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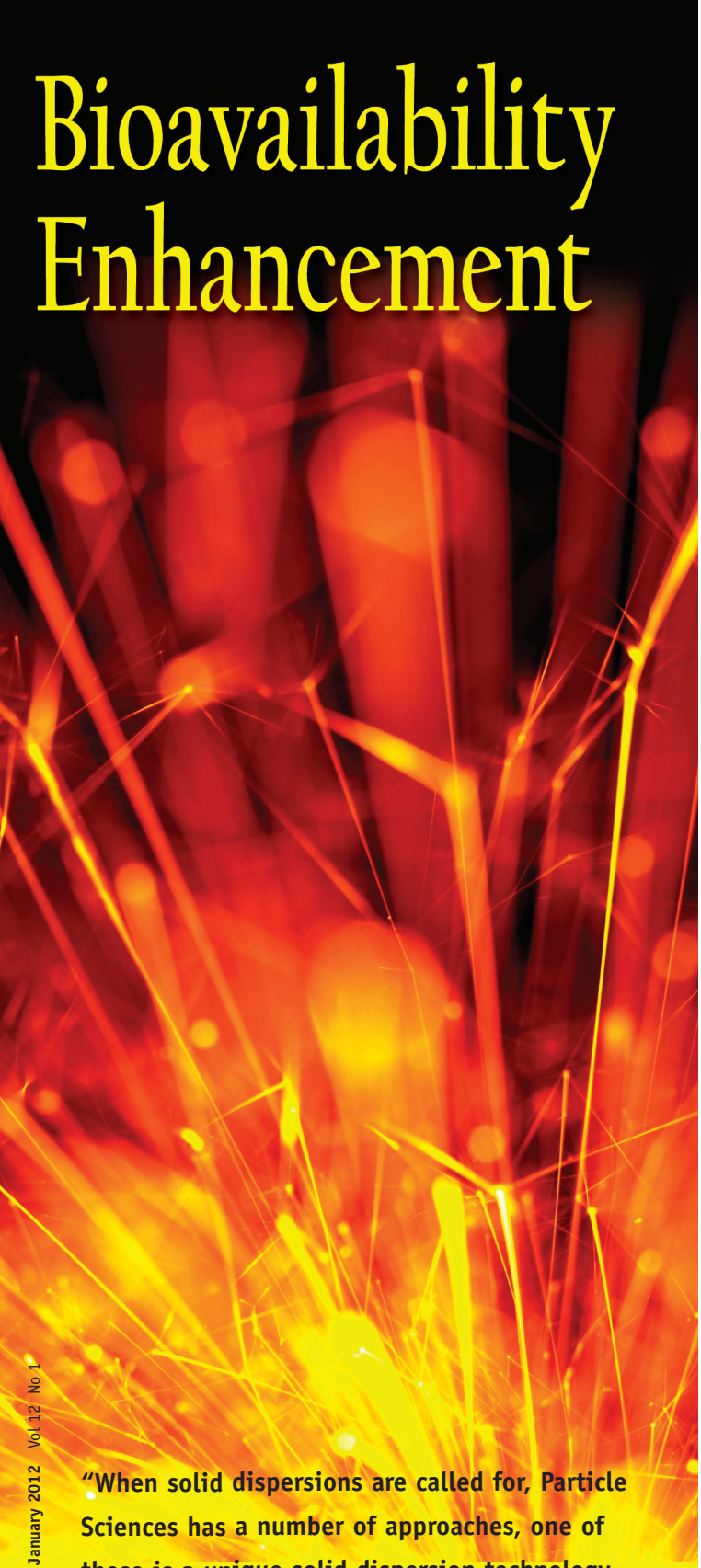

"When solid dispersions are called for, Particle Sciences has a number of approaches, one of these is a unique solid dispersion technology based on spray-drying using a dual polymer system that significantly improves the dissolution and bioavailability of poorly soluble APIs. The technology has been proven in human trials and has been scaled to commercial levels."

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Market News and Trends

Isotechnika & Vifor Pharma Enter Development & Commercialization Agreement

Isotechnika Pharma Inc. recently announced it has signed a global development and commercialization license agreement with Vifor Pharma Ltd., the specialty pharma company of Switzerland-based Galenica Group. The agreement grants Vifor Pharma an exclusive license for the company's lead drug, voclosporin, for the treatment of lupus and all proteinuric nephrology indications. The Vifor pharma license is for the US and other regions outside of Canada, South Africa, Israel, China, Taiwan, and Hong Kong.

While the details of the transaction are confidential, Isotechnika noted that it is eligible to receive significant up-front and milestone payments, as well as royalties on commercial sales. In connection with this agreement, Vifor Pharma will be purchasing voclosporin capsules from Isotechnika.

"While the successful development of voclosporin for the prevention of kidney transplant rejection remains our primary focus, we believe the expansion of our platform beyond that indication via partnerships like this may help to unlock the drug's full medical and commercial potential," said Dr. Robert Foster, CEO of Isotechnika. "Autoimmune diseases continue to represent a significant unmet medical need globally, and we are confident that the opportunity to advance voclosporin to provide much needed therapeutic choice in the treatment of lupus will be a benefit for patients suffering from this often debilitating disease."

Pursuant to a development, distribution, and license agreement between the company and ILJIN Life Science Co., Ltd, ILJIN held an exclusive license to voclosporin for transplant and autoimmune indications for some of the same geographic areas that comprise the Vifor pharma territory. In order to facilitate the Vifor pharma license, ILJIN and Isotechnika have reached an agreement in which ILJIN has licensed back to Isotechnika the autoimmune indications in the countries that fall within the Vifor pharma territory.

Vifor Pharma is one of the world's leaders in the discovery, development, manufacturing, and marketing of pharmaceutical products for the treatment of iron deficiency. The company also offers a diversified portfolio of prescription medicines as well as OTC products. Vifor Pharma, headquartered in Zurich, Switzerland, has an increasingly global presence and a broad network of affiliates and partners around the world.

Isotechnika Pharma Inc. is a biopharmaceutical company focused on the discovery and development of immunomodulating therapeutics designed to offer key safety advantages over currently available treatments. Its lead drug, voclosporin, is a calcineurin inhibitor, and is targeted at the estimated $3-billion market for this class of immunosuppressants.

Aegis Awarded Patent for Interferon Alpha, Beta, and Gamma Formulations

Aegis Therapeutics LLC recently announced it has been awarded US Patent No. 8,084,022 providing broad protection for stabilized formulations of alpha, beta, and gamma interferon suitable for non-invasive metered nasal spray delivery or traditional injection. The beta interferons are indicated for the treatment multiple sclerosis, and the alpha interferons are used for treatment of chronic hepatitis C and hairy cell leukemia. Gamma interferon is used in the treatment of chronic granulomatous disease and severe malignant osteopetrosis.

Aegis will begin seeking potential licensees for this most recently issued patent for its ProTek protein stabilization and immunogenicity reduction technology. Other issued ProTek-related patents provide for non-invasive delivery and stabilization of GLP-1 analogs, human growth hormone, and PTH, with others pending.

Aegis Therapeutics LLC is a drug delivery technology company commercializing its patented drug delivery and drug formulation technologies through product-specific licenses. Its Intravail drug delivery technology enables the non-invasive delivery of a broad range of protein, peptide, and non-peptide drugs that can currently only be administered by injection, via the oral, buccal, and intranasal administration routes, and with high bioavailability. Its ProTek excipients stabilize, prevent aggregation, and reduce unwanted immunogenicity of protein and peptide therapeutics while avoiding the oxidative damage caused by polysorbate surfactants currently found in most protein injectable drugs.

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Particle Sciences Expands Program With Additional Proprietary Modeling Capabilities

Particle Sciences recently announced it has added a third computational module to its DOSE program. The DOSE program uses a combination of empirical data and proprietary modeling tools to efficiently arrive at the optimal drug product for a given API and dosage form. Previously, Particle Sciences implemented software solutions for calculating and predicting solubilization systems for APIs and modeling the solubility of a given API in candidate polymers for drug-eluting polymeric devices.

A second module introduced in mid-2011 calculates inter-particle forces in dispersed systems, and leads to the design of stable nano- or microparticle suspensions. The third and latest addition accurately models the elution of a given API from a non-degrading polymeric device, such as an implant or an intravaginal ring. Based on well-established mathematics and a set of base measurements, this latest addition allows Particle Sciences to significantly reduce the time needed for prototyping drug-device combination products.

"These proprietary computational tools, combined with Particle Sciences' industry-leading formulation and process capabilities, give our clients a true competitive advantage, allowing them to get to the right product faster," said Dr. Andrew Loxley, Particle Sciences' Director of New Technologies. "Particle Sciences has also institutionalized the use of Design of Experiments (DOE) in the product development process. While there is no replacement for actual prototyping and measurement, the systematic use of these modeling tools to guide the DOE approach streamlines our efforts, providing our clients with the most expedient path to clinically relevant products."

Particle Sciences is an integrated provider of drug development services, focusing on BCS II/III/IV molecules, biologics, and highly potent compounds through a variety of technologies, including emulsions, gels, micro- and nanoparticulates, drug/device combination products, solid solutions, and others. Through a full range of formulation, analytic, and manufacturing services, it provides pharmaceutical companies with a complete and seamless development solution that minimizes the time and risk between discovery and the clinic.

Molecular Partners Expands Agreement in Deal Worth $800 Million

Molecular Partners AG recently announced it has entered into a strategic research collaboration and option agreement with Janssen Biotech, Inc. to research, discover, and develop DARPin products for the treatment of immunological diseases. The collaboration and expansion of its current agreement with the company and its affiliates aims to explore a defined set of targets, including the use of multispecific DARPins, to address diseases in which continued unmet needs for effective treatment options continue to exist.

Under the agreement, Molecular Partners and Janssen Biotech will collaborate on research of DARPins to selected targets. During the research phase, Janssen Biotech has the right to exercise four options to exclusively license DARPin-based products. Upon execution of each option, Janssen Biotech will be solely responsible for all clinical development, manufacturing, and commercialization activities. Molecular Partners has an option to co-develop one product on a global basis.

Molecular Partners will receive significant up-front fees, license payments, and research funding as part of an innovative agreement, as well as development and sales milestones of up to $200 million for each option. Upon commercialization, Molecular Partners will be entitled to a tiered and up to double-digit royalty on worldwide net sales.

"We are thrilled about entering into this broader alliance with Janssen Biotech as an expansion of our current agreement, which is a significant effort to build and expand our internal and external immunology pipeline. We see the enabling power of the DARPin platform as a compound engine for us and our partners to generate pioneering multi-specific compounds delivering true patient benefit," said Christian Zahnd, PhD, CEO of Molecular Partners.

"The strategic value of this deal is the collaborative approach with a multi-disciplinary team of world-class scientists, under which Molecular Partners expands its position of strength as a biopharmaceutical company pioneering innovative protein therapeutics, while retaining rights to develop novel assets not optioned by Janssen Biotech during the research collaboration."

Veloxis Pharmaceuticals & Athena Drug Delivery Solutions Announce Partnership

Veloxis Pharmaceuticals and Athena Drug Delivery Solutions recently announced an alliance in which Athena will obtain exclusive rights in certain emerging market territories to manufacture and, with third parties, develop, register, and commercialize Veloxis' AtorFen (Fenofibrate Atorvastatin fixed-dose combination).

AtorFen will contain the lowest fully effective dose of fenofibrate and is a combination of two effective dyslipidemia treatments in one tablet, thereby potentially improving patient compliance. The product has been developed by Veloxis through Phase II in the US.

Results showed significant improvements in HDL-C, triglycerides, VLDL, and fibrinogen compared with atorvastatin alone (Lipitor 40 mg) as well as significantly greater effect on non-HDL-C, LDL-C, triglycerides, and total cholesterol compared with fenofibrate alone (Tricor 145 mg).

Under this alliance, Athena will establish and fund AtorFen manufacturing capabilities in India and through partnerships with regional and country level pharmaceutical companies develop and, once approved, commercialize the product. Veloxis will transfer its technology for manufacturing of AtorFen to Athena, with all expenses funded by Athena, and Veloxis will retain 70% of all revenues generated (subject to a minimum royalty rate). Veloxis will retain the right to reclaim major territories or regions where third-party distributors are not established by Athena within certain time intervals.

"This alliance will enable Veloxis to establish a competitive presence for AtorFen in emerging markets," said William Polvino, MD, Chief Executive Officer of Veloxis. "Substantial future growth in the pharmaceutical industry is expected to come from this region where cardiovascular morbidity is on the rise. We're delighted to have the opportunity to work with Athena, a company that is well positioned in emerging markets. This agreement is part of our strategy to out-license our cardiovascular portfolio to partners who can realize the full value of these assets."

Alexion Pharmaceuticals to Pay $1 Billion for Enobia Pharma

Alexion Pharmaceuticals, Inc. and Enobia Pharma Corp. recently announced the companies have signed a definitive agreement under which Alexion will acquire 100% of the capital stock of Enobia. Enobia is a private biopharmaceutical company based in Montreal, Canada, and Cambridge, MA, focused on the development of therapies to treat patients with ultra-rare and life-threatening genetic metabolic disorders.

Enobia's lead product candidate ENB-0040 (asfotase alfa), is a human recombinant targeted alkaline phosphatase enzyme-replacement therapy for patients suffering with hypophosphatasia (HPP), an ultra-rare, life-threatening, genetic metabolic disease for which there are no approved treatment options. Alexion will acquire full worldwide development and commercial rights to asfotase alfa. Asfotase alfa was awarded orphan drug designation in the US and EU in 2008 and Fast Track status in the US in 2009, and is currently in Phase II clinical development.

"Hypophosphatasia is an ultra-rare and life-threatening disease, and those patients who survive live with debilitating morbidities, including skeletal deformity, severe muscle weakness, and progressive damage to vital organs," said Leonard Bell, MD, Chief Executive Officer of Alexion. "Asfotase alfa has shown very compelling Phase II clinical data in infants and juveniles with hypophosphatasia. The acquisition of Enobia is very well aligned with Alexion's objective to develop and deliver life-transforming therapies for patients suffering with ultra-rare, severe, and life-threatening disorders."

"Alexion has proven expertise in developing and commercializing therapies to transform the lives of patients with severe and ultra-rare disorders, making them the ideal partner to advance the work of the Enobia team and bring asfotase alfa to HPP patients around the world," added Jonathan Silverstein, General Partner of OrbiMed and Enobia Chairman.

Alexion will acquire Enobia in an all-cash transaction. Under the terms of the agreement, Alexion has agreed to pay $610 million in cash upon consummation of the transaction, and up to $470 million in cash to be paid upon achievement of various regulatory and sales milestones. Alexion is not issuing equity in connection with the acquisition. The transaction is subject to customary conditions, including the expiration or termination of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act. The Boards of both companies have approved the transaction and the companies currently anticipate that the transaction will be completed in the first quarter of 2012. Alexion intends to finance the acquisition through cash on hand and $300 million of committed bank debt.

Goldman, Sachs & Co. is acting as financial advisor to Alexion. Ropes and Gray LLP is acting as legal counsel to Alexion. Bank of America Merrill Lynch is acting as financial advisor to Enobia. WilmerHale is acting as legal advisor to Enobia.

Asfotase alfa is an investigational, highly innovative, first-in-class recombinant protein that addresses the underlying cause of HPP by targeting replacement of the missing enzyme to the necessary body tissues. Asfotase alfa is designed to normalize the genetically defective metabolic process and prevent or reverse the severe and life-threatening complications of life-long dysregulated mineral metabolism in patients with HPP.

Thermo Fisher Scientific Uses New Method to Determine Sialic Acids in Glycoproteins

Thermo Fisher Scientific recently announced a new method that uses high-performance anion-exchange chromatography with pulsed amperometric detection (HPAE-PAD) to determine sialic acids in glycoproteins. Application Update 181: Rapid Screening of Sialic Acids in Glycoproteins by HPAE-PAD demonstrates good recoveries, precision, and linear detection for N-acetylneuraminic acid (Neu5Ac) and N-glycolylneuraminic acid (Neu5Gc). Using the Thermo Scientific Dionex CarboPac PA20 Fast Sialic Acid column, this rapid method separates Neu5Ac and Neu5Gc with a total analysis time of < 5 minutes, providing high-throughput sample analysis while reducing eluent consumption and waste generation.

Glycoprotein sialylation is critical to bioavailability, stability, metabolism, and immunogenicity of therapeutic proteins. As a result, proteins such as Neu5Ac and Neu5Gc are routinely analyzed to determine sialylation amount and identity.

This application note and many others can be found at www.thermoscientific.com/dionex under the Documents tab.

Thermo Fisher Scientific Inc. is a world leader in serving science with a mission to enable its customers to make the world healthier, cleaner, and safer. With revenues of nearly $11 billion, it has approximately 37,000 employees and serves customers within pharmaceutical and biotech companies, hospitals and clinical diagnostic labs, universities, research institutions and government agencies, as well as in environmental and process control industries.

Abbott Laboratories Spends $400 Million on Development Deal

Abbott Laboratories and Reata Pharmaceuticals recently announced they have entered into a worldwide collaboration to jointly develop and commercialize Reata's portfolio of second-generation oral antioxidant inflammation modulators (AIMs). The agreement is in addition to the partnership between the two companies announced in September 2010 in which Reata granted to Abbott exclusive rights to develop and commercialize its lead AIM compound, bardoxolone methyl, outside of the US, excluding certain Asian markets.

The collaboration is a global agreement and includes a large number of molecules in a broad range of therapeutic areas, including pulmonary, CNS disorders, and immunology. Abbott and Reata will equally share costs and profits for all new AIMs in all newly licensed indications except for rheumatoid arthritis and select other autoimmune diseases, in which Abbott will take 70% of costs and profits, and Reata will take 30%. The deal also includes a research agreement in which the companies will work together to discover new molecules that exhibit the same pharmacology as the AIMs already in Reata's pipeline.

Abbott will make a one-time license payment of $400 million to Reata. The companies expect the first compound in this collaboration to enter into human clinical trials in 2012.

AIMs are potent activators of the transcription factor Nrf2. Activation of Nrf2 promotes the production of a wide range of antioxidant, detoxification, and anti-inflammatory genes. Activation of Nrf2 also inhibits NF-KB, a transcription factor that regulates many pro-inflammatory enzymes. Suppression of Nrf2 and activation of NF-KB have been associated with numerous chronic diseases, including multiple sclerosis, rheumatoid arthritis, chronic kidney disease, neurodegenerative disease, and COPD. Therefore, agents that activate Nrf2 and inhibit NF-KB may be beneficial in the treatment of these chronic diseases.

Pharmacyclics Could Get Almost $1 Billion in Licensing Deal

Janssen Biotech, Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, recently announced it has executed an agreement with Pharmacyclics, Inc. to jointly develop and market the anti-cancer compound, PCI-32765. A number of Phase I and II studies with PCI-32765 are ongoing across a panel of B-cell malignancy disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and diffuse large B-cell lymphoma. Interim data were reported at the 2011 American Society of Clinical Oncology Annual Meeting, and oral presentations on two separate Phase II studies were presented at the upcoming American Society of Hematology Meeting in December, along with several other poster presentations.

According to the terms of the agreement, the companies have entered into a worldwide 50/50 profit-loss agreement, sharing development and commercialization activities. Janssen has made an up-front payment of $150 million, which will be recorded in the fourth quarter, and will make additional payments based upon the achievement of certain development and regulatory milestones. This transaction is expected to have a dilutive impact to Johnson & Johnson's 2011 earnings per share of approximately $0.04 to $0.05.

PCI-32765 is an orally active, small molecule inhibitor of Bruton's tyrosine kinase (Btk), an essential element of the B-cell antigen receptor (BCR) signaling pathway. BCR signaling is a critical pathway required for tumor expansion and proliferation, and PCI-32765 exerts its anti-tumor function by blocking BCR signaling and thereby inducing cell death.

The Janssen Pharmaceutical Companies of Johnson & Johnson are dedicated to addressing and solving the most important unmet medical needs of our time, including oncology, immunology, neuroscience, infectious disease, and cardiovascular and metabolic diseases.

Pharmacyclics Inc. is a clinical-stage biopharmaceutical company focused on discovering and developing innovative small-molecule drugs for the treatment of cancer and immune-mediated diseases. Its pharmaceutical drug development candidates are synthetic small molecules designed to target key biochemical pathways involved in human diseases with critical unmet needs. Currently, the company has four product candidates in clinical development and several preclinical molecules in lead optimization.

Aptar Pharma's Ophthalmic Dispenser Chosen for Eyecare Product

Aptar Pharma recently announced its innovative and patented preservative-free multidose Ophthalmic Squeeze Dispenser (OSD) has found its first application for the treatment of dry eye with the launch of VISMED MULTI. Aptar Pharma has worked closely with the Swiss-German-based Eye Care specialist TRB Chemedica for improving patient safety, achieving dosing accuracy, and maintaining product stability on the ophthalmic spray device.

Dry eye patients instill regularly lubricant eye drops, and often for the rest of their life. Most of these patients are elderly and experience difficulties when using preservative-free multidose dispensers because dispensing systems currently available do not offer overall satisfaction for eye drop delivery. In particular, the fact that preservatives can be omitted with Aptar Pharma's OSD system, is well appreciated by the high number of patients experiencing eye irritation or allergic responses with preserved formulations.

Aptar Pharma's OSD system is the result of more than 10 years of development for the delivery of preservative-free ophthalmic solutions. TRB Chemedica's new VISMED MULTI, a patented, sterile, hypotonic lubricant eye drops formulation of 0.18% hyaluronic acid with essential ions calcium, magnesium potassium contains 10 ml of solution, equivalent to more than 250 drops and remains sterile for up to 3 months after first use.

