Solids (ointments, creams, and gels)
- Dispersed systems (emulsions, suspensions)
- Liquids (orals, ophthalmics, parenterals)

Clinical Trial Supplies Manufacturing & Packaging
- API or Powder Into Bottle
- Powder Into Capsule
- Tablets & Capsules
- Liquid in Capsule
- Semi-Solids
- Non-Sterile Liquids
- Reference Product Blinding
- Matching Placebo Formulation
- Blinded Reference Product
- Process Qualification, Definition, Optimization & Transfer
- Clinical Packaging & Labeling

Stability Program Management
- ICH Conditions
- Protocol Design
- Report Generation
- Sample Analysis
- Secure Storage Area
- SLIM (our stability laboratory information management system, meets FDA standards for 21CFR11 compliance)

FACILITIES
Xcelience operates out of a cGMP-compliant, DEA-licensed facility located in Tampa, Florida, one of the most desirable cities in the world.



AT LAST

Early drug development made easy.

Xcelience® is your premier source for formulation development and manufacturing solutions. From preformulation to clinical supplies manufacturing and stability, we have one focus: the success of your project.

Our state-of-the-art equipment, including the XRD, Xcelodose® 600 S, and TF-1 Blister Packaging Thermoformer, combined with our years of experience providing innovative solutions make the path from compound to clinic feel effortless.

X marks the spot for formulation development and manufacturing made easy – ***at last***.

Xcelience® Formulation Development | www.xcelience.com

Contact us today at **1.608.643.4444** or **info@xcelience.com**.

November/December 2011

Advertiser Index

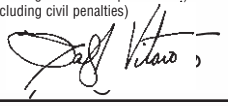
STATEMENT OF OWNERSHIP, MANAGEMENT, AND CIRCULATION

1. Publication title: Drug Development & Delivery 2. Publication number: 1537-2898 3. Filing Date: October 30, 2011 4. Issue frequency: Monthly with combined Jan/Feb, July/Aug and Nov/Dec 5. Number of issues published annually: 9 6. Annual Subscription price: N/A 7. Complete mailing address of known office of publication: 219 Changebridge Rd. Montville, NJ 07045-9998 8. Complete mailing address of headquarters or general business office of publisher: 219 Changebridge Rd. Montville, NJ 07045-9998 9. Full names and complete mailing address of Publisher, Editor and Managing Editor: Ralph Vitaro - 219 Changebridge Rd. Montville, NJ 07045-9998, Dan Marino - 219 Changebridge Rd. Montville, NJ 07045-9998,10. Owner: Drug Delivery Technology, LLC - 219 Changebridge Rd. Montville, NJ 07045-9998 11. Known bondholders, mortgages and other security holders: None 12. N/A 13. Publication: Drug Development & Delivery 14. Issue date for circulation data: October 1, 2011 15. Extent and Nature:

	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total # of copies	17,700	17,900
b. Legitimate Paid and/or Requested Dist.		
1. Individual Paid/Requested Subscriptions	17,140	17,109
2. Copies Req. by Employers for Dist. to Employees	0	0
3. Sales through dealers and carriers, Street Vendors, Counter Sales and other	0	0
4. Req. copies dist. by other mail classes through USPS	110	120
c. Total paid and/or req. circulation	17,250	17,229
d. Nonreq. distribution		
1. Nonreq. copies stated on PS form 3541	150	185
2. Nonreq. copies distributed through USPS	0	60
3. Nonreq. copies distributed outside the mail	200	325
e. Total nonreq. distribution	350	570
f. Total Distribution	17,560	17,799
g. copies not distributed	140	101
h. Total	17,700	17,900
i. Percent paid and/or requested circulation	98.2%	96.2%

16. Publication of Statement of Ownership for a requester publication is printed in the November/December 2011 issue

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested in the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties)



Company	Pg	Phone	Web Site
AAPS Biotechnology Conference	43		www.aaps.org/nationalbiotech
AAI Pharma	53		www.aaipharma.com
Aveva DDS	7,54,55	954-624-1374	www.avevaDDS.com
Baxter Biopharma Solutions	56,57		www.baxterbiopharmasolutions.com
Cambridge Healthcare Institute	58,59	888-999-6288	www.chicorporate.com
Catalent	60,61,92	877-576-8457	www.catalent.com
Conference Forum The	62,63	646-350-2580	www.theconferenceforum.org
Dow Pharmaceutical Sciences	64,65	707-793-2600	www.dowpharmasci.com
DPT	2,66,67	1-866-CALL-DPT	www.dptlabs.com
Drug Delivery Partnerships	52		www.drugdeliverypartnerships.com
Evonik Industries	68,69	732-981-5383	www.eudragit.com/products
ExcipientFest	91	787-714-3000	www.excipientfest.com
Frost & Sullivan	70,71		www.frost.com
Gateway Analytical	72,73	724-443-1900	www.gatewayanalytical.com
Gattefosse	74,75		www.gattefosse.com/pharmaceuticals
Innercap Technologies	76,77	813-837-0796	www.innercap.com
Lacerta	4		www.lacertabio.com
Ligand	78,79	888-436-6910	www.ligand.com
Particle Sciences	80,81, Insert	610-861-4701	www.particlesciences.com
Patheon	82,83	1-866-728-4366	www.patheon.con
PharmaCircle	84,85	760-436-1199	www.Pharmacircle.com
ResearchDx	3	866-225-9195	www.researchdx.com
UPM	86,87	410-843-3738	www.upm-inc.com
Xcelience	88,89	608-643-4444	www.xcelience.com

IPEC AMERICAS — INTERNATIONAL PHARMACEUTICAL EXCIPIENTS COUNCIL

presents

EXCIPIENT FEST® Americas

April 24 - 25, 2012

The Ritz Carlton · San Juan, Puerto Rico

The Excipient Industry's Best EXPO for Regulatory, Science and Sourcing Education.

Media Sponsor — Drug Development & Delivery

Gold Sponsors

AsahiKASEI · AVANTOR Performance Materials · Colorcon · Mutchler Inc. Pharmaceutical Ingredients · Emerson Resources Inc · Peter Greven · Meggle · FMC · USP · Dober Cleaner with Chematic

Silver Sponsors

DOW · DOW Water & Process Solutions · GenerichemCorp · Lancaster Laboratories · Budenheim · Kerry · BASF The Chemical Company · Roquette · Covidien Mallinckrodt · JRS Pharma LP The Excipient Family · CornProducts International · DMV-Fonterra Excipients The ingredients of success · NSF · EMD · Univar

Media Sponsor — Pharmaceutical Technology · Life Science Leader

Tel. 787-714-3000 Fax 787-714-6000 marisol.perez@excipientfest.com Register online at **excipientfest.com**

Catalent®

CATALENT TO BECOME #2 GLOBAL CLINICAL SUPPLY LEADER WITH PENDING ARTIST CTS ACQUISITION

more products to market faster.

We have the advanced technologies and broad drug development expertise to solve even the most complex challenges, and drive faster timelines with lower risk.

OPTIMAL API SCREENING

With our proven Optiform™ technology, we can help you find optimal solid forms and solve your bioavailability and delivery challenges.

BROADER DEVELOPMENT EXPERTISE

Our broad range of services, including formulation, analytical, and regulatory expertise, helps ensure better product filing and in-market success.

IDEAL DOSE FORM CREATION

With dose forms from oral and parenterals to biologic and inhalation, we provide optimal delivery and route of administration selection, feasibility, development, scale up, and supply.

ADVANCED BIOLOGIC SOLUTIONS

Our proprietary GPEx® technology creates stable, high-yielding mammalian cell lines with high speed and efficiency to take you from gene to clinic in one-third the time of traditional approaches.

Every molecule has a challenge.
We have a solution.

Call: + 1 888 SOLUTION
Email: solutions@catalent.com
Visit: www.catalent.com

DEVELOPMENT DELIVERY SUPPLY