For this solution, Aptar Pharma's OSD system features intrinsic intuitiveness of a squeezable container, user friendliness for all adult age groups due to a low actuation force, precise and reproducible drop ejection, and ergonomic and pocket size design. With choosing the worldwide trend toward safe, patient-friendly, cost-effective, and preservative-free multidose dispensers, such as Aptar Pharma's OSD system, VISMED MULTI is able to maintain its status as the gold standard in lubricant eye drops.

Marketing Matters

Best Practices for Targeted Marketing Communications

A multiple part series on effective messaging and insights to the contract services provider industry.

By: Kelly Bray, Writer at Nice Insight

It is no secret that the contract research and manufacturing market is an extremely competitive landscape in which a plethora of companies, offering similar services, are seeking to differentiate themselves from competitors and form strategic relationships with Big Pharma and Biotech companies. The breadth of opportunities is narrowing as the markets continue to streamline. Based on data from its quarterly survey from executives in outsourcing roles, Nice Insight developed a best practices model for determining which modes of marketing communication are most effective for conveying the key drivers that influence CRO and CMO partner selection.

Through in-depth conversations with industry thought-leaders, Nice Insight established six key attributes (quality, reliability, affordability, productivity, accessibility, and regulatory compliance) that decision-makers consider when selecting potential partners. However, data indicates that the common notion of pricing as the ultimate influencer does not apply to outsourcing partner selection. Rather, for four quarters in a row, respondents from Nice Insight's Pharmaceutical and Biotechnology Outsourcing survey indicated that quality was their primary consideration in regard to partner selection. This was followed by reliability, affordability, productivity, regulatory compliance, and accessibility.

All CROs and CMOs seeking to position themselves as an optimal strategic partner need to have their baseline brand, messaging, and communications in good order. Market intelligence covering the competitive space and also the focused needs of the audience helps companies to position their brand with the right visual aesthetic and messaging. A website is the base communication for every company because it is always available and allows viewers to explore a depth of detail. Marketing in pharmaceuticals and biotechnology is also largely driven around tradeshows, so effective management of the overall presence at the right profile of shows is another fundamental.

When considering the ranking of the six key outsourcing drivers, there can be differences in optimal tactics within the marketing mix depending on what audience a CRO or CMO is seeking to attract, and whether they need to prioritize customer awareness (if they're not well known) or customer perception.

Relating back to that hierarchy, when it comes to perceptions of both quality and reliability, Nice Insight recommends focusing on targeted messaging and visuals. The use of websites and literature are better suited for communicating compliance, as they allow for a more in-depth description of a company's capabilities and regulatory processes. Motion graphics is another good option, as it has the advantage of easily conveying a complicated message in a memorable, engaging way. Websites are best suited to convey productivity because they can be easily updated with detailed, timely, and targeted information. When it comes to accessibility and affordability, tradeshow booths are ideal because they allow for face-to-face dialogue with potential partners. This is especially true when it comes to conveying accessibility, which involves the ease and effectiveness of communication between a sponsor and CMO.

FIGURE 1

SIDEBAR

Survey Methodology

The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to 40,000 outsourcing-facing pharmaceutical and biotechnology executives on a quarterly basis/four times per year (Q4 2011 sample size 2619). The survey is composed of 1200+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 300 companies that service the drug development cycle. Over 1600 marketing communications, including branding, websites, print advertisements, corporate literature, and tradeshow booths are reviewed by our panel of respondents. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing (Quality, Accessibility, Regulatory Compliance, Pricing, Productivity, and Reliability), which are ranked by our respondents to determine the weighting applied to the overall score.

If a company needs greater customer awareness to attract growth - intelligence that is readily available via Nice Insight quarterly reporting - it may want to consider tactics focused on this need. One of the most effective ways to boost awareness is through advertising with customized messaging in targeted trade media. Direct communications (such as personalized emails, print pieces, and web updates) around tradeshow events, company news, and products/technology are also efficient means of generating interest. Finally, increasing PR and editorial efforts (with a focus on publications and news outlets that reach the desired audience) is another solid strategy for increasing awareness.

After identifying the most effective forms of marketing communication for each particular driver, it makes sense to take a look at the frequency at which CROs and CMOs update their marketing materials. According to Nice Insight's data, between Q1 and Q2, 3.50% of companies rebranded (14/400), 4% updated their logos (16/400), 8% created new ads (32/400), 14% updated their websites (56/400), and 19% of companies updated their trade show booths (75/400). Between Q2 and Q3, updates to tradeshow booths, advertisements, and websites, again, were the most prevalent. However, by Q4, the number of companies that rebranded decreased to 0.33%, logo updates dipped to 2.01%, new ads increased to 14.38%, website updates dipped substantially to 3.34%, and updates to tradeshow booths remained most common at 19.06%.

The fact that the numbers for rebranding and logo updates appear fairly low across the board when compared to other forms of marketing communications can likely be attributed to the fact that (often unrightfully so) companies are more hesitant to alter their branding strategy unless it is painfully clear that what they are currently doing is not working (or in the case of a merger or acquisition). Willingness to change branding can also vary depending on the time of year, and is often least likely to happen in Q4. On the other hand, website updates and new advertisements are often easier to approve and execute from both a creative and business standpoint. The fact that tradeshow booths are more frequently updated is unsurprising, given that in order to be effective, they should be customized for specific audiences at different shows throughout the cycle.

There are no cut-and-dry answers when it comes to increasing customer awareness and perception to improve potential partnership opportunities. The best strategies to employ may vary depending on factors such as audience, timing, resources, and budgets. Above all else, it is essential for contract service providers to implement a strategic marketing plan with targeted messaging that communicates core differentiating benefits, while focusing efforts at the right audience for their capabilities.◆

BIOGRAPHY

Kelly Bray is a writer for Nice Insight and has been with the company since its inception. She has extensive experience writing in the life sciences, chemical, and other technical industries, including editorial, advertising, literature, and web work. Her background includes previous positions as a writer at Waterfront Media and McGraw-Hill Publishing. Currently based in New York City, Ms. Bray earned her Masters Degree in Publishing from Pace University in 2007.

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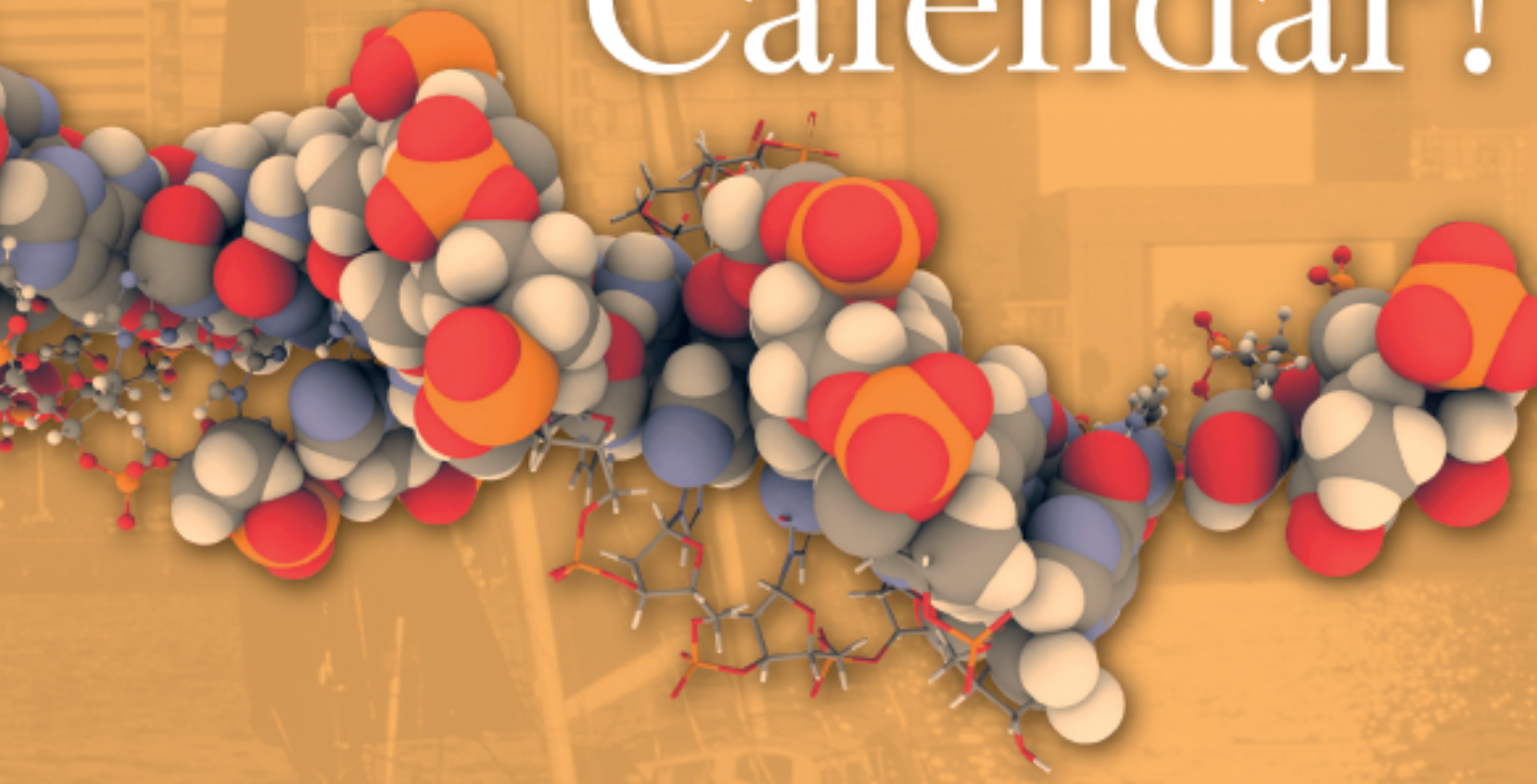

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Biometric Tamperproof Drinkable Drug Dispenser (BTD3)

By: S. Craig Dyar, PhD, and Tomas J. Svoboda, BSc

The market for pain medications is continually expanding as evidenced by the 680% increase in global consumption of morphine from 7.2 tons in 1990 to 41.8 tons in 2009.[1] Along with the rise in legitimate use, a corresponding increase in the misuse, abuse, and diversion of pain medications has also been observed.[2] To combat the increase in abuse and diversion, several technologies have been employed to decrease the potential for abuse of solid oral dosage forms. These technologies range from the formulation of extended-release morphine coated over naltrexone hydrochloride pellets, an abuse deterrent, as seen in Embeda® to a tablet that when it is crushed and inhaled turns into a nasal irritant gel when exposed to the fluid in the nasal mucosal as seen in Oxecta®. However, the authors are unaware of any misuse, abuse, or diversion prevention drug delivery technologies currently on the market or in development for any medications to be delivered in liquid form for oral use.

DEVICE REQUIREMENTS

Due to the high abuse potential of liquid drinkable morphine, the development of an affordable inviolable personalized liquid medication dosing device that is easy to use in an ambulatory setting was seen as an unmet medical need. Several key parameters were taken into consideration in the development of a delivery device to fill this unmet medical need. Namely, the device must have restrictive access to the content. If the device were breached, then it would need a means for the medication to be inactivated. A data recording feature to not only aid in abuse or misuse detection, but also ensure compliance with the medication regiment was another key design requirement. Other key parameters were taken into consideration to make the device affordable and durable, while keeping it intuitive to use for healthcare staff and patients.

FIGURE 1

Biometric Tamperproof Drinkable Drug Dispenser (Closed)

FIGURE 2

Biometric Tamperproof Drinkable Drug Dispenser Showing Fingerprint Actuation

TECHNICAL DETAILS OF THE DEVICE

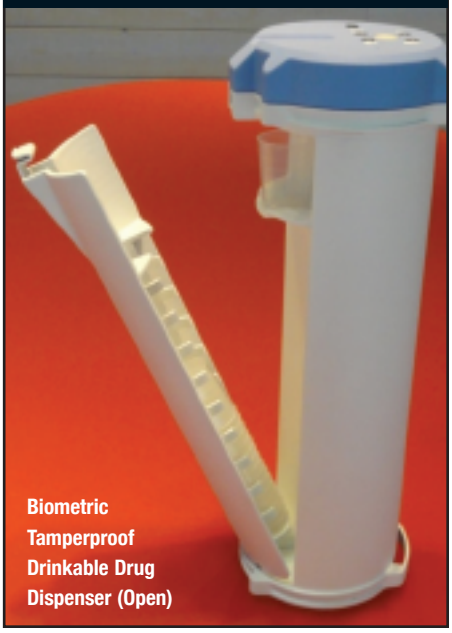
The Biometric Tamperproof Drinkable Drug Dispenser (BTD3) (Figure 1) is a device that was developed to fit these requirements and has a pending patent with 10 unique and innovative claims, the most significant of which are outlined further.[3] The BTD3 is easily filled, programmed, locked, and armed by a pharmacist, nurse, or other healthcare provider. The programming can include limits on the dose volume and frequency of dosing to prevent the patient from accidentally or intentionally overdosing. Access to the dose is in the form of a third-generation fingerprint scanner easily operated by the patient or caregiver (Figure 2). The device can hold up to 1 L of liquid medication as a solution or suspension in a single-use elastomeric bag and can deliver from a 5-mL to a 25-mL size dose per actuation with a dispensing accuracy of greather than 90%, thereby providing between 40 and 200 doses before requiring a refill. The dispensing cup can be easily seen in Figure 3. The dispenser contains an area around the elastomeric bag where a constant pressure is maintained by a micropump. If the device is breached, the resulting pressure drop in the system will trigger the armed safety cartridge containing activated charcoal of specific particle size, which will then be released, and the medication will be absorbed into the activated charcoal. An additional feature designed into the system to prevent the bypassing of the inactivation step by freezing the liquid was the addition of a temperature monitor that will activate the safety cartridge following a sudden temperature drop in the system. If the activated charcoal is not an appropriate inactivating agent, then other solutions, suspensions, or powders can be released to inactivate the medication. It also contains auditory and visual reminders to alert the patient to the next dose and subsequently can record medication usage in both frequency and volume. The low energy requirements of the pump and the electronics lead to a non-rechargeable battery life of more than 2 years, while the robust design provides for a product functionality warranty of 2 years. The secure infrared wireless data transmission built into the device can be used for dose programming, access control, recorded data transfer, and other electronic functions. The software is based on Java, making it compatible with a multitude of operating systems, including Linux, Windows, and Mac for application control. In addition, it can be programmed via many Smartphones that are capable of running Java. In order to keep the cost as low as possible, the device will be manufactured using injection molding technology. Based upon a use expectancy of the device for at least 2 years, the cost of the device, including the cost of drinkable morphine sulfate, is expected to be less than $1 a day, and is significantly lower than the $5 to $15 a day for tablets, injections, or patches, which makes it a more economical means of delivering pain control than most of these delivery systems.

An early stage prototype version has already been evaluated in a hospital-based patient setting under extreme environment conditions in Tanzania to evaluate the ease of use of the device by less technology savvy users. The assessment confirmed the intuitiveness and simplicity of the design, which features a one-button operation with fingerprint access.

A renowned South African distributor of pain treatment products for sub-Saharan Africa expressed in writing his strong interest in the BTD3 for his customers on cancer and HIV treatment plans. In addition, a survey of 20 key worldwide opinion leaders specializing in palliative pain management was performed to gather feedback about the clinical need and usage of the BTD3. The response received indicated that 88% of contacted experts in chronic pain management would use the device for their patients once it was made available in their respective markets.

The device is in its industrialization

FIGURE 3



Biometric Tamperproof Drinkable Drug Dispenser (Open)

and regulatory clearance phase of development. The company performing the development work on the device and who will also manufacture it is based near Ethimedix's corporate headquarters in Geneva, Switzerland. The first commercial units of the BTD3 will be provided to patients in need by early/mid 2013 in selected geographic regions.

MULTITUDE OF USES

The BTD3 was primarily developed for oral around-the-clock patient-controlled analgesia (PCA) in a hospital, ambulatory, or homecare environment for cancer and non-cancer patients with chronic pain to deliver liquid morphine. It can also be used for the treatment of narcotic addiction in a methadone treatment program. Another application for the device is as a more economical dispensing system in a pharmacy or on a medical unit in the hospital where it could replace the more expensive unit-dose containers while at the same time adding an increased level of security of the narcotic and improved dosing accuracy. It also has utility in these same settings to replace bottles of liquid medication, thereby providing for increased security of the controlled substance.

There are numerous other uses for the device, such as to deliver non-controlled pharmaceuticals in liquid form requiring stringent prescription adherence and overdose protection that are used in the homecare environment for treatment of conditions, such as depression, Alzheimer's, seizures, attention deficient disorder, emesis, narcolepsy, AIDS, transplant rejection, osteoporosis, inflammation, and allergies. An extremely common problem in the child and adult daycare setting is to ensure the delivery of the correct medication to the proper patient at the correct time and in the proper dose. In this environment, you commonly have workers that are not as well trained as those in the hospital setting and are extremely busy; this combination can lead to the wrong medication and dose being given to a child or adult. The BTD3 provides an ideal economical solution to this problem. Obviously, the deterrent function is not needed for delivery of a non-controlled medication and is not a required function of the dispenser, but the medication dosing alert and patient-specific delivery functions are important components and could significantly improve the care of these patient populations. Additionally, the electronic controls can be customized for the specific application.

The manufacturer of the device plans to develop a portfolio of various product configurations that will be customized for the delivery of a specific medication for a relevant clinical indication. The technical requirements of the respective device will be defined based on the end-user's need with input from the patient and healthcare provider and/or by the pharmaceutical or medical device company that markets the medication intended to be dispensed by the specific device design configuration. Strategic partnering with global players to provide a customized BTD3 under co-marketing or licensing agreements is part of the business strategy of the manufacturer in order to provide a broader use of the device across different applications as previously outlined. The range of the BTD3 device configurations can be from a simple and disposable device to a more sophisticated version that could be remotely controlled to allow for two-way communications with healthcare providers at a distant location. The intention is to provide the most suitable, cost-effective, and easy-to-use drinkable drug dispenser for delivery of the appropriate liquid medication for a particular clinical indication to a specific patient population, and thus to ensure optimal patient compliance to the drug regimen.

SUMMARY

The increase in misuse, abuse, and diversion of pain medications coupled with the high daily cost of the oral tablet technology designed to prevent abuse led to the development of the BTD3. It is uniquely positioned to fill an unmet medical need for the secure storage and patient controlled delivery of both controlled and non-controlled medications, while also improving patient compliance and preventing potential overdose situations. The next stages of development are to secure funding for the industrialization, CE marking (a mandatory conformity mark for products placed on the market in the European Economic Area), and to complete clinical observations. ◆

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BIOGRAPHIES

Dr. S. Craig Dyar is President of SCD Pharma Consulting. A company providing consulting services in drug delivery R&D, project management, business development, patents, life-cycle management, technology assessment, and drug development from discovery to post-launch. He is also an Assistant Professor at South University School of Pharmacy, where he teaches Pharmacokinetics and Pharmaceutics. He joined Warner Lambert in New Jersey as a Scientist developing novel drug delivery systems and assessing external drug delivery companies. He then progressed to a management level position focusing on external drug delivery assessment and intellectual property. In 2001, he was assigned additional responsibility as a team member on the Worldwide Pharmaceutical Sciences (WWPS) Licensing Team. In 2004, he assumed a new role with responsibility for managing the COX-2 franchise for WWPS, where he was an active member of the COX-2 lifecycle team, chaired a reformulation sub-team, and chaired two COX-2 related Product Management Teams. Dr. Dyar served as a key member on a number of teams, including the Intellectual Property Team, Global Drug Delivery Team, and the Technology Board, which he also chaired. He was the WWPS Team Leader for Ophthalmology and a member of the Ophthalmology Development Teams, where he served as the single point of accountability for WWPS. In this role, he communicated and negotiated the project strategy and investment tactics across the globe. To accomplish this task, he led several WWPS Project Teams in planning, tactics, problem-solving, risk assessment, and scenario analysis. Later, he held the same position for the Dermatology portfolio. Dr. Dyar earned a bachelor's degree in Biology from the University of South Carolina and a bachelor's degree in Pharmacy and PhD in Pharmaceutical Science at the Medical University of South Carolina.

Mr. Tomas Svoboda co-founded Ethimedix, a medical device company focused on drinkable drug delivery systems with the first focus on chronic pain management. He has spent 29 years in the Life Science industry working in medical instrumentation, in vitro diagnostics, implantable devices, and drug delivery/combination product companies. He worked and lived in the UK, Germany, France, US, Austria, and Switzerland while employed with corporations including Serono, Haemonetics, and Boston Scientific. During his corporate curriculum, he worked in a number of executive functions, including Head of European RA & QA (pre- and post-Medical Device Directive, implementation of ISO 9001 Quality System), responsible for Medical Vigilance Reporting (implantable products, MoH relationships), Head of Marketing (largest EU subsidiary), member of M&A team, Director of Intl. Product Supply and R&D department. Since 2000, he has been involved in several start-ups as a CEO of a drug delivery and pharmaceutical company, Managing Director of surgical instrumentation, and eventually founding his own service company specialized in management mandates in business development, sales & marketing, and regulatory affairs quality assurance, including those for large and mid-sized corporations as well as the Swiss government agency OPET as a Coach CTI Start-up. Mr. Svoboda earned his BSc in Medical Technology (Pharmaceutical Production Process) in Prague and Zurich, International Marketing at INSEAD and rounded it up with an e-MBA. He holds board positions in Swiss and Czech Life Science companies.

BIOAVAILABILITY ENHANCEMENT

A Novel Spray-Drying Technology to Improve the Bioavailability of Biopharmaceutical Classification System Class II Molecules

By: David Shi, PhD; Andrew Loxley, PhD; Robert W. Lee, PhD; and David Fairhurst, PhD

INTRODUCTION

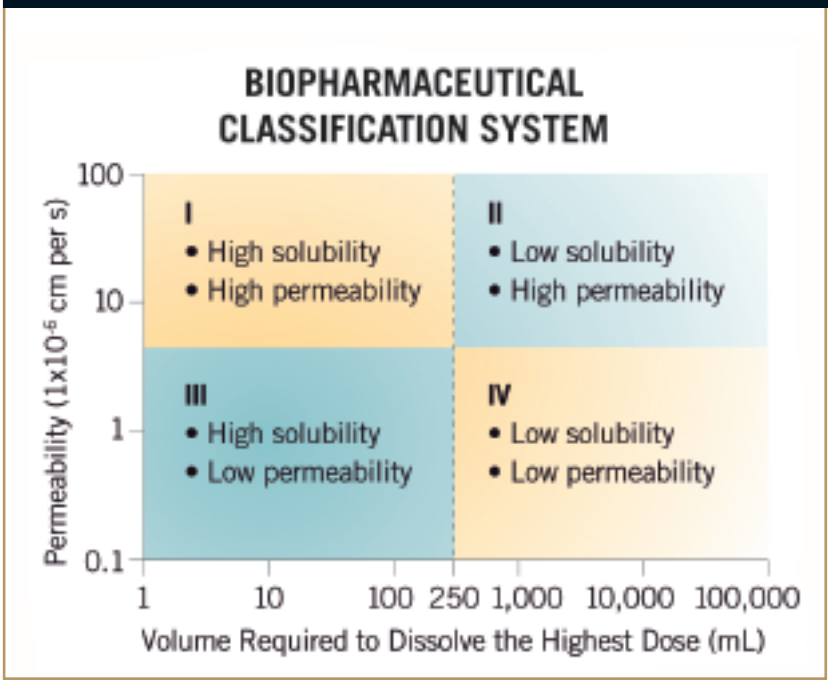
In life-cycle management of pharmaceutical products, novel drug delivery technologies that offer positive differentiation over first-generation products provide an important means for staying competitive in today's business environment. This article will briefly discuss a proven and scalable solid dispersion approach based on spray-drying that is suitable for Biopharmaceutical Classification System (BCS) (Figure 1) Class II active pharmaceutical ingredients (APIs) and new chemical entities (NCEs).[1-4]

Many existing APIs and NCEs are poorly water soluble and subsequently have low oral bioavailability if formulated in unmodified form. Traditional approaches to overcoming this include (1) improvement of water miscibility by employing self-emulsification, lipid-based techniques, solubilization into micellar cores, or alternatively complexation with cyclodextrins; (2) reduction of particle size to nano-scale via mechanical milling or high-shear processing accompanied by particle stabilization; and (3) impacting crystal lattice energy using polymorphs or co-crystals, or through the creation of solid dispersions of drug in inert carriers or matrices.[5-11]

Increasingly, solid dispersions are being looked at as a viable solution to this pervasive issue. Although only a few solid dispersions are currently marketed, the approach has some inherent advantages over other approaches. Presence of an active compound as a molecular or nano-particle dispersion combines the benefits of decreasing crystal lattice energy and maximizing surface area, thus facilitating better contact with dissolution media. Fortuitously, many of the carriers that can be employed for the production of solid dispersions are generally recognized as safe (GRAS) and are already extensively used as excipients in marketed products, easing the regulatory burden.

Particle Sciences has developed DOSE™ a formulaic approach to dosage form development that rapidly narrows in

FIGURE 1



What does something cost to make? Not in pennies per unit, but in worry? How much does it cost you, emotionally and psychologically, to work with a CMO? How many sleepless nights? How many stomachaches? How many frustrating conversations with people who can't seem to understand that while you sell a product, what you really make is a brand?

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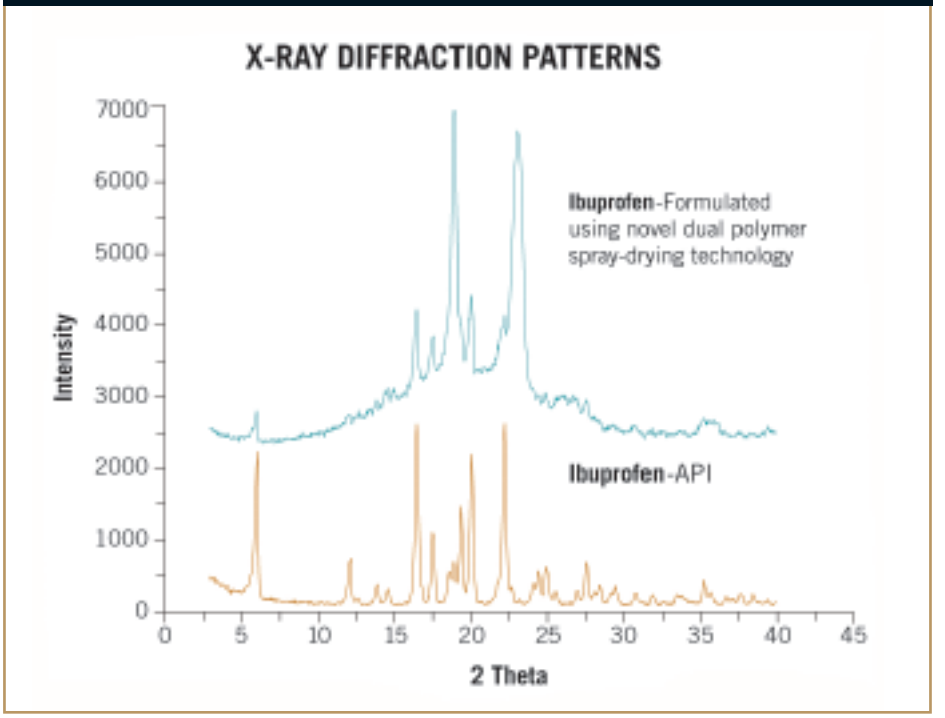
on the drug delivery technology of choice. When solid dispersions are called for, Particle Sciences has a number of approaches, one of these is a unique solid dispersion technology based on spray-drying using a dual-polymer system that significantly improves the dissolution and bioavailability of poorly soluble APIs. The technology has been proven in human trials and has been scaled to commercial levels. Under Particle Sciences DOSE system, APIs are first extensively characterized as to their physicochemical characteristics, including a proprietary solubility screen. Then after excipient compatibility studies, formulation prototypes are screened for their impact on solubility and permeability. This methodical iterative approach allows one to rapidly narrow in on the formulation approaches most likely to yield the desired results.

THE DRUG DELIVERY PROBLEM

An increasing number of compounds coming out of discovery are poorly soluble. By some estimates, 40% to 70% of new lead compounds in development fall into this category.[12,13] Additionally, many new compounds also exhibit poor permeability. In 1993, the BCS was proposed as a way to facilitate the marketing of generic drugs. The system classifies a given compound by its aqueous solubility and gut permeability.

Beyond its regulatory use, the BCS provides a very useful framework in which to evaluate APIs and chart a logical course to achieve the desired pharmacokinetics (PK), including greater bioavailability. For BCS II and IV molecules, in which solubility is the main or largely contributing limiting property, there are a number of approaches, including increasing surface area through particle size reduction, surface morphology modification, and solid solutions.

FIGURE 2



A NOVEL DUAL-POLYMER SPRAY-DRYING SOLUTION

Generating human data as quickly as possible is the goal of every drug developer, and there are several philosophies as to how best to achieve first in human (FIH) dosing. It has been estimated that three to six formulation changes occur from FIH to commercialization.[14] At Particle Sciences, we believe that FIH experience should be in a formulation that will provide useful developmental data. For a BCS I molecule, the prototypical formulation could be a simple powder-filled capsule. For a poorly water-soluble molecule, BCS II or IV, such a simple system is unlikely to provide any commercially helpful data, speed development, or bring to light clinically relevant findings. Therefore, an FIH formulation designed to deliver the drug in a commercially viable way is, in our view, important. For drugs with limited aqueous solubility, one such approach discussed in this paper involves a patented dual-polymer system utilizing GRAS excipients and traditional processing techniques.

In this approach, the API is solubilized in a water-miscible organic solvent, usually ethanol. A mixture of an amphiphilic and a hydrophilic polymer are prepared as a mixed

FIGURE 3

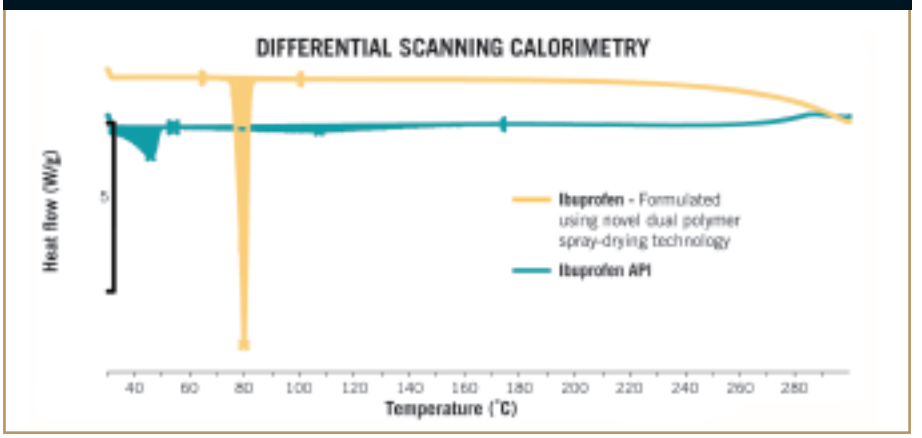
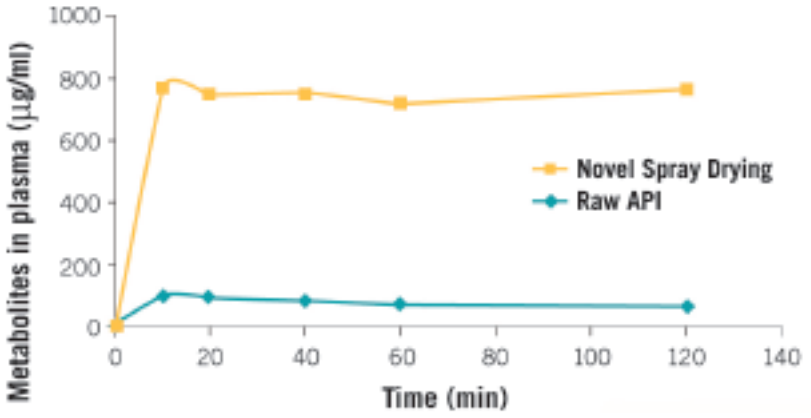
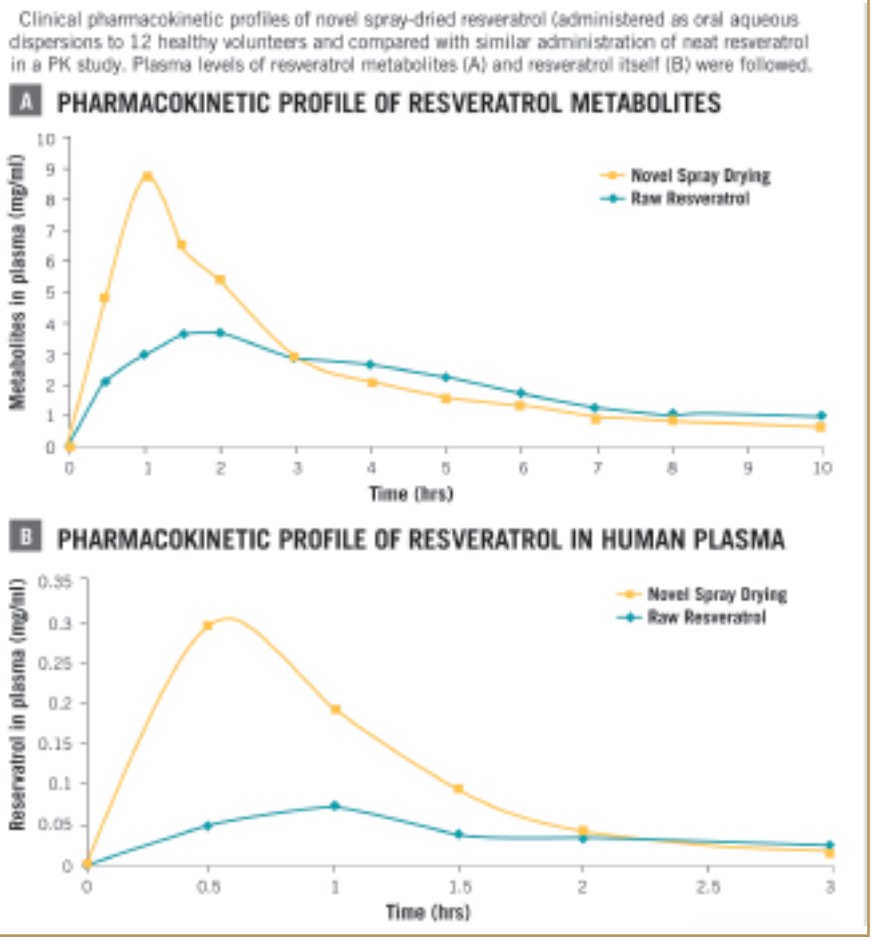


FIGURE 4



aqueous solution. The organic API solution and the aqueous polymer mixed solution are then mixed under carefully controlled temperature and agitation rate to form a transparent or hazy solution, which is subsequently spray-dried. The exact compositions of the feed stocks are determined in an extensive, yet efficient, preformulation phase utilizing Design of Experiment (DoE) methodology, when appropriate. Key drivers include the API's solubility in various organic solvents, the API's molecular weight, the solubilities of the polymeric excipients, and the compatibility of the API and polymeric excipients in the spray-drying solution.

FIGURE 5



In the context of this technology, amphiphilic polymers are defined as soluble both in organic solvents and in water. Examples of amphiphilic polymers suitable for use include but are not limited to polyethylene oxides (PEO, also commonly referred to as polyethylene glycol or PEG), PEO derivatives, PEO copolymers, such as PEO/polypropylene glycol (PPG) copolymers, PEG-modified starches, poloxamers, poloxamines, polyvinylpyrrolidones, hydroxypropyl cellulose, hypromellose, and esters thereof, vinyl acetate/vinylpyrrolidone random copolymers, polyacrylic acid, and polyacrylates.

Hydrophilic polymers are defined as those soluble in water or in a single-phase mixture of organic solvent and water, but not soluble in organic solvent alone. Examples of hydrophilic polymers include but are not limited to starch, sodium carboxymethylcellulose, hydroxyethylcellulose, polyvinyl alcohol, sodium alginate, chitosan, and carrageenan. Notably, these formulations utilize only FDA-approved polymers.

The use of hydrophilic polymers that ionize at different pH allows for the design of formulations targeted either to the stomach or the intestine. For example, chitosan, which is ionized at low pH, promotes drug release in the stomach, while sodium carboxymethyl cellulose and sodium alginate, ionized at neutral conditions, facilitate release in the small intestine.

The resulting powder is free flowing and will contain 25% or more API. Characteristics of the drug product include the following:

- Solubilized drug homogeneously interwoven into a polymer matrix.
- Drug in crystalline form within the polymer matrix.

- Depressed API melting temperature and enthalpy of fusion (Figure 1).
- Spontaneous formation of colloidal dispersions upon contact with aqueous media.
- Enhanced dissolution rate/solubility of the drug in aqueous media as well as prolonged supersaturation in relevant biological fluids, and GI site-targeted release of the drug.

CHARACTERIZATION

Powder X-ray diffraction (PXRD) is first used to characterize the API powder and the spray-dried formulation. As can be seen in Figure 2, the model drug (Ibuprofen) shows characteristic PXRD diffraction peaks, and a drug product containing 25% of the API, prepared by the novel dual-polymer spray-drying approach also shows some of the these same peaks, indicating that the API is present in crystalline form. In contrast to some systems that are dependent on amorphous API forms, this technology results in very stable particle constructs because the crystalline form of the drug is the most thermodynamically favored state.

In Figure 3, the impact of the technology on melting temperature and enthalpy of fusion is clearly demonstrated. It is believed that these thermal property alterations are at least in part responsible for the significant increase in solubility provided by this technology.

Several commercial compounds have been thoroughly evaluated using this novel technology. Figure 4 shows the dissolution profiles and clinical two-way pharmacokinetic data for Resveratrol. Clearly, the rate of dissolution is faster using the novel dual-polymer spray-drying approach, and reaches a higher final concentration than neat API.

Figure 5 shows clinical data showing higher C_{max} and AUC for the novel spray-dried resveratrol formulation in comparison with neat API, indicating significant increases in bioavailability when using this novel spray-drying approach.

FIGURE 6

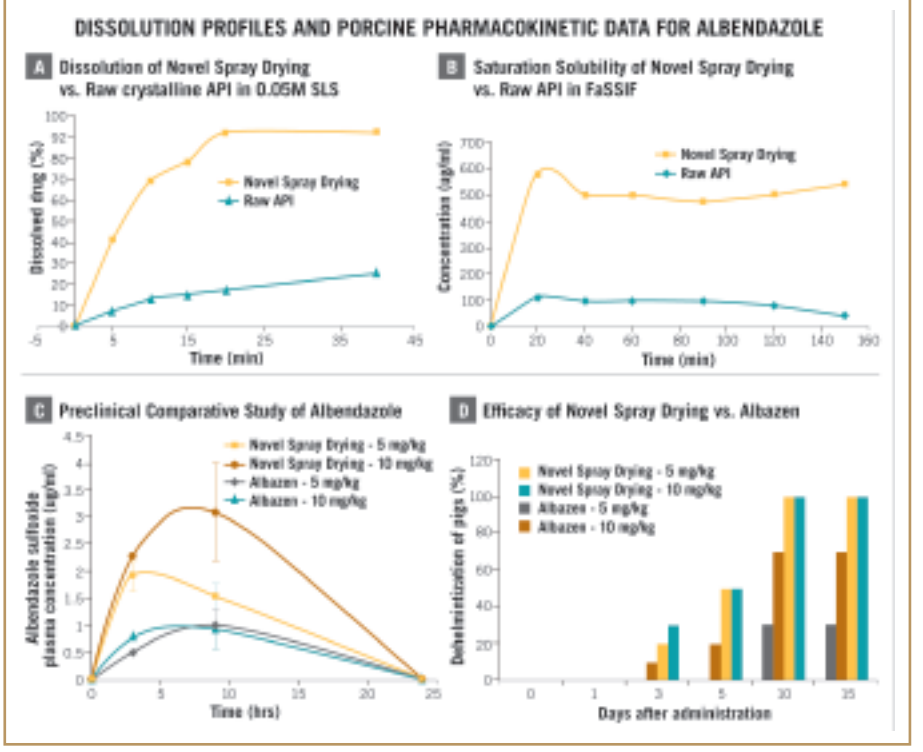


Figure 6 shows the dissolution profiles and porcine pharmacokinetic data for albendazole (A: dissolution profiles in 0.05 M SLS of raw API and API product formulated using the novel dual-polymer spray-drying approach; B: dissolution profiles in fasted simulated intestinal fluid of raw API and drug product formulated using the novel dual-polymer spray-drying approach; C: porcine PK data for commercial product versus product made by the novel dual-polymer spray-drying approach; and D: efficacy in porcine model of commercial product versus product made by using the novel dual- polymer spray-drying approach (data generated by Solubest, Ltd, Israel). The API solubility is enhanced, PK data are improved compared to a commercial product, and efficacy in the animal model is improved.

CONCLUSION

Whether reformulating an existing compound or working with an NCE, the ability to understand and manipulate those factors within our control that dictate PK behavior is key. For compounds with low solubility, we have presented one approach to oral dosage form development. Using GRAS ingredients and a readily scaled and patented process, employing this novel spray-drying technology results in stable crystalline constructs that increase API bioavailability by increasing the solubility of the API. To date, the technology has been demonstrated in more than a dozen compounds and is currently being scaled for Phase III for at least one. ◆

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BIOGRAPHIES

Dr. David Shi, as a Polymer Scientist with a PhD in Polymer Chemistry, has more than 15 years experience in development of new materials and drug delivery systems for bio/medical applications. He joined Particle Sciences, a contract research organization in Bethlehem, PA, as Formulation Scientist in 2009. He specializes in pharmaceutical formulation development and drug delivery technologies. In the past 10 years, his research has been focused on improving drug delivery in oral, topical, inhalation, and injectable dosage forms. His expertise includes nanoencapsulation, microencapsulation, liposomes, spray-drying, and organic and polymer synthesis. Dr. Shi is co-inventor of 10 issued patents related to novel drug delivery systems, some of which have been licensed, and has authored several peer-reviewed journal articles.

Dr. Andrew Loxley is Director of New Technologies at Particles Sciences Inc., a contract research organization in Bethlehem, PA, specializing in pharmaceutical formulation development. He leads a variety of projects, based on novel and proprietary nanotechnologies and combination devices, in fields from HIV vaccine and microbicide development, to gene-silencing SiRNA delivery. Prior to joining Particles Sciences, he led development efforts in next-generation lithium ion batteries at A123 Systems Inc, electrophoretic displays at EINK Corp., and emulsion polymers at Synthomer Ltd. British-born, he earned his BSc in Chemistry from the Univeristy of Sussex and his PhD in Physical Chemistry focusing on microencapsulation from the University of Bristol.

Dr. Robert W. Lee is Vice President of Pharmaceutical Development at Particle Sciences Inc. He is responsible for product development as well as providing support to clinical manufacturing operations and business development. His responsibilities include oversight of formulation development, drug delivery, analytical sciences, quality control, and quality assurance. Before joining Particle Sciences, Dr. Lee held senior management positions at Novavax, Inc., Lyotropic Therapeutics, Inc., and Imcor Pharmaceutical Co. He has also been in research positions at élan Drug Delivery, NanoSystems, and Sterling Winthrop. Dr. Lee holds bachelors in Biology and Chemistry from the University of Washington and a PhD in Physical Bioorganic Chemistry from the University of California-Santa Barbara. He has published articles in numerous peer-reviewed journals and three book chapters plus holds 11 issued patents and 14 provisional or PCT patent applications. Dr. Lee has more than 20 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. He maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas in 1992, and serving as a reviewer for both the International Journal of Pharmaceutics and Journal of Pharmaceutical Sciences and Editorial Advisory Board member for Drug Development & Delivery.

Dr. David Fairhurst is Corporate Research Fellow at Particle Sciences Inc. He earned his PhD in Physical Chemistry in 1968 from Liverpool Polytechnic, UK, where he was also a Lecturer (in Physical Chemistry) for 4 years. He spent 2 years as a Visiting Associate Professor in the Center for Surface and Coatings Research at Lehigh University and subsequently held senior research positions with the UK Chemical Defense Establishment, Porton Down, and with Union Carbide Corporation, USA. The work encompassed exploratory and basic research, product formulations, and development and technical services. He has spent the past 40 years in using colloid and surface chemistry to solve problems in industrial and pharmaceutical applications and has published more than 100 technical papers, scientific articles, and book chapters in the open literature. Prior to joining PSI in 1993, he was, for 7 years, Director of Applications at Brookhaven Instruments Corporation and is an internationally recognized authority on dispersion and emulsion technology and in the assessment and characterization of particle size.

Oral Administration of an Insulin-Soybean Suspension in Streptozocin Rats: Effect of Aqueous Soybean Extract Vehicle

By: Antoine Al-Achi, PhD; Brijesh Patel, MS; and Sejal Patel, MS

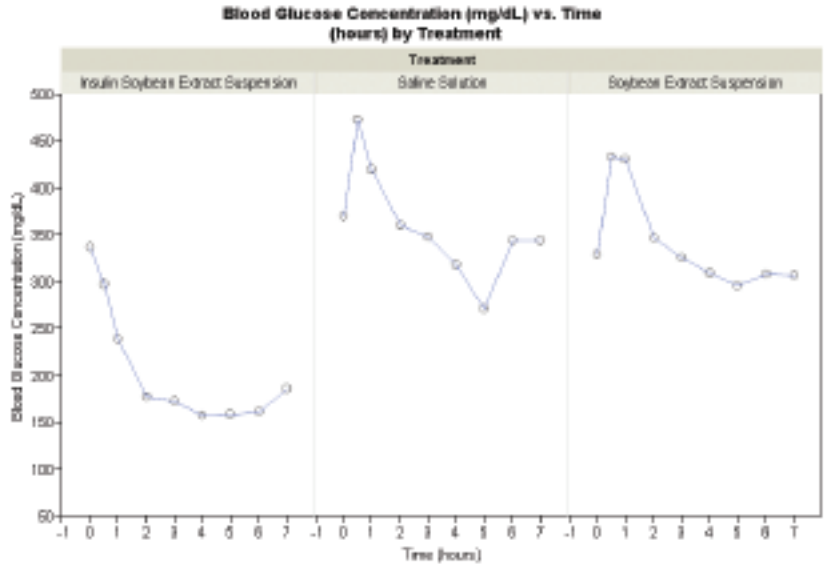
ABSTRACT

The use of human insulin (HINS) in the management of diabetes mellitus is well documented. HINS preparations are available in the form of sterile solutions and suspensions for parenteral administration. Other routes of administration, such as the oral route, have been investigated for delivering HINS. The gastrointestinal tract provides a hostile environment for HINS due to the presence of proteolytic enzymes and extreme variation in the pH. In this study, we administered a suspension of HINS (particle diameter ~30 micrometers; pH 4.1) orally to streptozocin diabetic rats to elucidate the effect of this preparation in the presence of soybean protease inhibitors. When compared to saline solution or soybean extract vehicle, rats receiving HINS in a soybean extract showed a notable drop in blood glucose concentration as soon as 30 mins post-administration and achieved a nadir level at 4 hours following administration. The reduction in blood glucose level at 4 hours post-administration was nine-fold or four-fold lower in the HINS group than that in rats receiving soybean vehicle or saline, respectively. This study demonstrates the potential of using a suspension of HINS in soybean extract vehicle for delivering HINS orally.

INTRODUCTION

Diabetes mellitus is a disease managed by the hormonal drug insulin and/or oral anti-diabetic medications. Available insulin preparations in the United States are sterile solutions for intravenous administration and suspensions for subcutaneous or intramuscular routes. Although an inhaled form of insulin was available for a short period on the US market, the manufacturer withdrew this dosage form citing practical considerations for its administration. Certain countries have approved the use of an insulin aerosol for buccal application that may be used in conjunction with parenteral insulin. Clinical trials on this type of administration are promising.[1] Research in the area of non-invasive types of insulin has been the subject of numerous investigations. In addition to the

FIGURE 1



Graphs represent blood glucose concentration (mg/dL) versus time following treatment. Data points are the average values (n = 6-9) of blood glucose concentration at different time points.

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

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aforementioned respiratory and buccal routes, investigators have sought other ways for insulin delivery, including nasal, vaginal, rectal, and oral routes. Perhaps the most practical is the oral route, affording better patient compliance and ease of administration. In addition, the oral route provides a way to simulate the physiological handling of insulin by the body. Following its secretion by the pancreas, insulin is delivered to the liver via the portal vein. The oral route provides a similar path for insulin following its absorption from the small intestine to the liver via the portal vein. However, the presence of a hostile environment in the gastrointestinal tract, namely the proteolytic enzymes and extreme variation in pH, renders this delivery route for insulin rather challenging.[2] Insulin has a large molecular weight (approximately 6,000 Daltons), can occur as larger aggregates in solutions, and is highly hydrophilic. Because of the hostile environment and its molecular characteristics, the bioavailability of insulin from the oral route is said to be about 1.6%.[3] The main strategies for enhancing the oral bioavailability of insulin are the use of carrier systems (natural and synthetic) and the administration of insulin with absorption enhancers or protease inhibitors, among others.[4-6] Excellent review articles on the oral delivery of insulin as well as other non-invasive routes are found in the literature.[7-12] Soybean (Glycine max) contains proteins possessing the ability to inhibit trypsin and chymotrypsin proteolytic activity. Protease inhibitors, Bowman-Birk and Kunitz, are the predominant proteins found in soybean. Soybean powder was found to contain up to 19.6 mg/g of Kunitz and 4.9 mg/g of Bowman-Birk inhibitors.[13] In addition to proteins, soybean contains monosaccharides, polysaccharides, cellulosic substances, and isoflavones.[14,15] The repeated oral administration of soybean Kunitz enzyme inhibitors in rats for 10 days resulted in a slight increase in insulin secretion, and the weight of the pancreas was also increased (hypertrophy and hyperplasia).[16,17] However, a single-dose administration of soybean inhibitors is not expected to cause any abnormal clinical or laboratory effects.[18] In this study, the hypoglycemic activity of an insulin suspension given orally in a vehicle of soybean extract to streptozocin diabetic rats was investigated.

TABLE 1

Treatment Groups (number of subjects = n)	Weight of rats before injecting streptozocin (g) (Mean ± S.D.)	Weight of rats 2 days after streptozocin injection (g) (Mean ± S.D.)	Average initial blood glucose level (mg/dL) (Mean ± S.E.M.)
Insulin soybean extract suspension (9)	279.1 ± 60.3	252.8 ± 52.3	336.2 ± 32.8
Saline solution (6)	299.0 ± 47.7	292.0 ± 9.2	369.7 ± 29.6
Aqueous Soybean Extract suspension (6)	291.3 ± 55.2	262.5 ± 48.0	329.3 ± 44.6

Average initial blood glucose level (mg/dL) and weight of rats before and after 2 days of streptozocin injection for each treatment groups.

MATERIALS

The following materials were purchased from Sigma: α-Chymotrypsin (Lot No. 78H7026); calcium chloride dehydrate (Lot No. 09504LH); ketamine HCl/xylazine HCl solution (Lot No. 098K4616); N-Benzoyl-L-Arginine ethyl ester HCl solution (Lot No. 108K1002); N-Benzoyl-L-Tyrosine ethyl ester (Lot No. 066K1053); sodium phosphate dibasic (Lot No. 129H0091); streptozocin (Lot No. 019K1022); trizma base (Lot No. 098K5414); trypsin, Type II-S, from porcine pancreas (Lot No. 029K7012); and trypsin inhibitor, from soybean (Lot No. 107K7015). The 0.2 N HCl solution (Lot No. 967340) and sodium phosphate monobasic (Lot No. S369-500) was obtained from Fisher Scientific. Other chemicals included 10 M citrate buffer (Lot No. 1026) from Dyna Scientific, Logan, UT; Humulin® R (100 U/mL, Lilly, rDNA origin, NDC- 0002-8215-01) from NC Mutual; and 0.2 N sodium hydroxide (Lot A08582) from Mallinckrodt-Baker. Soybean was bought from a local store in Raleigh, NC.

METHODS

Preparation of Soybean Powder

Almost 57 g of soybeans (Whole Foods) were weighed and reduced to a fine powder (average particle size of 45.5 micrometers) using a coffee grinder (Model IDS50, Mr. Coffee, Sunbeam Products).[19]

Preparation of Soybean Extract

To prepare aqueous soybean extract, 5 g of the finely reduced soybean powder was weighed and mixed with 25 ml of double deionized water. The mixture was stirred for 2 minutes using a glass rod to ensure thorough mixing and wetting of soybean powder. The resulting mixture was incubated in gyratory water bath shaker for 1 hour at 37°C. The incubated mixture was then centrifuged for 20 minutes at 12,000 rpm. Supernatant was collected, and the centrifugation procedure was repeated twice, each time for 20 minutes at 16,000 rpm. Final supernatant was collected and filtered initially with 0.45-micrometer nylon filter (Whatman International Ltd.) and then through 0.2-micrometer nylon filters (Life Sciences) using a vacuum filtration assembly. The resulting filtrate was a clear, yellowish solution with pH of 6.7 to 6.9 at room temperature.[20]

Preparation of Aqueous Insulin-Soybean Extract Suspension

Aqueous insulin-soybean extract suspension was prepared by mixing 1 mL of Humulin R (100 IU/mL) with 1 mL of aqueous soybean extract. The pH of the mixture was adjusted to 4.1 using 0.2 N HCl.

Animals & Treatments

A total of 21 male Wistar rats (Charles River Laboratory) with an average weight of 300 g were used to carry out this study (Table 1). The rats were divided into three different groups, two control groups of six rats each and one treatment group of nine rats. Food and water were provided ad libitum. The diabetic condition was induced using a single intra-peritoneal dose of streptozocin (50 mg/mL in citrate buffer) (80 mg/kg). The

fasting blood glucose level was measured 2 days following streptozocin injection to confirm the diabetic state. Rats with blood glucose level above 200 mg/dL were considered diabetic (Table 1). During overnight fasting, the rats had free access to water before experimentation. On the day of experiment, one control group received soybean aqueous extract (1 mL), another control group received saline solution (1 mL), and a third treatment group was given a suspension of human insulin in soybean extract (1 mL, 50 IU/mL). The dosage forms were administered to rats orally by gavage. Anesthesia was induced with a single intra-peritoneal injection of Ketamine HCl (80 mg/mL) and Xylezene HCl (12 mg/mL) (80 mg/kg and 12 mg/kg). A maintenance dose (20 mg/kg) of the anesthetic agents was given intramuscularly every half an hour for the first 4 hours and then every hour up to the end of the experiment. Rats were covered with cloth to prevent hypothermia. Blood samples (one drop) were collected from the tail prior to dosing and at time 0.5, 1, 2, 3, 4, 5, 6, and 7 hours. The blood samples were immediately analyzed for blood sugar level using a One Touch Ultra glucometer (Lifescan). The rats were sacrificed with carbon dioxide gas inhalation at the end of experimentation.

Preparation of Dosage Forms

A) Saline solution: 0.9 g of sodium chloride was dissolved in enough distilled water to make 100 mL.

B) Soybean extract suspension vehicle: aqueous soybean extract was made using the method explained earlier. The pH of the extract was adjusted to 4.1 using 0.2 N HCl.

C) Insulin soybean extract suspension: prepared by mixing 1 mL of Humulin R with 1 mL of aqueous soybean extract suspension. The pH was adjusted to 4.1 using 0.2 N HCl.

Soybean Trypsin-Chymotrypsin Inhibitors Assay

A) Trypsin inhibitors assay from Sigma-Aldrich: briefly, the trypsin soybean inhibitor assay was based on continuous spectrometric rate determination of the reaction between trypsin substrate Nα-Benzoyl-L-arginine ethyl ester (BAEE) with water in the presence of trypsin at 25°C and pH of 7.6. The reaction generated Nα-Benzoyl-L-arginine that absorbs light at 253 nm. Inhibition of trypsin by soybean trypsin inhibitors resulted in the reduction in the amount of Nα-Benzoyl-L-arginine produced. One trypsin unit was defined as a change in absorbance (ΔA253 nm) of 0.001 per minute with BAEE as substrate at pH 7.6 at 25°C in a reaction volume of 3.2 mL. A standard curve was generated (r^2 = 0.959) with the soybean trypsin inhibitors, and the activity of these inhibitors present in the aqueous soybean extract was determined from the standard curve.

B) Chymotrypsin inhibitors assay from Sigma-Aldrich: similar to the trypsin inhibitors assay, this chymotrypsin soybean inhibitor assay was based on continuous spectrometric rate determination of the reaction between substrate N-benzoyl-L-tyrosine ethyl ester (BTEE) and water in the presence of chymotrypsin at 25°C and pH 7.8. The absorbance of the reaction mixture was continuously monitored at 256 nm. This reaction was inhibited by chymotrypsin soybean inhibitors. A standard curve was generated (r^2 = 0.972) with the soybean chymotrypsin inhibitors and was used for determining the amount of these inhibitors in the aqueous soybean extract.

Statistical Analysis

Data were reported as mean ± standard error of the mean (S.E.M.) or ± standard deviation (S.D.), unless otherwise indicated. The difference in blood glucose concentration among the three groups at different collection times was analyzed with an analysis of variance test (ANOVA) followed by a post-hoc test, comparing all pairs using Tukey-Kramer HSD. The area under the blood glucose concentration (% of initial) versus time curve (AUC) was calculated using the trapezoidal rule. The units for AUC were (%.hour). A higher AUC value indicated better extent of absorption of HINS from the dosage form. Average AUC values for the three groups were compared using an ANOVA test followed by comparisons with the best using Hsu's MCB as a post-hoc test. Hsu's MCB test evaluated that each average AUC value was the highest (null hypothesis). A p value of less than 0.05 was considered significant. JMP® Statistical Discovery Software (SAS Institute) was used for statistical analysis.

RESULTS & DISCUSSION

The oral administration of insulin in the management of diabetes mellitus has been and remains to be a challenging endeavor. In this

TABLE 2

Treatment	Number of Rats	0	0.5	1	2	3	4	5	6	7
Insulin Soybean Extract Suspension (ISES)	9	336.2 ± 32.8	297.2 ± 49.9	239.0 ± 47.0	177.1 ± 47.5	172.6 ± 53.6	157.1 ± 47.8	158.6 ± 46.8	161.1 ± 49.6	186.0 ± 55.0
Saline Solution (SS)	6	369.7 ± 29.6	473.2 ± 29.6	419.7 ± 41.8	360.8 ± 38.1	348.3 ± 38.0	318.2 ± 36.1	270.8 ± 38.4	343.8 ± 42.9	343.8 ± 33.8
Soybean Extract Suspension (SES)	6	329.3 ± 44.6	433.8 ± 29.2	431.2 ± 15.9	347.2 ±20.9	326.0 ± 25.4	309.5 ± 27.3	296.0 ± 28.7	308.2 ± 36.2	307.5 ± 34.9
p Value		0.7311	0.0253	0.0124	0.0221	0.0228	0.0184	0.0618	0.0226	0.0549
Group Comparison (Tukey-Kramer HSD; *p* Value)		None	ISES vs. SS (0.0311)	ISES vs. SES (0.0104); ISES vs. SS (0.0159)	ISES vs. SES (0.0233); ISES vs. SS (0.0142)	ISES vs. SS (0.0353)	ISES vs. SES (0.0475); ISES vs. SS (0.0353)	None (borderline)	ISES vs. SS (0.0297)	None (borderline)

Blood glucose concentration (mg/dL) over a 7-hour period following treatment (fasted state).

study, HINS was administered in the form of suspension in an aqueous soybean vehicle to diabetic rats. In general, suspensions have, among other characteristics, the ability to produce a sustaining pharmacological effect for drugs. This is due to the equilibrium existing between the drug in solid suspended particles and the drug in solution. Because only the drug amount in solution is available for absorption, any amount that is lost for absorption is immediately replenished by an equal amount of the drug available from the suspending solid particles. This provides a constant amount of the drug in solution available for absorption, thus a sustaining effect. The effect of HINS administration was monitored by measuring the fasting blood glucose concentration over a 7-hour period. Figure 1 represents the blood glucose profile following the oral administration of HINS soybean extract suspension, saline solution, or soybean extract vehicle. Following administration of saline solution and soybean extract vehicle, there was a rapid rise in the blood glucose concentration due to the stress reaction. Interestingly, rats receiving the HINS soybean extract suspension did not show this initial rise in the blood glucose level, indicating a rapid absorption of HINS overshadowing the stress hormones effects. Table 2 shows that beginning at 30 minutes post-administration, the decline in blood glucose concentration was statistically significantly different than that of at least one of the control groups. This effect on blood glucose was sustained for several hours post-administration. As seen in Figure 1, the decrease in blood glucose level reached a nadir value at 4 hours post-administration. The blood glucose concentration at 4 hours post-administration for the rats that received HINS in a soybean extract vehicle was significantly lower than that of rats receiving the soybean extract vehicle alone (157.1 ± 47.8 vs. 309.5 ± 27.3; p = 0.0475) or saline solution (157.1 ± 47.8 vs. 318.2 ± 36.1; p = 0.0353). The concentration of blood glucose at 4 hours post-administration was 53.3%, 13.9 %, and 6% less than the initial value for HINS soybean extract, saline solution, and soybean extract vehicle, respectively. This constitutes approximately a nine-fold or four-fold difference in blood glucose lowering between the suspension containing HINS and its vehicle or saline, respectively. The presence of the enzyme inhibitors in the aqueous soybean extract may have contributed to the enhanced physiological effect of HINS in diabetic rats. We have shown previously that the presence of protease enzyme inhibitors in soybean extract was capable of partially protecting HINS from degradation by pepsin, trypsin, and chymotrypsin in vitro.[20] The amount of the trypsin and chymotrypsin inhibitors measured in the aqueous soybean extract was 3.8 mg/mL and 1.2 mg/mL, respectively. This value agreed with that found in the literature.[13] However, protease inhibitors alone might not have been the only factor affecting HINS absorption from the GI tract. For example, the incorporation of insulin in a polymeric matrix (Eudragit L100; polyacrylic) along with protease inhibitors resulted in no hypoglycemic activity when given orally (20 IU/kg) to normal or diabetic rats, despite a protective effect afforded by the protease inhibitors observed in vitro.[21,22] When insulin was formulated with soybean trypsin inhibitors and cholate (a surfactant and absorption enhancer) in an enteric-coated micro-tablet preparation and given orally to diabetic dogs, plasma glucose concentration was decreased as the insulin level in blood increased. The presence of cholate facilitated the dissolution of the solid particles in the GI juices and enhanced its absorption, producing a minimum reduction in blood glucose of 40% lasting more than 90 minutes.[23] Other factors, such as the particle size of HINS solid particles, may have affected the hormone intestinal absorption. Badwan et al studied the effect of particle size on the absorption of insulin from an oral dose. They reported a better enhancement in the oral bioavailability of insulin (3.0%) in human volunteers receiving 2 IU/kg dose with insulin particle size of 0.057 micrometers.[24] Our HINS suspension contained particles many folds larger (approximately 30 micrometers in diameter) than those used by Badwan et al.[25] It is interesting to note here that the administration of microcrystals (0.95 micrometers) of human insulin (5 IU/kg) in rat lung along with soybean trypsin inhibitor resulted in an improvement in blood glucose lowering from 42.68% (no inhibitors) to 55.78% (with 5 mg/mL inhibitors).[26] Overall, it is reasonable to conclude that a smaller particle size would yield a better absorption profile because the dissolution rate of the solid particles increases with a decrease in particle size, and therefore, more of the drug becomes available for absorption. As shown in Table 3, the AUC for soybean extract and saline groups was not significantly different from zero ($p > 0.05$). Moreover, the analysis of variance test combined with Hsu's MCB post-hoc test showed that the AUC for HINS soybean extract group was the highest (compared to soybean extract vehicle $p = 0.0134$ and saline $p = 0.0219$) (Table 3). The fast drop in blood glucose level following administration indicates that HINS absorption began in the proximate regions of the GI tract. Similar fast insulin action was seen with oral insulin administration in the form of a micro-tablet (containing cholate and trypsin inhibitors) to diabetic dogs. This produced a rapid decline in blood glucose concentration occurring as early as 60 minutes post administration.[23] HINS absorption from the

TABLE 3

Treatment	AUC (%.hour) (Mean ± S.E.M.)	95% CI
Insulin soybean extract suspension (n = 9)	259.95 ± 76.89	[82.6, 437.3]
Soybean extract suspension (n = 6)	-4.10 ± 71.73	[-203.3, 195.1]
Saline solution (n = 6)	34.64 ± 25.29	[-30.4, 99.6]

Area under the blood glucose (% of initial) vs. time curve.

GI tract, however, is not only limited to the small intestine. Studies have shown that the absorption of insulin in the presence of protease inhibitors was possible (and perhaps even better) from the large intestine as well.[27] This in vivo study demonstrated that the oral administration of human insulin in the form of a suspension in soybean aqueous extract vehicle to streptozocin diabetic rats has the potential to produce a remarkable hypoglycemic effect.

CONCLUSION

In this study, an oral suspension of HINS administered to fasting diabetic rats produced a state of hypoglycemia that was sustained for 4 hours. The reduction in blood glucose level was fast and began within 30 minutes post administration. In comparison, the oral administration of a soybean extract vehicle or saline resulted in no significant reduction in blood glucose level. The presence of protease enzyme inhibitors in soybean extract may have contributed to the improved bioavailability of insulin from this suspension.

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BIOGRAPHIES

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INDUSTRY PLAYERS

Stakeholders Portrait in the Pharmaceutical Industry

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

INTRODUCTION

The underpinning issue in the development of personalized medicine, regarding its broadly applicable therapies, is related to the real comprehension of all the industries involved, as well as the actual extent of the relations among different stakeholders.

It is currently a crucial moment for personalized medicine. Just now, pieces on the board are seen to move forward in different directions. Thus, new models for collaboration networks between academia and industry have arisen, while significant investment has been given to medical approaches that strive for personalized medicine. Completing this landscape, governmental parts have also started to actively participate through the development of novel regulatory and policy frameworks that facilitate a progressive and organized clinical evidence translation. In this regard, government and private sectors are also beginning to develop methodologies, along with diagnostics and pharmaceutical companies, to clearly innovate the use of technology and information to achieve clinical and economic effectiveness.

Even though pharmaceutical and biotechnology companies, as with healthcare industry representatives, will continue to play a leading role, many players characterize the current industry landscape with many disciplines and technologies.

PHARMACEUTICAL INDUSTRY

As industry representatives, pharmaceutical companies have driven the development of personalized medicine from the beginning through a variety of applications based on genome sequencing results for both therapeutics and diagnostics products. The primordial role of pharmacogenetics and pharmacogenomics in such developments, as well as their relevance in preclinical and clinical trials, has pointed the pharmaceutical industry toward a strategic position to leverage the impulse of the technologies to allow advancements toward a personalized approach to medicine. Thus, companies having a relevant molecular diagnostics platform integrated with therapeutic solutions are expected to be in a preferential position.

BIOTECHNOLOGY & LIFE SCIENCES COMPANIES

Omics technologies, also supporting the personalized approach, are mainly driven by biotechnology and life sciences companies. These companies establish solid collaboration networks with both academic research groups and major pharmaceutical companies. In that sense, disciplines such as pharmacogenetics are principally pulled by industrial players due to their resources platform, which allows them access to both higher investment opportunities and large amounts of data from clinical studies. On the other hand, the development of extensive database and bioinformatic tools belongs to the field of action of academic research groups. It is important to highlight that both approaches have many issues in common, which attempts to empower the basis for these developments.

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- **Paragraph IV**

CLINICAL LABORATORIES

Regarding personalized medicine, clinical laboratories actively participate in preclinical pharmacogenetic testing, in addition to their services for the pharmaceutical industry in drug discovery and development. With the flourish of the personalized approach, clinical laboratories are expected to augment their activities, evolving from genetic tests performing and validating, toward high-throughput (HTS) genotyping for candidates to clinical protocols.

The improved version of these players is given by point-of-care diagnosis. In this particular case, all of the information is contained in a small piece that acts as the "molecular diagnostics lab" itself. Information regarding biosensing activities could be also sent to a clinical laboratory or directly toward an electronic database for storing or reprocessing.

PHYSICIANS & BIOMEDICAL PROFESSIONALS

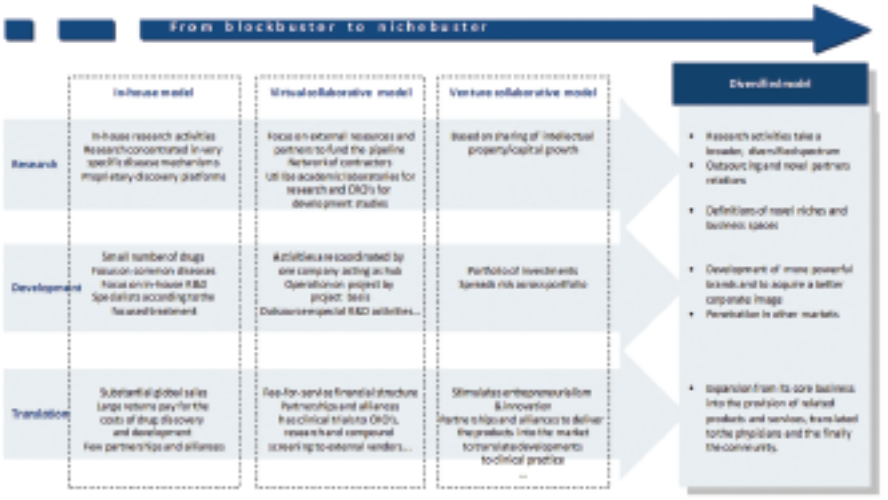
Personalized medicine expects to be part of the routine medical practice in no more than 10 years. Although driving technologies, such as genomics and proteomics, along with the associated biomarkers, among others, are taking a relevant part in the practice of medicine, the adoption of a personalized approach to medical practices and the encompassing of this paradigm shift, move physicians into an increased involvement in these emerging disciplines related to clinical developments.

Currently, physicians do not have any formal education in molecular medicine. However, naturally, they possess enough background to learn and specialize in personalized medicine-related issues through appropriate extra courses, online educational programs, and industry webinars, in addition to symposiums, conferences, seminars, and scientific congresses. It is important that the pharmaceutical industry promotes such forms of extracurricular education for the short term in order to prepare the scenario for a successful introduction to personalized medicine in routine practice that combines professional experience with novel trends and optimal treatment based on disruptive technologies.

In the medium term, such extracurricular education efforts should be properly integrated to conventional university programs, in order to give new professionals novel insights on genetics- and genomics-branched technologies. On the other hand, biomedical scientists and professionals should also be trained to apply such an emerging biological knowledge to the human treatment of diseases.

In this regard, it is of significant importance to denote the knowledge accumulation trend that medical sciences have experienced along the history of medicine and physiology. According to this, personalized medicine becomes in itself an opportunity to reform several aspects of current medicinal university programs.

FIGURE 1



Migration from the Current Blockbuster Model Toward a Nichebuster, Characterized by Important Collaboration Lines, Partnerships & Strategic Alliances (Source: Frost & Sullivan)

PUBLIC & SOCIAL NETWORKS

Ethical and regulatory issues should be extensively covered throughout the whole development and implementation of personalized medicine. Education for the appropriate management of all the genetic information and its implications will be needed in order to protect the privacy and other legal rights of individuals and avoid controversial discussions.

Cooperation from the public will also be necessary to achieve a successful utilization of the personalized approaches to medicine. In addressing this concern in 2007, the U.S. propelled a project conducted by the National Human Genome Research Institute (NHGRI), the National Cancer Institute (NCI), the Group Health Cooperative (GHC), and the Henry Ford Health System (HFHS), denominated as the MultiPlex Initiative, to test the public reaction facing a personalized approach to medicine.

FIGURE 2

Some Necessities for Partnering in the Pharmaceutical Industry. (Source: Frost & Sullivan)

Finally, but no less important, Web platforms have played an essential role in the emerging of personalized medicine as a novel mega trend. Wide varieties of online solutions are now available on the Internet. In addition, health bloggers constitute a major expectation in the development of personalized medicine. The number of people utilizing social networks, where individuals load the most relevant information about their health conditions, has enormous prevalence for both rare and common diseases. Thus, a considerable amount of statistical data is available on the Web. PatientsLikeMe© was a pioneering Web site for those initiatives. On the other hand, GeneSage, Inc. constitutes the first exclusively dedicated solution to develop healthcare platforms from detailed information about genetic conditions.

GOVERNMENT

Governmental decisions about healthcare systems represent an essential, but also a controversial, issue in any country. The U.S. is a remarkable example. In fact, the U.S. healthcare system faces crucial challenges of escalating medical costs and poor or no health insurance for a large percentage of the overall population.

Indeed, an action plan was launched in the U.S. on the base of the Health Care Reform Law, enacted in March 2010. Two different parts constituted the act: the first corresponding to The Patient Protection and Affordable Care law, which was signed into law on March 23, 2010; and the second, which was amended by the Health Care and Education Reconciliation Act on March 30, 2010, being commonly known as the Affordable Care Act.

These actions constitute the next step of the previous bill, titled Genomics and Personalized Medicine Act of 2006. This bill aimed to advance personalized medicine and pharmacogenomics, pushed by Senator Barack Obama, our current president. The Genomics and Personalized Medicine Act of 2008, by means of which the Genomics and Personalized Medicine Interagency Working Group is proclaimed, including the National Institute of Health (NIH), FDA, Centers for Disease Control and Prevention (CDC), and other groups outside of the Department of Health and Human Services (HHS).

Other initiatives propelled on these bases include the creation of an extensive database for collecting and integrating individual genetic information with clinical studies, as well as the associated regulatory issues. The National Biobanking Initiative is an example of such a policy. Additional funding and tax credits for the enhancement of the current research platforms based on molecular diagnosis are also taken into consideration.

This initiative aims to ensure access to health systems for the overall population and, additionally, tends to improve the national budget while reducing the deficit by more than $150 billion from 2011 to 2018.

BUSINESS STRATEGY

As it was defined in the first sections, personalized medicine results from the convergence of a broad spectrum of disciplines and technologies. It is precisely these nuances of the personalized medicine landscape that have majorly contributed to the enrichment of this discipline, moving it into a highly differentiated branch of learning, able to transform the current conception of the healthcare industry.

Naturally, business models exhibit such heterogeneous behavior, representing the major opportunities for both big companies and small and medium enterprises (SMEs). Such entrepreneurial companies are used to taking high risks due to their permanent focus on developments. On the other hand, direct-to-consumer companies, providing a genetic profiling service, have found great opportunities in this regard, demonstrating a business model of such characteristics that works well.

THERAPEUTICS MARKET

The paradigm shift around personalized medicine necessarily derives a change in the

current business models utilized by the pharmaceutical and biotechnology industries. In particular, pharmaceutical companies have to face the challenge of transforming their blockbuster model toward a more accurate, flexible, and cost-effective model that involves the development of therapeutics for a reduced pool of patients.

Although the pace of these changes in companies' business models, as well as in their value chain, appears to be slow, the pharmaceutical industry has seen some progress regarding a personalized approach. Indeed, the prevalent knowledge regarding the inefficiency of the current drug discovery and development process and their associated climbing costs, pull industry players toward a more sustainable model.

In appearance, drugs whose intellectual property protection has expired constitute a genuine resource for pipeline stratification. The right selection could lead to a very suitable business model, adjacent enough to the traditional scenario so that minimal changes are needed. In order to achieve good profitability, stratification by genetic profiling should reach the point of a 100 percent satisfactory response to the market re-positioned drug for the set of patients treated. Such a successful stratification could also lead to increased precise clinical trials.

DIAGNOSTICS MARKET

Molecular diagnosis constitutes one of the most compelling technologies. Indeed, it represents one of the most robust pillars of personalized medicine. From the point of view of business models, it is also remarkable that the past two years have experienced a revolution in merger and acquisition (M&A) activities regarding molecular imaging and diagnosis. Additionally, myriad small companies have started to play new roles in the diagnostics market. Their innovative capacity, as well as their constant nutrition within academic fields, makes these companies strategic players, leading to a novel trend of M&A activities and licensing agreements, according to the emergence of new and improved diagnostic tests and imaging technologies.

Moreover, a current trend is incorporating therapeutics programs into the diagnostics ones, so that the final product results from a combination of therapy and testing. More traditional business models proposed to manage these activities separately, eluding the associated risk around the utilization of just one of the programs, therapy, or testing, with fails leading to the failure of the whole project. On the other hand, the former option leverages clinical trial data and the reimbursement scenario.

THERAPEUTICS/DIAGNOSTICS MARKET

Following with the aforementioned trend, strong market positions are reached when therapeutics and diagnostics converge, also known as "theranostics," providing a road toward a more personalized approach to medicine. These advances enable the development of novel technology platforms, which are enriched from genetic profiling, giving more specific and sensitive approaches. Moreover, by integrating these platforms into the drug discovery and development process, more accurate and efficient therapies can be achieved, which represents both a significant improvement in treatment quality for patients and a solid position into the market by providing real-world solutions for a broad spectrum of diseases.

PARTNERSHIPS & ALLIANCES

Current trends leading to commercial success, especially in early stage biotechnology companies, are partnerships and alliances. This makes sense, considering that the delivery of a therapeutic product into the market under the traditional value chain takes about 12 to 15 years, and costs including preclinical and clinical trials exceed $5 billion.

The conventional and still prevalent partnership and alliance models between the biotechnology and pharmaceutical industries rely on a complementary concept by which the former is considered to be more involved in scientific affairs and innovative ideas, while the latter is associated with financial, regulatory, and marketing issues. Therefore, the strategy comprehends the genuine development of novel therapies and biomarkers, leveraging the scientists' expertise, and the final commercialization through the well proved apparatus of the pharma companies.

Precisely at this point, it is relevant to mention the role of universities and academic environments in shaping innovative alliance strategies and branding models. Personalized medicine represents a wide and attractive field to perform different paths and models.

In principle, as a simple case, early stage companies maintain or culture close relations, or even partnerships, with different universities and institutes. In general, founders and scientific advisors still belong to the academic environment in different ways. With time, according to the maturation of the company and its technology, close relations begin to

migrate toward the alliances with pharmaceutical firms. The former relations are commonly known as upstream alliances, while the latter are downstream alliances.

In the U.S., such a model is quite common, especially leveraging the natural trend of intellectual property protection from part of the academic units, as well as the transference of technological approaches to society, creating value and establishing new collaboration branches.

The remaining players come from venture capital, under which the propitious depicted scenario aligns perfectly, helping companies achieve robustness and strong positioning to both strengthen the present upstream relations and face the future downstream alliances.

Beyond this generalization, the main aspect is the prevalence of the early stage biotechnology companies' relations with academic environments, which provides reliability based on scientific support, intellectual property and further developments, representation facing grant or governmental funding requirements, and human resources involving highly qualified and talented people, as well as access to patient samples and clinical trials. In addition, certain inherent features of the early stage or start-up companies, such as dynamics, responsiveness, innovation, and targeting, become valuable instruments to face the development of novel diagnostics and therapeutics issues, and evaluate the risk associated with the activity.

OUTSOURCING & COLLABORATION

Strategic partnerships, alliance models, outsourcing, licensing agreements, and collaborations all contribute to enabling companies to gain competitive advantage through access to partner's resources and experience, including human resources, modern technologies, regulatory and policy know-how, enhanced production capacity, time acceleration, and global reach.

In recent years, outsourcing to contract research organizations (CROs) has gained increasing importance in the pharmaceutical industry landscape, in order to assume bigger strategic roles while reducing costs and improving efficiencies. On that note, novel, innovative ways to partner with CROs to shift fixed costs, accelerate timelines, improve data quality, and begin the evolution toward a more productive R&D model are continuously emerging. In this regard, such integrative models suggest the creation of living entities comprehending a series of complex relationships that requires observation along their life cycle. This goal and flexible and reasonable governance structures, as well as executive relationships on both sides at a status level as a function of the risk shared by both companies, are essential for the success of the collaboration line.

In addressing this concern, the core competencies of each organization should be precisely determined and communicated in order to set strong and solid foundations with the aim of developing an outsourcing or partnering strategy.

Regarding the needs of both parts, pharmaceutical clients often look to outsourcing to reinforce their R&D platforms, requiring a variety of scientific expertise fields to complement their proprietary technology bases. These companies could require the venturing into a therapeutic area in which no clinical experience is available, require scientific and regulatory advice to file an investigational new drug (IND) application, apply for funding and investment opportunities, reach a key decision point along the value chain, look for a licensing partner in the near term, or the need for custom solutions to deliver a drug to the market, among a broad spectrum of necessities.

LICENSING TRENDS

In recent years, extensive timelines for drug discovery and development activities, in addition to the subsequent delay in return of the investment, has made life science and pharma companies less attractive to venture capitals (VCs) and investors in general who used to prefer short-term, less-risk, high-yielding returns.

From this perspective, innovative companies have been forced to outlicense their technology in order to cover the funding gap. On that note, beyond the need for funding opportunities, Big Pharma offer expertise to prospective smaller partners in order to perform the clinical development and clear the regulatory issues on the path to commercialization.

Big Pharma is also benefitted by such licensing agreements that provide access to a bigger innovation pool and reduces certain risks related to in-house development. Moreover, new therapeutic areas can be boarded without having to put in place the basic discovery and development technologies. Indeed, small and medium companies (SMEs) provide the technology platform to enhance existing Big Pharma's projects, while diminishing risk. In fact, even though licensing agreements do not confer exactly full ownership rights, less risk for the licensee and

more flexibility for the licensor are involved, thus allowing optimization of the value of intellectual property rights.

CASE STUDIES & FINAL REMARKS

Among the more recent case studies supporting important licensing agreement models, the deal signed between Vical Incorporated and Japan's number two drugmaker, Astellas Pharma, aimed at developing and commercializing its cytomegalovirus vaccine while sending its shares up as much as 10 percent in after-market trade, is remarkable. Such a successful deal implies up to $130 million received by Vical in up-front and development milestones plus double-digit royalties for the DNA vaccine, TransVax, which attempts to improve immune responses in blood cell transplant patients whose immune system has been impaired by disease or treatment. In addition, both companies expect to begin a multinational late-stage trial of the vaccine in stem cell transplant patients in the first half of 2012. This case illustrates the benefits and crucial necessity of establishing solid collaboration lines between main companies leveraging their strengths in order to achieve unreachable goals by themselves.

Another example is the agreement between CEL-SCI Corporation and Teva Pharmaceutical Industries Ltd. for its cancer drug Multikine. Teva is currently funding part of the global Phase III clinical study at three clinical sites in Israel. Recently, under this new deal, Teva's exclusive license to market and distribute Multikine, the company's investigational Phase III drug for the treatment of head and neck cancer, in Israel and Turkey will be extended to include Croatia and Serbia.

More related to patent appliances, Sartorius Stedim Biotech has entered into a patent cross-licensing agreement with GE Healthcare Life Sciences in order to face the further development of each company's current and future biopharmaceutical manufacturing technologies. With this new relationship, both companies become even stronger in the pharmaceutical market.

Sequenom Inc., a life sciences company providing innovative genetic analysis solutions, has taken a similar pathway by partnering with LifeCodexx AG, a company focused on the development of clinically validated next-generation molecular diagnostics for the commercialization of prenatal laboratory testing services in Europe. Under this deal, the companies have agreed to collaborate in the development and launch of a trisomy 21 laboratory-developed test and other aneuploidies testing in Germany, Austria, Switzerland, and Liechtenstein, with the potential for additional launches in other European countries. The agreement also includes key patent rights, including European Patent EP0994963B1 and pending application EP2183693A1, that enable the development and commercialization of a non-invasive aneuploidy test utilizing circulating cell-free fetal DNA in maternal plasma. ◆

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).

ROI Optimization Through Contract Management

By: Laszlo Fabriczi

INTRODUCTION

Life science organizations are turning to technology to address the shifting challenges of contract management, particularly with respect to controlling potential revenue leakage, safe-guarding against compliance issues, and facilitating government reporting. Contemporary contract management solutions offer flexible and configurable capabilities that aid in harmonizing pricing guidelines and terms. The crucial but often overlooked element of implementing technological solutions is an examination and alteration of the existing business processes - rather than an application of new technology to existing archaic processes.

Contract management organizations are typically engaged in contract administration rather than contract management; the focus is centered on managing payment rather than profitability and optimal pricing strategies. With sales divisions continually creating new and increasingly complex pricing terms to maintain competitive advantage, fluctuating discounts and rebates are commonplace but difficult to trend. Business process remains constant and fails to keep pace with contract needs, yielding an incomprehensible management task that prohibits effective contract strategy decisions. This disparity leaves contract management departments without the resources to provide their sales teams with robust data to ultimately improve profitability.

The ultimate goal of implementing contract management technology is to redistribute resources freed up through a more automated contract administration process into strategic contract management positions. Staff whose energy was focused on administration details will then redirect attention to more thorough collection and analysis of contract data to provide valuable feedback to sales and marketing teams, improving profitability and maximizing return on investment. According to the 189 participants of a new Aberdeen study, the percentage of an enterprise's revenue that is dictated by a contract is likely to rise from 56% to 68% on average throughout the next 2 years.[1] Therefore, it is becoming more and more essential for enterprises to have contract information at their fingertips for historical analysis, forecasting, risk assessment, analysis, and revenue recognition.[2]

Effective transformation of the contract development process has emerged as a crucial function to increase profit margins. To fully leverage the benefits of technological solutions, it is imperative to verify that the underlying business process is optimized, through the fundamentals illustrated in Figure 1, and avoid the pitfall of assuming that implementing technology inherently improves process.

THE METHODOLOGY

The implementation of new technology is often the key focus, if not the only focus of many organizations' change initiatives; accordingly, the approach to this portion is usually clearly understood, with several competing methodologies that all vary slightly from the same basic standard. A company must adopt a structured approach in order to achieve success in an implementation. Change management programs have been found to help increase the return on investment up to 143% when included as

FIGURE 1

Change Management Fundamentals

part of the initiative. The return on investment dropped to about 35% when there was a poor change management program or no program at all.[3]

Studies have shown that having an effective change management program to help manage the implementation can greatly increase the success of the project, and the value captured is highly correlated to the program's effectiveness. The following statistics are derived from a 2009 study that consisted of 575 change management practitioners and project leaders from 65 countries:[4]

- 71% of respondents were able to be on or ahead of schedule
- 82% of respondents were able to stay on or under budget
- 95% of respondents were able to meet or exceed project objectives

To be truly successful, however, initiatives must recognize and incorporate three additional elements to realize business benefits promised by the technology platform. These elements comprise a four-phase model that effectively addresses the new environment: strategic alignment, organizational evaluation and redesign, business process transformation, and implementation of new technology. A further description of the first three phases, which typically requires increased emphasis to realize the return on investment, is discussed further.

1 - STRATEGIC ALIGNMENT

To ensure the initiative will deliver recognizable value to the enterprise, a critical first step is to align the objectives of the project with the overall corporate strategic direction. This will provide the stakeholders across all affected organizations with the knowledge of how the initiative will improve their situation, and will demonstrate that the benefits will not be limited to a single sponsoring organization.

FIGURE 2

$$\text{Value}^* = \frac{[\text{Quality} \uparrow]\ [\text{Service} \uparrow]}{[\text{Cost} \downarrow]\ \ [\text{Time} \downarrow]}$$

*Value is derived by some combination of increasing quality and service, and decreasing cost and time.

Value Model

Many of these stakeholder organizations will be key partners not only in deploying the technology solution, but in driving its adoption throughout the enterprise. Aligning corporate strategies will ensure the initiative has the existing support of these organizations when it becomes critical.

In a recent study conducted by the Corporate Executive Board (CEB), 50,000 employees representing more than 50 companies across a sample of industries and geographies were surveyed. More than 88% of employees experienced a change and/or expect changes in their business.[5] Increasingly, employees find themselves operating in a different environment. More important than measuring employee recognition of change, companies should be trying to understand whether employees are aligned with the new organizational strategy.

2 - ORGANIZATIONAL EVALUATION & REDESIGN

When the focus of activities within a department is changing from an administrative role to a more strategic one, it is important to evaluate how the organization and its functions fit into the new paradigm. Individual roles and responsibilities frequently change, which can lead to either a recasting of job descriptions or the creation of brand new roles. Organizational redesign requires a process that starts with a structure, proceeds to defining those roles, and then staffing that structure.

Transitioning an organization to a new set of roles and responsibilities can have significant consequences to the existing staff. Individuals often need to be evaluated to ensure their skills and capabilities are appropriately matched to the new descriptions. This process creates a tense and stressful time for many employees, but also yields new opportunities for training and development. It is very important to understand the natural resistance to change, as resistance is one of the top reasons a change initiative will fail. To overcome this resistance, an organization must clearly communicate the reason for the change and help employees understand why it is needed. Budgeting sufficient time for training and development is critical for allowing employees to expand their knowledge and capabilities to thrive in the new environment.

3 - BUSINESS PROCESS TRANSFORMATION

One of the greatest barriers to success for a technology-based solution occurs when the technology itself does not address the core inefficiencies within the underlying business process. Sometimes this occurs because the inefficiencies exist in process areas outside the scope of the application, and other times it occurs because the implementation of the technology fails to appropriately address the business requirements.

By focusing the overall initiative on the transformation to occur within the business, rather than simply on the implementation of technology, the project team will be held accountable for the end result rather than a

basic go-live milestone. True business process transformation will also ensure design elements are addressed with the end goal in mind. Additionally, scope decisions regarding business needs will be based on the overall needs of the enterprise, and not solely on the configuration checklist of the selected technology.

The implementation of new technology offers organizations a more streamlined operation, significantly improving business process efficiency throughout the contract management lifecycle with an automated workflow; however, businesses must take a proactive approach in modifying the business processes in order to fully experience the benefits of the new technology.6

Solid change management methodology enables an integrated contracting process across the enterprise, which allows for greater predictability and flexibility. Organizations will align systems and processes to support stability and profitable growth, lowering the total cost of ownership and increasing the flexibility to address the future. Failure to do due diligence with respect to this approach has critical ramifications, including further fragmentation of the collaboration among sales, marketing, and finance departments. It additionally leads to the lack of enterprise end-to-end visibility.

SUSTAINED VALUE IN BUSINESS PERFORMANCE

Effectively addressing the technology implementation, as well as the business process transformation and change management, can lead to significant business value. One can examine the ability to translate the impact into value, as illustrated in Figure 2, with some of the following examples:

- Quality: Implementation of best practice contracting processes can improve compliance to internal and regulatory guidelines, improve data accuracy and consistency, and reduce risk of penalties.
- Service: More accurate strategic intelligence allows for greater pull-through and optimized pricing guidelines.
- Cost: Reduction in revenue leakage; typically 15% of rebate submissions processed have some degree of error, and reducing this can lead to revenue enhancement.
- Time: Reduced payment cycle times can be achieved by eliminating process redundancies through the implementation of technology, also allowing resource availability for higher level activity.

Contract management system implementations typically cause significant shifts from the manual processes in place to a more automated contracting culture. Therefore, to effectively realize the benefits, an integrated approach must be taken that includes not only the technology, but business process transformation and associated change management to fully derive significant benefits for the business.

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BIOGRAPHY

Laszlo Fabriczi has more than 18 years of experience providing program management and enterprise level technology solutions to a broad spectrum of industries, including pharmaceutical, investment banking, manufacturing, software, and healthcare. He joined Alliance Life Sciences in 2007 and is currently a Director within the Contract Management practice providing strategic, change management, and implementation expertise. He has proven to be successful at bridging the gap between business and technology to maximize value and competitive advantage for clients.

Nanonization: A Dissolution Enhancement Approach for BCS Class II Drugs

By: Anand Shah, MPharm; Sunny Shah, MPharm; Vipul Patel, MPharm, PhD; and Arti Potdar, MPharm

ABSTRACT

Formulation of drug candidates from Biopharmaceutical Classification System Class II (BCS II) is a general intractable problem in the pharmaceutical field. Conventional formulation approaches ranging from salt formation to cyclodextrin complexation prove to be less beneficial for such drugs with good permeability and poor solubility, which may defer its complete absorption from the gastrointestinal tract. Their efficacy could also be enriched by improving the dissolution characteristics by micronizing the drug, and because it does not alter the saturation solubility, the next obvious step is nanoization. Various important chemical and physical properties change significantly at the nanosized range of the drug. Nanonization is the process of size-reducing the drug particles with or without stabilizer to less than 1000 nm and preferably less than 100 nm. The present article reviews the various approaches adapted to nanonize the drug, the characterization of the prepared drug nanoparticles, and their applications.

INTRODUCTION

Approximately 40% or more of the new chemical entities (NCEs) generated during drug discovery are poorly soluble in water.[1] The basic challenge faced by the researcher for the formulation of such poorly soluble drugs is the low oral bioavailability and erratic absorption of the drugs from the gastrointestinal tract due to their low saturation solubility and dissolution velocity. The low saturation solubility results in a low concentration gradient between the gut and blood vessel and leads to a limited transport of drug.[2] For poorly soluble drugs as seen in BCS Class II, the dissolution of the drugs in the gastrointestinal fluid media is the rate-limiting step for the absorption of the drugs.[3] Hence, for efficient absorption of drugs from the gastrointestinal tract for improving their therapeutic efficacy, there is an imminent need for studies in designing novel strategies for their dissolution enhancement.

There are number of formulation approaches, such as salt formation, pH adjustment, cosolvency, complexation, etc used for enhancement of dissolution, but none of these approaches has achieved the merits of being universal. Micronization of poorly soluble drugs has been applied for many years to improve dissolution velocity of poorly soluble drugs, but reducing the drug to micron size does not increase the saturation solubility of the drug, and at such a low saturation solubility, as generally observed in BCS Class II drugs, the increment in the dissolution characteristics does not help to a great extent.[4-5] Consequently of late, nanonization has been employed for treating the BCS Class II drugs. When the drug is being reduced to a nanosized level, there is an obvious increase in its saturation solubility assisted by improvement in the dissolution characteristics, which could be attributed to the effective increase in particle surface area, according to the Nernst Brunner-Noyes Whitney equation.[6] The drug nanoparticles are generally suspended in an aqueous media and are termed nanosuspensions. Nanosuspensions can prepared using various techniques, namely nanoprecipitation, sonication, high-speed homogenization, milling, and high pressure homogenization.[7-12] The following examines the various advantages, disadvantages, characterization, and applications of drug nanosuspensions.

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PREPARATION METHODS OF DRUG NANOSUSPENSIONS

Nanosuspensions can be prepared using various techniques, which could be classified broadly in two groups (Bottom Up and Top Down) based on the principle on which the nanosize is achieved. The Bottom Up method, in which the drug nanoparticles are assembled from a solution of drug by controlling the rate and growth of nuclei formed. The Bottom Up method consists of nanoprecipitation, supercritical fluid technology, and using emulsions and microemulsions as templates.

Top Down production, in which the drug macrosuspension is size-reduced to a nanosuspension. The Top Down method consists of media milling, dry cogrinding, and high-pressure homogenization.

Bottom Up Techniques

Nanoprecipation:[13-16] In the precipitation technique, the poorly water-soluble drug is dissolved in a suitable solvent, and the solution is added into a miscible anti-solvent with stirring and agitation. Stabilizers are used to avoid the spontaneous aggregation of molecules. Types of solvents, the volume ratio of anti-solvent to solvent, stirring rate, drug content, etc are the factors that affect the final morphology of the nanoparticles.

Supercritical Fluid Technology: In supercritical crystallization, the supercritical fluid expands into a liquid solvent, and the dissolved drug precipitates due to decompression of supercritical fluid. The particles' growth is controlled by co-solvents, polymers etc.[17]

Emulsions & Microemulsions as Templates:[6] Nanosuspensions can be produced by using emulsions as templates and is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. There are two ways for preparing nanosuspensions using the emulsification technique. In the first method, an organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitate immediately to form a nanosuspension stabilized by surfactants. In another method, partially water-miscible solvents are dispersed in the aqueous phase to form an emulsion. Here, the drug nanosuspension is obtained by just diluting the emulsion. Dilution of the emulsion with water causes complete diffusion of the disperse phase into the continuous phase, leading to immediate formation of a nanosuspension.

Top Down Methods

Media Milling:[18] The pearl milling technique was developed by Liversidge et al.[19] In media milling, the drug is milled with milling media in simple glass vials to specific milling chambers for certain hours to some days, and nanosuspensions are produced on a principle of high energy and shear forces generated as a result of the impaction of the milling media with the drug. Media such as zirconium oxide beads, highly cross-linked polystyrene resin beads, and glass beads are used. The sizes of beads, number of beads, milling time, milling speed, characteristics of drug, and temperature are the factors affecting the final product.

Dry Co-Grinding: Nanosuspensions can be obtained via dry milling techniques. Nanosuspensions in this case are prepared by dry grinding of poorly soluble drugs with soluble polymers and copolymers.[20-22] Polymers and co-polymers like polyvinylpyrrolidone (PVP), sodium dodecylsulfate (SDS), polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives are used in dry co-grinding techniques for preparation of nanosuspensions.[23-25]

High-Pressure Homogenization:[26-29] In high pressure homogenization, the drug powder is first dispersed into an aqueous surfactant solution and passed through a homogenizer to obtain a desired size range. Nanosuspensions are produced on the principle of cavitation forces, high-shear forces, and the collision of the particles against each other. The pressures, number of cycles, and concentration of drug are the factors that dictate the final product. The advantages include homogenous particle size distribution, reproducibility, lower production time, and continuous production.

EVALUATION PARAMETERS: SHAPE, SIZE & SIZE DISTRIBUTION

Structural characterization like shape, size, surface morphology, size distribution, etc is a parameter that plays an important role in determining various attributes of a nanosystem. The shape of the nanosuspension can be determined using a transmission electron microscope (TEM) and/or a scanning electron microscope (SEM).[30] Size and size distribution

are important evaluation parameters of the nanosuspensions because they affect the saturation solubility, dissolution velocity, and physical stability of drugs. The mean particle size and the width of particle size distribution, ie, polydispersity index (PI), are determined by Photon Correlation Spectroscopy (PCS).[31] However, due to a narrow measuring range of PCS, (approximately from 3 nm to 3 µm), laser diffractometry (LD) is needed to study the content of particles in the micrometer range of approximately 0.05 to 80 µm up to a maximum of 2000 µm, depending on the type of equipment used.

EVALUATION PARAMETERS: PARTICLE CHARGE (ZETA POTENTIAL)

Zeta potential is used to determine the charge at the particle surface. Particle charge is measured by electrophoresis and expressed as electrophoretic mobility [(µm/S)/(V/cm)] or converted to the zeta potential (mV). A minimum ± 30 mV zeta potential is required for stable suspension.[32]

EVALUATION PARAMETERS: CRYSTALLINE STATUS

Differential scanning calorimetry (DSC) and X-ray diffraction can be used to evaluate the crystalline structure of the drug nanosuspension.[33] The evaluation of the crystalline state is necessary in case the drug exists in different polymorphic forms.

EVALUATION PARAMETERS: DISSOLUTION VELOCITY & SATURATION SOLUBILITY

Measurement of the saturation solubility and dissolution velocity is a very important parameter that helps measure the benefits compared to the conventional or microparticle formulations. Dissolution velocity is measured by the method given in pharmacopoeia. Saturation solubility is measured by shaking the drug in different solvents at different temperatures up to equilibrium. The Kelvin equation and the Ostwald-Freundlich equations can explain the increase in saturation solubility.[34]

APPLICATIONS[6]

The oral route is the primary choice for drug delivery due to its abundant advantages, such as safety, patient convenience, etc. At present, most nanosuspension products on the market are for oral delivery.[30] From the formulation point of view, nanosuspensions meet almost all the needs of an ideal drug delivery system for the parenteral route. Nanosuspensions also show a great prospective for the pulmonary delivery of the drugs that are poorly soluble in the pulmonary region. Nanosuspensions may also be beneficial in ocular drug delivery for drugs that show poor solubility in lachrymal fluids.

SUMMARY

Drug nanonization can be considered as a universal formulation approach for poorly soluble drugs. This approach is used to improve the oral bioavailability of drugs by improving their dissolution characteristics. The nanosuspensions are not only applicable to oral delivery, but also the parenteral, pulmonary, and ocular delivery routes. In addition, drug nanosuspensions can also be formulated into various dosage forms, such as tablets, capsules, injections, aerosols etc. Nanosuspensions are a promising drug delivery strategy, and could be a boom, especially for BCS Class II drugs.

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DRUG DEVELOPMENT
NANOSMART™ Pharmaceuticals, Inc. Executive

NanoSmart Pharmaceuticals: Patented Delivery Platform Using Human Autoimmune Antibodies to Target Cancers & Other Debilitating Diseases

Dr. James Smith
President

Nanosmart Pharmaceuticals, Inc.

"The idea of improving cancer drugs using immunoliposomes has been around for decades, but to date no immunoliposomal drugs are available on the market due to the lack of effective tumor-targeting antibodies. NanoSmart's autoimmune antibody specifically targets the DNA that is normally hidden inside the nucleus of normal cells, but gets exposed outside the cells in cancer patients because an increased amount of cell death (necrosis) that is characteristic of cancerous tumors. The result is that the antibody-coated liposomes preferentially target the tumor."

While the biopharmaceutical industry contemplates the demise of its existing drug portfolio with dwindling patent lives, players are continuously searching for ways to mitigate expanding costs and timelines to get to market approval. NanoSmart Pharmaceuticals, Inc., a small drug development biotechnology company in Laguna Hills, CA, has discovered the solution to each of these problems facing the industry. The company was co-founded by Dr. Henry Smith and his son Dr. James Smith, both interested in cancer immunology. Together, they have focused on how to improve upon various existing medical technologies. NanoSmart has discovered and patented a novel tumor-targeting platform using human autoimmune antibodies (not to be confused with "humanized" monoclonal antibodies) that target areas of necrosis found in many different types of tumors and other diseases. Drug Development & Delivery recently interviewed Dr. James Smith, President of NanoSmart Pharmaceuticals, to discuss its innovative approach to drug delivery using immunoliposomes and their unique targeting ability.

Q: How do immunoliposomes function?

A: NanoSmart uses a human antibody that is produced by the human immune system in people who have an autoimmune disease called Systemic Lupus Erythematosus (SLE). This is an antibody that attacks the human cells of multiple organs and is specific for, and targeted at, DNA in human cells. By coating the surface of drug-filled liposome nanoparticles with SLE autoimmune antibodies, we have the ability to develop novel drugs for many different types of cancer and other diseases while also increasing drug localization at the tumor site, thus improving the safety and efficacy of existing drugs. Essentially what we have here is a guided missile that hones into tumors, gains entry to cancer cells, and then ejects the payload, which is typically a cytotoxic drug.

In general, cancer tumors have leakier blood vessels than normal blood vessels. When the immunoliposome arrives at the cancer tumor, because of the liposome's size and shape, it leaks into the tumor through its leaky vessels. The

immunoliposome that is coated with the anti-DNA SLE antibody then attaches to its targeted DNA molecules in the necrotic tissue at the center, and surrounding the outside, of the cancer tumor, thus anchoring it there. The liposome then slowly and steadily releases the anti-cancer drug into the center, and onto the surface, of the cancer tumor (and only minimally to healthy cells) on its way to the tumor site. This focuses the cell-killing power of the drug on the cancer cells, bypassing the normal healthy cells.

Q: How was the idea conceived to use autoimmune antibodies to target tumors?

A: Actually, this idea was first conceived about 40 years ago when my father was using radiolabeled antitumor antibodies to target tumors. He found that the antibodies concentrated in the necrotic region of the tumor and speculated that maybe in addition to tumor antigens there was some cellular material present, such as DNA or other nuclear material that could be targeted. As an immunologist, he also knew that patients with SLE had high titers of an antibody called antinuclear antibody (ANA) that potentially could be used as a tumor-targeting antibody. However, at the time, it seemed unethical to ask a patient with SLE to donate a pint of blood to benefit another, so the idea was shelved. However, in the mid-1990s, a method of treating SLE using apheresis was reported. Apheresis is a process, somewhat similar to kidney dialysis, in which the patient's blood is passed through a column to remove the bad antibodies (eg, ANA) and the cleaned blood is returned to the patient. When Henry saw the articles on apheresis, he realized that this solved the ethical dilemma because instead of throwing away these bad antibodies, they could instead be collected, purified, and used to prepare immunoliposomes to target the necrotic regions of many different types of solid tumors.

There is an old saying that "one man's medicine is another man's poison." This phrase teaches a principle that toxicity is just a matter of dose and that with a high enough exposure, even a normally beneficial substance can become toxic. Our invention teaches the exact reverse of this principle, namely that "one man's poison can be another man's medicine." We believe that we are the first to describe taking a material that is pathogenic from one patient (eg, taking ANA from someone with SLE) and using it to treat a different patient for an unrelated illness (eg, using the ANA as a drug carrier to treat a person with cancer).

The idea of improving cancer drugs using immunoliposomes has been around for decades, but to date no immunoliposomal drugs are available on the market due to the lack of effective tumor-targeting antibodies. NanoSmart's autoimmune antibody specifically targets the DNA that is normally hidden inside the nucleus of normal cells, but gets exposed outside the cells in cancer patients because an increased amount of cell death (necrosis) that is characteristic of cancerous tumors. The result is that the antibody-coated liposomes preferentially target the tumor.

Q: What types of cancer tumors could NanoSmart's platform potentially target?

A: NanoSmart's immunoliposomal formulations have very broad applications because of the commonality of the target: necrotic tissue. Solid tumors typically have significant areas of necrotic tissue associated with them, so we should be able to target many different types of cancers for which the medical community is actively pursuing additional therapeutics. These include prostate cancer, breast cancer, lung cancer, and liver cancer. NanoSmart's platform can also target many orphan cancer indications desperately needing targeted treatments.

This is a true platform technology in which different cancer drugs can be enclosed within the same basic immunoliposomal formulation. Even though we will be using existing cancer drugs that have proven safety and effectiveness, each immunoliposome-

drug combination represents a novel biopharmaceutical with improved targeting and improved safety and efficacy profiles. The variety of new immunoliposomal cancer drugs that can be developed using our technology is virtually unlimited.

Q: What is NanoSmart's regulatory strategy?

A: NanoSmart has crafted a regulatory strategy that focuses on demonstrating our ability to rapidly and efficiently commercialize our drug delivery platform while also demonstrating the potential for a very broad product pipeline. The two big unknowns in any drug development are safety and efficacy. Many drugs fail in late-stage clinical trials because of the lack of safety or poor efficacy. In our case, these developmental risks are substantially mitigated because NanoSmart uses clinically proven, approved drugs as the payload. NanoSmart will take advantage of an established, and abbreviated, regulatory pathway, 505(b)(2), to file NDAs. Under the 505(b)(2) development scheme, the FDA acknowledges the efficacy of the active therapeutic ingredient that has been previously reviewed and approved. This essentially enables a more efficient approval process that may not require extensive Phase III clinical trials or full animal toxicology studies, which can take several years for a more traditional NDA.

Therefore, we expect to move very fast on the drug development timeline. The primary regulatory hurdle that NanoSmart must meet is limited to showing "non-inferiority" in efficacy for approval. However, it is expected that the NanoSmart technology will improve efficacy and safety by targeting the tumor and by limiting exposure to non-tumor tissues, respectively.

Q: Can you please discuss your development status to date?

A: Many start-up companies get bogged down in basic discovery research for several years attempting to pick the right molecule to develop. Attrition is very high during the research phase for these companies, with approximately only 5% of molecules moving into evaluation in animals. However, NanoSmart resources were focused on product development from the very beginning. We were able to do this because we sought to develop improved versions of drugs with proven efficacy and safety. This decreases our development timeline significantly and has resulted in getting to the preclinical proof-of-concept milestone in just a couple of years. Pilot-scale manufacturing and preliminary animal studies are currently underway, and NanoSmart expects to have a drug product that can go into clinical trials in less than 12 months. GMP manufacturing and GLP animal testing are planned for early next year. Also, NanoSmart recently entered into a research collaboration with Children's Hospital Los Angeles, one of the nation's top pediatric hospitals, to help develop and assess NanoSmart's novel drug delivery platform in Ewing's Sarcoma.

Q: The trend for Big Pharma has been to look outside of internal R&D departments for innovation. How do you see NanoSmart adding value to a potential partner, licensor, or acquirer? How does this fit in with your business model?

A: Pharmaceutical companies can use the NanoSmart platform to create new cancer drugs with increased safety and efficacy. Existing cancer drugs that are FDA approved and have lost their patent protection, or are about to lose their patent protection, can be plugged into the NanoSmart platform to create newly formed drugs with additional patent life. Companies can also put drugs that are currently in development showing limited efficacy, or drugs that have failed in clinical trials, into the NanoSmart drug delivery platform to improve the safety and efficacy of these

drugs to obtain FDA approval.

Our immunoliposomes protect normal cells in the body by sequestering the drugs until they reach their tumor tissue targets. With our new targeted immunoliposomal technology, it's also possible to bring drugs back to life that were discarded in late-stage clinical trials because of safety issues. This is an entirely new dimension to our platform that remains to be explored.

NanoSmart will continue to make its own drugs by putting off-patent FDA approved drugs into the NanoSmart platform, thus creating a new novel drug that can target different types of cancer. We have the ability to develop drugs for multiple indications as our antibody is not tumor-antigen specific, but instead targets necrosis found in many solid tumors.

In addition, our core team has a strong history of enabling acquisitions of the drugs they developed in start-ups and biotechs. So naturally, we anticipate being able to partner out some of our drug products at various stages of development.

Q: What are the next critical steps for NanoSmart?

A: There are abundant opportunities for NanoSmart Pharmaceuticals in the current cancer market. NanoSmart is shooting for its initial IND filing in 2012, with initiation of clinical trials soon after. On the regulatory front, NanoSmart has already filed one orphan drug designation application for Ewing's Sarcoma and plans to file additional orphan drug applications throughout 2012. In parallel, NanoSmart is pursuing various other oncology and non-oncology indications. In the meantime, we are always on the look-out for collaborators to expand our product pipeline across multiple indications.

Our unique technology, which enables targeted delivery, offers a huge potential for partnering with biologic companies (Ab drugs) as well as small molecule drug companies. There is potential for both local (such as topical) as well as systemic delivery of drugs. For example, this technology can be easily adopted for a pain medication as a slow depot-type delivery. Another potential area is in the treatment of wounds. We can easily place an antibiotic or a wound-healing or regrowth biologic such as a peptide as the payload and target the necrotic tissue of the wounds.

Even in the oncology arena, there are several good drugs that have been abandoned because they were found to be too toxic following intravenous administration. This toxicity limits the total dose that can be provided due to the risks of serious adverse effects. In essence, the patient risks dying from the treatment in an effort to kill the cancer tumor. Our immunoliposome technology has the potential to resuscitate these otherwise efficacious drugs by improving the safety profile of these therapeutic compounds.

One advantage of increasing the safety and efficacy of cancer drugs by incorporating them into the NanoSmart immunoliposomes is the dosing schedule and/or the dose can be adjusted to increase the benefit to the cancer patient. Therefore, higher doses could be given to eliminate the tumor quicker, with less drug reaching normal tissues and causing adverse effects.

Finally, the future could hold the possibility of co-formulation of drugs that target different stages of cell division. This modality continues to take advantage of improved safety and tolerability to affect a more positive outcome for the patient. The potential to explore a wide variety of potentially superior drug combinations in our unique platform is something we are eager to focus on after making initial progress with our first formulations. ◆

Technology & Services Showcase

Drug Development Services

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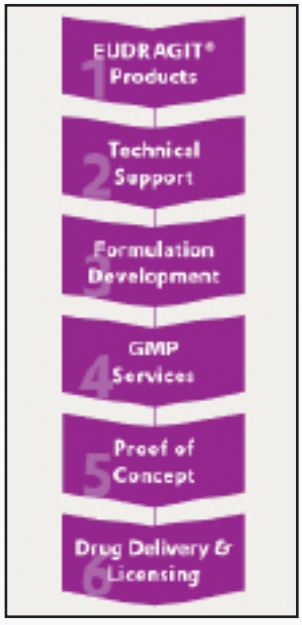
Pharma Polymers



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Technology & Services Showcase

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Development & Delivery Solutions

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Manufacturing & Development

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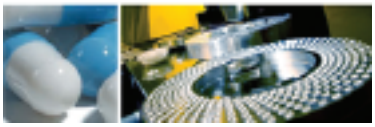

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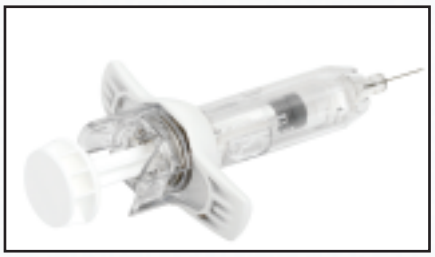
Technology & Services Showcase

Contract Diagnostics

ResearchDx is a leading Contract Diagnostics Organization (CDO) for the biopharmaceutical and diagnostic industries. As a CDO, ResearchDx integrates clinical research, clinical laboratory, GMP manufacturing, and consulting to achieve the fastest path to market for companion diagnostics. Experts manage the entire diagnostic development process - from initial assay concept and discovery through clinical research to regulatory approval. Services include research project design, conduct, and FDA submission; laboratory assay develop¬ment, validation, and sample testing in our CAP/CLIA lab; cGMP assay and reagent manufacturing; and expert guid¬ance across the entire process. For more information, contact ResearchDx at (866) 225-9195 or visit **www.researchdx.com**.

Passive Safety Device



Rexam Healthcare has received 510(k) approval from the FDA for Safe'n'Sound™, its passive safety device for staked prefilled syringes. The approval is the crowning achievement of significant investment and design efforts by the Rexam teams. The aim of the project was to design a safety device that meets the current regulations in North America and Europe. These regulations are aimed at protecting workers in the health sector from needle injuries and contamination from blood-borne pathogens. The fully passive Safe'n'Sound device provides effective protection against the risks of being pricked by a soiled needle due to the protective sheath that activates automatically once the medicine has been administered. This 510(k) approval shows Rexam's commitment to innovation, safety, and quality and allows the product to be marketed in the US. For more information, contact Rexam Healthcare at (800) 537-0178 or visit **www.rexam.com/healthcare**.

Development Services

UPM Pharmaceuticals® is an independent provider of contract formulation development, analytical services, and cGMP manufacturing. We continue a legacy of intellectual distinction and uncompromising performance with every new project. The talent and experience of our team, our dedication to science-based formulation design, and our commitment to communication and timeliness enables us to offer the highest level of customized drug development services. Our 30,000-sq-ft main facility in Baltimore features cGMP pharmaceutical manufacturing and packaging suites as well as analytical and R&D laboratories staffed by industry veterans. Whatever form your product takes, we ensure rigorous and technically sound product characterization, methods development, and QC release. Our clients enjoy service that is highly responsive and fast with total quality management characteristic of a customer-focused business. For more information, contact UPM Pharmaceuticals at 410-843-3738 or visit **www.upm-inc.com**.

Development Services

Xcelience is a premier provider of formulation development and manufacturing solutions with a solid reputation for accelerating early phase small molecule development. Our outstanding quality record, significant drug development expertise, willingness to customize, and disciplined project management enable us to deliver real advantages to clients needing to speed potential drugs to clinical trials. Since 1997, Xcelience has been renowned for reliably expediting drug development. Our formulation development scientists have considerable experience overcoming challenges associated with physical and chemical properties of drug substance, or limited quantities of API, in a manner that results in compounds with improved solubility and bioavailability. Partnering with a specialist like Xcelience for early phase development can significantly reduce product risk and accelerate development timelines. For more information, contact Xcelience at (608) 643-4444 or visit **www.xcelience.com**.

Oncology Studies

Overview of Challenges in Oncology Studies

By: David Underwood, CEO & Chairman, Quanticate

Introduction

Oncology clinical programs represent a significant investment in terms of costs, resources, and time. Understanding the challenges at all stages is vital to success of the study/program. The purpose of this article is to provide an overview of some of these challenges (and associated recommendations) in setting up, conducting, and reporting oncology studies.

In the UK and US, approximately 1 in 4 people die from a cancer or cancer-related disease, making it the second most likely cause of death (after cardiac-related diseases). There is a major focus on developing new treatments to improve the survival of patients with cancer. Oncology studies in just one specific cancer, non small cell lung cancer (NCLC), account for more than 22,000 patients being recruited worldwide in Phase III clinical trials today, leading to intense competition for patient recruitment.

With so many studies ongoing, it is important to select clinical research organizations with the appropriate expertise to ensure that the myriad complexities associated with oncology studies are considered. Clinical research organizations will often have expertise in specific cancers (eg, prostate, NCLC, etc). Specialist biometric organizations are likely to have a broad range of experience across many types of cancer. Multiple suppliers with their specialties may be involved in the reporting of a full clinical program.

Study Design

From the study design perspective, there are several study designs in the early development phase specifically tailored for oncology studies. These include dose escalation designs based on safety and efficacy considerations and incorporation of overlapping dose groups. Phase I studies are almost always based on patients due to the

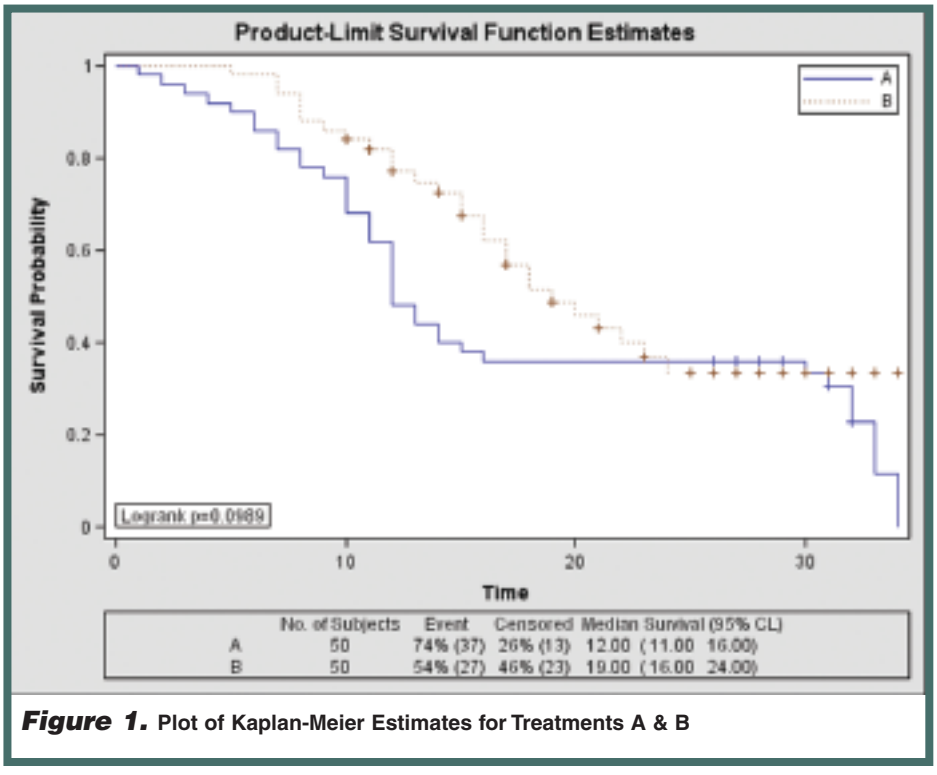


Figure 1. **Plot of Kaplan-Meier Estimates for Treatments A & B**

anticipated toxicities. It is rare even in Phase I to be able to include placebo as a comparator due to ethical considerations, although some Phase I Cohort designs can incorporate random placebo insertion. The challenge for all phases is to keep the length of recruitment to a minimum - particularly challenging for rare cancers. This is compounded in the later phases, where larger numbers of patients are required and there is a need to balance both the recruitment and the length of follow-up with large numbers of sites and countries. Discussions with investigators to identify realistic recruitment rates (adjusting for competing studies where appropriate) will help in these planning aspects.

The Gold Standard for oncology studies from the regulatory perspective (FDA Guidance Document: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007) would be the endpoint of overall survival (OS) in a randomized double-blind study or studies demonstrating the required clinical superiority compared to the current standard therapy in the chosen indication. Overall survival can take years to collect, and surrogate or alternative endpoints, such as progression-free survival (PFS) or Quality of Life (QOL) data, may be accepted as interim approval endpoints. Double-blind studies are difficult to achieve: treatment regimens differ in length, delivery, and complexity, making single-blind studies more common. Use of double-dummy is rare, so if it is the only means to blind the patient from the treatment allocation, then open-label studies may be the only option. Open-label studies can be subject to intense scrutiny by the regulatory bodies because it is difficult to achieve unbiased assessments.

The sponsor is responsible for the provision and blinding of any comparators used, along with funding the standard-of-care treatment at each of the sites. To allow for effective usage of study and comparator medication, an Interactive Voice (or Web) Randomization System (IVRS/IWRS) is strongly recommended. Whilst these systems are efficient in managing the Investigational Product, it is important to allocate additional time to the set-up phase to establish the system.

Consideration of follow-up for overall survival should be built into all studies as part of the Informed Consent (IC) to enable easy access to patient records for 1, 2, or more years of follow-up for the restricted information pertinent to the key endpoints of interest. This requires considerable forethought in the planning processes and will generate more complete follow-up at the later stages of the program, compared to post-hoc data collection that can be both costly and only partially successful.

Patient Recruitment & Retention

Treatment-naïve patients are rare. Competition for patients in most areas is intense, and many patients (although suitable for inclusion in the trial) are often exhausted from previous chemotherapy or radiotherapy and are subsequently unwilling to consent. Study-related tests that are additional to their current care may also deter participation. To maximize recruitment within each center, it is recommended to discuss with as many sites as possible prior to finalizing the protocol, to balance the minimum number of invasive/additional tests against recruitment targets.

Eligibility for the study will be impacted based on previously failing treatment with the selected comparator, thus reducing the recruitment pool further. Recruitment of 1 to 2 patients per year is not uncommon, and this will have a significant effect not only on the quality of the data and the duration of recruitment, but also on treatment by center analyses.

Study Setup & Conduct

Oncology studies are resource-intensive both at the site and for the Sponsor due to all the set-up and monitoring aspects that such studies entail. Some of the major challenges are listed further, and these range from site set-up, protocol approval with the appropriate authorities, data collection (verification of source data, samples, follow-up, serious adverse events), and independent committees.

Ethics committees (ECs) often raise issues regarding patient recruitment, comparator usage (as these may have different labels in various countries), and the privacy and legal requirements for anonymization of scans and samples. This may drive long EC approval timelines (impacting study start-up timelines) and may lead to subtle protocol differences across countries. It is recommended to assume at least another two EC review cycles per site (for a 10-site study) and four EC review cycles (for a 100-site study) in the planning phase before 100% of sites are recruiting.

Source Data Verification (SDV) is more difficult than for some indications as the patient notes are complex and voluminous, hence requiring more time to conduct. Clinical Research Associates (CRAs) will be able to monitor only three to four sites at any one time due to the high workload and will need to be familiar with the RECIST criteria [Revised RECIST Guideline (version 1.1): New response evaluation criteria in solid tumours, 2009] as part of the assessment of evaluability of the patient.

A high proportion of patients are likely to experience a serious adverse event (SAE),

and these cases are often complex. The assessment of causality and distinguishing from underlying disease and concomitant therapies can be especially challenging and emphasizes the need for high-quality and complete SAE reports. Many oncology trials will be conducted in high-morbidity and high-mortality diseases and may have efficacy endpoints that could also be reportable adverse reactions. The systematic breaking of the blind for such cases (as required for expedited reporting to EU-competent authorities) could compromise the integrity of the clinical trial; under such circumstances, it may therefore be appropriate to reach agreement with competent authorities in advance concerning SAEs that would be considered disease related and not subject to systematic unblinding and expedited reporting.

Differences between regulatory authorities currently exist on this particular aspect, but the most comprehensive reporting requirements need to be considered. For blinded trials with agreement not to undertake systematic unblinding and expedited reporting, the appointment of an independent Data Monitoring Committee to review safety data on a regular basis is also recommended. Robust procedures for SAE collection, assessment, follow-up, and ongoing evaluation is imperative. The volume of SAEs, follow-up, regulatory requirements, and tracking will be time-consuming and requires significant pharmacovigilance and medical expertise, in addition to input and support from the CRAs. Early involvement of pharmacovigilance experts in the protocol will ensure these aspects are adequately covered, both in the protocol and any regulatory interactions prior to the study start.

There will be potentially a large amount of data/samples to collect/track for the study. These can include (but not be limited to): biopsy samples, images/scans, and blood samples (including PK and biomarkers). Collection and shipping may require multiple approvals from multiple countries, potentially creating delays and degradation of samples, rendering them unusable, so this aspect needs to be considered as part of the site assessment. Some of these samples/scans may be required for central (blinded) reading, leading to dummy patient numbering to protect the identity of both patients and sites. All these data will be eventually required to be analyzed so storage in a central place is helpful for the end of study reporting.

Given the potential toxicity of such treatment(s) under investigation, it is likely that the study will have a Data Safety Monitoring Board (DSMB) overseeing the overall patient safety. This will necessarily require continuous monitoring and data collection to ensure all appropriate data available at the required time points for the DSMB.

Reflective of the disease complexity with multiple treatment regimens and endpoints, the Case Record Forms (CRFs) need to be clear, concise, and unambiguous to enable accurate completion. With electronic capture becoming more prevalent, this is enabling on-line validation as data are entered, allowing immediate corrections (as needed) to be completed by site personnel. This is increasing the accuracy of entry and enabling queries to be restricted to more complex cross-page checks. This is especially helpful for interim database locks (eg, for a DSMB) to reduce the time required for answering any outstanding queries. SDV can be recorded on the e-CRF by the monitors, providing an easy way of tracking the SDV required/performed.

Tumor assessment pages continue to be the CRF section that generates the most queries. This is not that surprising because tumor shrinkage is likely to be a key secondary endpoint, and it is important to track the right lesions and ensure they are consistently assessed and recorded and collected at the appropriate time intervals.

The volume of adverse events and concomitant therapies require a significant amount of review to ensure data accuracy and co-correspondence with the safety (SAE) database and ability to report in a consistent format. The number of therapies ongoing will be high and indicative of the seriousness of the patient's condition.

Structuring the (electronic) CRF for ease of entry at site will support the study nurse and investigator in the entry of data and help the CRA with the monitoring aspects. However, it is important to consider the data management and analysis requirements to ensure the study can be reported as planned. Consideration should also be given for all the external sources of data up-front and how they will be incorporated both into the database and the analysis. In particular, survival follow-up that may continue for many years following study reporting needs to be linked to the original study for ease of reporting.

Analysis Considerations

Several of the key endpoints in oncology use survival methodology, such as overall survival or progression-free survival, which can account for patients that do not achieve the endpoint and can be censored at the point of no further information available. These can be illustrated using Kaplan-Meier plots over time and analyzed using the Log Rank test, with summary statistics for median survival and associated 95% confidence intervals. Adjustment for covariates of interest can be applied in proportional hazards modelling or accelerated failure time modelling, depending on the underlying model distributions with appropriate treatment comparisons described using hazard ratios.

More complex models to adjust for interval censoring, competing risks, and multiple states are available for use as sensitivity models or the main analysis.

Even for the more simple analyses, the data collection and understanding of the data available are important in the interpretations drawn from the data. Considerable care needs to be taken for patients censored prior to time point of interest - the reason for lack of information needs to be scrutinized to ensure the patient does not represent a patient with "informative censoring."

This can easily be demonstrated with an example: 100 patients recruited on two treatments A and B using 1:1 allocation; the number of deaths in treatment A is higher (74%) than B (54%), and the median survival time is 12 and 19 months, respectively, over a 36-month time period (Figure 1). For treatment A, all patients have either died prior to the time point or censored/alive after 24 months. For treatment B, 46% of patients were censored prior to 36 months (20% of patients prior to 19 months) due to lost to follow-up and withdrawal of consent. Further investigation indicated that the lost to follow-up were because the patients were so poorly that their care was transferred to hospice, and the withdrawal of consent was to enable the patient to take additional treatments due to poor prognosis. In all cases, the censoring would be considered informative with the potential to bias the results of the analysis. If the 20% of patients censored prior to 19 months in Treatment B had died within the confines of the time period (36 months), the results would be very different. This extreme example demonstrates how important the data collection of follow-up and the care and attention of censoring applied in survival methodology. It is entirely possible that the difference observed between treatments A and B of 7 months in median survival is much smaller, and that the indication of treatment effect provided by the Log Rank ($p = 0.0989$) is inflated.

Progression-free survival can give rise to other challenges: progression can be identified by predetermined criteria but will be generally assessed at intervals. When did the progression actually occur? If considered at day of visit, then this is a potential over-estimation of time to progression. Bias can also be introduced by a visit schedule that is scheduled to the treatment needs; visits need to be frequent and spacing of visits identical for each treatment. By understanding the importance of how the data are collected and minimizing the bias as much as possible with appropriate data collection in place, the data can be appropriately analyzed, and the analysis plan appropriately set-up to take these aspects into account.

Concluding Remarks

As a sponsor conducting oncology trials, a fine balance is required between the requirement for accurate, appropriate, and timely information versus the complexity, cost, and quality of such trials. It is important to allocate enough time in the set-up phase to ensure the scientific expertise is built into the study, with all the design considerations thoroughly scrutinized to maximize the likelihood of a successful study with appropriate sites, endpoints, analyses, and reporting. Like many other indications, the relationship between sponsor and clinical partner(s) will be critical in successful recruitment and retention of patients. Follow-up of patients is critical, and success is governed by early identification of requirements and building in survival follow-up at the earliest stages of clinical development. Understanding of the best ways to collect and ultimately report the data will be critical in any successful submission and ability to register new treatments. ■

David Underwood

CEO & Chairman
Quanticate

David Underwood is CEO and Chairman of Quanticate. He has been in the pharmaceutical industry for over 30 years, starting his career at GlaxoSmithKline as a statistician. Mr. Underwood started his own company 15 years ago to provide specialist biometrics services and fully understands that data and their interpretation are the final product of clinical trials and their importance cannot be overstated. Part of this remit is the provision of statistical consultancy expertise to the industry. He is delighted to present this paper on behalf of the statistical consultancy team on the unique challenges involved in setting up, conducting, and reporting on oncology clinical studies. He can be reached at david.underwood@quanticate.com.

Advancing Personalized Medicine: A Seamless Solution to Discover & Deliver Novel Diagnostic Tests

By: Mathew W. Moore, PhD, and Philip D. Cotter, PhD, Principals & Co-Founders, ResearchDx

Introduction

The use of companion diagnostics in conjunction with custom pharmaceuticals is expected to expand as the promise of personalized medicine continues to be realized. However, a concurrent development cycle of both diagnostic and therapeutic requires a complex synergy of both diagnostic and drug development, and represents a significant deviation from the current pharmaceutical model. In response, ResearchDx, LLC of Irvine, CA, launched the first-ever Contract Diagnostics Organization (CDO) in February 2011. This new business model facilitates simple, straightforward options to initiate the parallel development of companion diagnostic tests in synergy with drug development.

Trends in Personalized Medicine

Personalized medicine refers to the customization of medical treatment to the individual characteristics of each patient.[1] Methods to determine genetic variation have thus far included testing for variations in genes, gene expression, proteins, metabolites, and new treatments that target molecular mechanisms. More recently, the use of composite biomarker signatures is commonly seen in the clinical development of therapeutics.

Initially, the driving force behind personalized medicine was the science. As this understanding grew, the demand and need for pharmacogenomics and patient-tailored therapeutics became evident. Currently, regulations guiding and mandating the process for companion diagnostics have been directing pharmaceutical companies as they seek to develop commercial strategies and products in personalized medicine.

Regulatory Environment

The Critical Path Initiative (CPI) is the US FDA's national strategy to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured.[2] It launched in 2004 with a document identifying increasing challenges and slowdowns in the delivery of effective

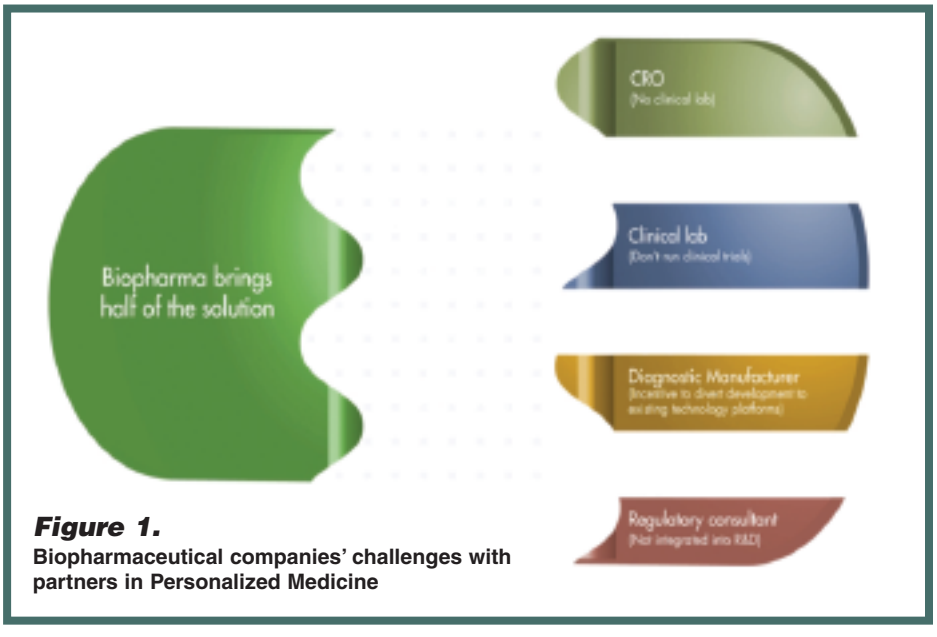


Figure 1.
Biopharmaceutical companies' challenges with partners in Personalized Medicine

and safe products for patients in a time of incredible scientific growth in the field of personalized medicine. The report called for a national effort to identify specific activities along the critical path of medical product development to help this process along. Areas in which the sciences of product development had the greatest need for improvement and potential were identified. Following this, the FDA created a website that tracks progress it is making in laying down the infrastructure to meet this goal.

The FDA's guiding document The Drug-Diagnostic Co-Development Concept Paper was drafted in 2005 to help outline a process to prospectively co-develop a therapeutic product and diagnostic test in a scientifically robust and efficient way.[3] The document identified and outlined the recommended multi-step path from basic research to, ultimately, FDA filing/approval and product launch.

Following this, the FDA's Guidance on Pharmacogenetic Tests and Genetic Tests for Heritable Markers document was released in 2007 and intended to recommend a basic framework for the types of data and regulatory issues that should be addressed in a genetic test submission and provide a common baseline from which both manufacturers and scientific reviewers can operate.[4]

Unfortunately, there is currently insufficient evidence of a downstream market to entice the private sector to explore most of this scientific potential. In order to counteract this, the National Institutes of Health (NIH) and FDA and have begun steps to develop a more integrated pathway that connects all the steps between the identification of a potential therapeutic target by academic researchers and the approval of a therapy for clinical use.[5]

A common thread throughout the various regulatory guidance is that the development of successful companion diagnostics is necessary, but the process is complex, multi-step, and individually time-consuming.

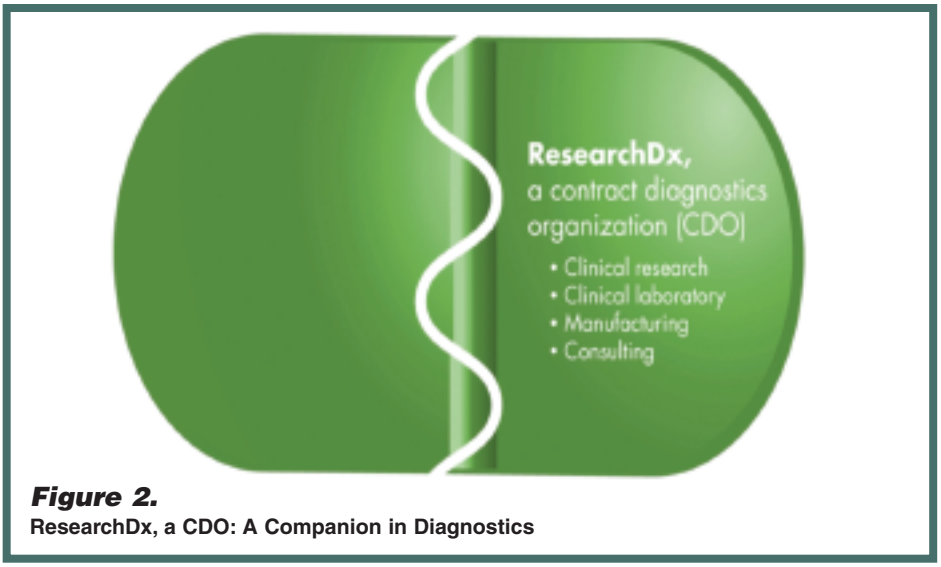


Figure 2.
ResearchDx, a CDO: A Companion in Diagnostics

Companion Diagnostic Challenges for Pharmaceutical Companies

As outlined in regulatory initiatives and guiding documents, the difficulties faced in coordination of therapeutics development with the companion diagnostics process are numerous. The need for specific expertise in the diagnostic industry is paramount, as no initial scientific concept for a molecular diagnostic test can be successfully hypothesized or carried out without a strong knowledge base at its core. This begins at the initial assay conceptualization, to discovery, to optimization, and finally to validation. Few pharmaceutical companies have this expertise in-house, so outsourcing or partnerships become necessary.

The traditional choices for partnership include Contract Research Organizations (CROs) and large diagnostics companies. However, CROs cannot provide the in-depth diagnostics knowledge, and unfortunately, large diagnostic companies may also have other motivations that can complicate the path to a successful companion diagnostic. For example, they may choose an existing technology platform for their current commercial products in an effort to capitalize upon synergies and increase efficiency even if that technology may not be the best choice for the new diagnostic. In the end, that choice could ultimately cost the pharmaceutical partner time, effectiveness, safety, and revenue.

Coordinating the timeline for both pharmaceutical and diagnostic development can be challenging from a regulatory standpoint as well. Most diagnostic companies will likely wish to ensure that a therapeutic will earn FDA approval before they initiate the costly process of seeking FDA approval for an In Vitro Diagnostic (IVD). Again, such delays will cost the therapeutic's manufacturer precious time in the marketplace.

In addition, pharmaceutical companies want to ensure that clinical trials conducted for development of a companion diagnostic are run in an environment that can ensure consistent analytical validity. Therefore, many are turning to laboratories accredited by the College of American Pathologists/Clinical Laboratory Improvement Amendments (CAP/CLIA). This necessitates partnering with a laboratory possessing and maintaining those credentials, a service many traditional diagnostics companies and CROs do not offer.

Lastly, there are numerous logistical challenges when managing and coordinating

multiple partners in the process. All of these can cause product delay and introduce points of inefficiency (Figure 1).

The Contract Diagnostics Organization: A New Business Model

With a shared passion for and experience in the field of personalized medicine, ResearchDx created the concept of a CDO in response to the numerous pitfalls we experienced in the companion diagnostics process. As a result, ResearchDx provides all of the necessary services in an integrated, technology-independent manner that stays focused on our customers' business objectives. CDOs offer clinical research, a clinical laboratory, manufacturing, and consulting all in one organization - eliminating the need for outsourcing to multiple partners. This also builds in flexibility and the ability to implement an efficient, nimble strategy that may naturally shift as development continues.

As a CDO, ResearchDx can build, validate, and perform any assay that a business demands, or alternatively work with competing technology vendors to ensure the best fit for the application. As well, clients can trust that the focus and motivation from a CDO are solely on the diagnostic development, as it has no competing interests (Figure 2).

With our team's extensive experience in managing clinical laboratories, designing and managing clinical research, and navigating the complex regulatory environment specific to diagnostics, we saw the opportunity to fill an unmet need for partnership with the biopharmaceutical and diagnostics industries. A CDO takes contract R&D for diagnostics to the next generation. Our partners trust ResearchDx to provide everything they need to develop a diagnostic product, and that we make their business objectives our priority.

The Future

Basic science behind personalized medicine will continue to offer a myriad of choices for pharmaceutical companies to create companion diagnostics in healthcare, making the need for them even higher. In addition, there is already more investment in the field of personalized medicine due to regulations being a stronger influence. The downstream market for custom therapeutics has significant untapped potential. Yet, the traditional bench-to-bedside development can be arduous and inefficient. Opportunities may be lost in this process due to numerous barriers. ResearchDx, as the first-ever CDO, seamlessly provides everything a company needs, from start to finish, to develop a successful diagnostic product. ■

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Dr. Philip D. Cotter earned his PhD from Mount Sinai School of Medicine in New York. He is Board Certified by the American Board of Medical Genetics, is a Fellow of the American College of Medical Genetics, and a Fellow of the Faculty of Science Royal College of Pathologists of Australasia. Dr. Cotter is extensively published and has served as Laboratory Director for many diagnostic laboratories throughout his career.

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Principal & Co-Founder ResearchDx

Dr. Mathew W. Moore, in addition to his role with ResearchDx, has served as Vice President of Research and Development of Neogenomics, Inc. since July 2006. He earned his PhD from the University of New South Wales in Sydney, Australia. Dr. Moore is a renowned leader in the field of molecular diagnostic development and a seasoned industry expert and technology advocate.

Executive Summary

Dr. Marc Mansour
COO & CSO
Immunovaccine

Immunovaccine, Inc: Developing More Effective Cancer Vaccines

Cancer vaccines represent a multibillion-dollar market opportunity for pharmaceutical companies, but numerous vaccines have failed in Phase III clinical trials despite promising results in early phase testing. One of the primary challenges researchers face in developing effective cancer vaccines is trying to effectively introduce cancer antigens into a patient's body to trigger the immune system effectively to elicit a therapeutic effect. Cancer patients often have weakened immune systems due to extensive treatments, and the tumor environment actively inhibits the immune response against it. This creates a very difficult setting in which to stimulate the patient's immune system to both recognize and destroy tumor cells. Immunovaccine, Inc., a publicly traded Canadian biotechnology company, is making significant advances to address these challenges through the use of its vaccine delivery and enhancement platform, known as DepoVax™. The generation of positive safety and efficacy data in both preclinical and clinical studies using DepoVax-formulated vaccines has attracted multiple partnerships for the company, including those with Pfizer and Merck KGaA. Immunovaccine's focus on developing novel therapeutic cancer vaccines has led to the in-licensing of a survivin-based vaccine known as Survivac from Merck KGaA. Survivac is a novel cancer vaccine, which targets multiple survivin-expressing solid tumors. The company has exclusive, worldwide rights to develop and commercialize this vaccine and has formulated it in DepoVax. The result, a new vaccine called DPX-Survivac that harnesses the benefits of DepoVax. Taking DPX-Survivac into an accelerated clinical program is a priority for the company because of its broad market potential for targeting multiple cancer indications. The National Cancer Institute (NCI) has ranked survivin among the world's top 25 most promising antigens, based on its broad expression by cancer cells, its limited expression in normal tissue, and its critical role in cancer cell survival. Immunovaccine is also currently advancing DepoVax-based vaccines in a variety of indications that range from cancer to autoimmune and infectious disease through its own pipeline, combined with a number of strategic collaborations and alliances around the world. Specialty Pharma recently interviewed Dr. Marc Mansour, Chief Operating Officer and Chief Science Officer of Immunovaccine, to discuss the DepoVax platform and the company's clinical trials for DPX-0907 and DPX-Survivac.

Q: ***Cancer immunotherapy has gained more attention recently as an effective target in treating cancer. Why is that?***

A: Interest in cancer immunotherapy is increasing as more products get approved. Two recent examples include the approval of Provenge for prostate cancer and Yervoy (ipilimuab) for melanoma. There are also many new anti-cancer therapies currently in clinical trials, and this is building traction within the cancer immunotherapy space. We know the immune system is capable of suppressing tumor progression before a tumor takes over. The challenge is how to reactivate the immune system in the clinic once the cancer has been diagnosed. We are used to traditional cancer chemotherapy that interferes with the ability of cancer cells to grow and spread, but these drugs can only delay the cancer's recurrence, as most tumors will eventually develop resistance to the treatment. Chemotherapy also

kills normal cells, which is why it has negative side effects. The next generation of therapeutic cancer vaccines is a more attractive approach as it uses the body's internal defenses to keep cancer away. By focusing on the body's immune system, which is designed to fight and kill invaders, there is hope that the body may develop a long-term ability to stop cancer and prevent it from returning.

Q: ***Can you provide our readers more background on your vaccine delivery platform, DepoVax™?***

A: Immunovaccine's DepoVax vaccine delivery platform uses liposomes to carry the antigens plus adjuvant into an oil. The result is a depot effect that increases the immunogenicity of the antigens and presents the vaccine ingredients to the immune system in a special way. DepoVax-based vaccines are a dry product and inherently stable. It takes less than a minute to re-suspend the active components of the vaccine in the oil. Upon injection, the depot vaccine remains at the site of immunization for a prolonged period of time. By exposing antigen-presenting cells to the optimized mixture of antigens and immune activators that make up each DepoVax-based vaccine, the platform allows for the generation of strong cellular and humoral immune responses with a single dose. All components of the DepoVax platform formulation are necessary for the optimal immune response. DepoVax formulations have successfully been scaled up to commercial-size batches and have potential for years of stability. DepoVax has also established positive safety results in human clinical trials.

Q: ***What are some issues researchers face in formulating effective cancer vaccines, and how does DepoVax combat these issues?***

A: One of the primary challenges researchers face in developing effective cancer vaccines is trying to introduce enough cancer antigens into a patient's body to elicit a therapeutic effect, without over-stimulating the immune system and triggering a regulatory T-cell response (T-Reg), causing it to combat the vaccine. Once the body's immune system has triggered this T-reg response, the cancer vaccine becomes inactive, leaving the patient unsuccessfully immunized. To date, finding a mechanism of delivery that minimizes a T-Reg immune suppression response has been a significant challenge facing cancer vaccines.

By formulating its immunogens and immune enhancers in liposomes, and then in oil carriers, DepoVax creates a significantly enhanced immune response. The active components are retained in the vaccine's oil and elicit a long-lasting effect with a single dose. The DepoVax formulation also minimizes the T-Reg immune suppression response, while stimulating the immune system, overcoming the problems most cancer vaccines have.

Q: ***How did the DepoVax technology come about?***

A: DepoVax was invented after the Canadian government asked researchers at Dalhousie University to come up with a humane way to control the Atlantic grey seal population by using an immuno-contraceptive vaccine. By formulating the contraceptive vaccine in the liposome-in-oil delivery platform, scientists found that 90% of vaccinated seals were still immuno-contracepted when tested again 10 years later, after only one dose of the vaccine. With this early success in animal health, Immunovaccine has chosen to focus on optimizing the DepoVax platform and developing premium vaccines for human health applications.

Q: ***What cancer vaccines does the company currently have in clinical trials?***

A: We have two vaccines in clinical trials, DPX-0907 and DPX-Survivac. DPX-0907 is our first therapeutic cancer vaccine. DPX-0907 contains seven antigens indicated for breast, ovarian, and prostate cancer and has completed a Phase I clinical trial at five US sites. This clinical trial has demonstrated that DepoVax-based vaccines are safe for administration, and we have been able to demonstrate the generation of vaccine-specific immune responses in treated cancer patients.

Our second is DPX-Survivac, a therapeutic cancer vaccine with broad market potential as it is designed to target multiple solid tumors and hematological malignancies. DPX-Survivac is currently being prepared for Phase I and II clinical trials targeting patients with ovarian cancer. It uses survivin-targeting antigens, in-licensed exclusively from Merck KGaA, that are formulated in our DepoVax platform.

Q: ***Is there clinical data demonstrating the efficacy of DPX-0907?***

A: Immunovaccine has completed Phase I clinical trials and recently presented the clinical safety and immunogencity data of DPX-0907. These data confirm the activity of DepoVax in humans and its potential to enhance immune responses to peptide vaccines. The results also provide important data to advance the clinical development of DepoVax-based vaccines.
The Phase I trial for DPX-0907 was an open-label, dose-escalating study. Patients received three injections of either 0.250-mL or 1-mL doses of the active immune therapy DPX-0907, 3 weeks apart. The Phase I trial met the primary objective of safety at both dose levels. The overall results demonstrate that DPX-0907 is well tolerated, and there were no vaccine-related serious adverse events reported. The secondary objective was to assess whether DPX-0907 could generate an immune response specific to the seven cancer antigens. Immunovaccine performed a detailed analysis of patients' blood samples that showed cell mediated immunity (CMI) to vaccine targets in all three breast cancer patients, five of six ovarian cancer patients, and three of nine prostate cancer patients. Both dose levels produced targeted immune responses in vaccinated patients. The data shows, in most cases, T cells specific to the vaccine targets displayed multiple activation markers following vaccination, and these poly-functional T cells are believed to be more effective in targeting cancer cells.

Q: ***Can you tell our readers some more information on DPX-Survivac?***

A: The DPX-Survivac program was initiated after Immunovaccine in-licensed Survivac, a survivin-based vaccine, from Merck-KGaA in July 2010. As Survivin is a critical molecule for cancer cell survival and is highly associated with many types of tumor cells which why the National Cancer Institute ranks survivin as one of the top 25 most promising antigens. To date, survivin-based vaccines have yielded encouraging results in human Phase I and investigator-driven Phase II clinical studies.

While DPX-Survivac has the potential to target at least nine different cancers, Immunovaccine is developing DPX-Survivac to treat ovarian cancer for initial clinical trials. In preclinical studies, DPX-Survivac was found to significantly enhance immune response over the control formulation used in previous clinical trials. In June 2011, Immunovaccine's Investigational New Drug Application (IND) was accepted by the US Food and Drug Administration (FDA) for DPX-Survivac.

Q: ***What other vaccines are in Immunovaccine's pipeline?***

A: Earlier studies have shown the DepoVax platform is well suited for development of effective single-dose vaccine products because it can raise a much stronger antibody response than conventional vaccine formulations. Immunovaccine is conducting proof-of-concept and preclinical research for a number of potential infectious disease vaccines.

Among the target diseases for the development of DepoVax-based vaccines are Hepatitis B, and pandemic influenza. Immunovaccine's preclinical studies have also demonstrated its capability to develop a single-dose DepoVax platform-based pandemic influenza vaccine for emergency stockpiling and use.

Q: ***What is Immunovaccine's partnering strategy?***

A: Immunovaccine has a number of active partnerships and research agreements with companies in North America, Europe, and Asia to provide enhanced delivery of other companies' vaccines by formulating their antigens in DepoVax. We are currently seeking additional partnerships.

In May 2011, Immunovaccine signed a research agreement with Cuba-based CIMAB S.A. Together, we will formulate the CIMAvax-EGF peptide antigen in the DepoVax system to potentially enhance the immunogenicity of a novel therapeutic vaccine candidate.

Other recent collaborations include preclinical research collaborations with IRX Therapeutics, Oncothryeon Inc., and OncoTherapy Science. With IRX Therapeutics, we are evaluating the combination of IRX's primary cell-derived biologic, IRX-2, with DepoVax-based therapeutic cancer vaccines with the goal of demonstrating a superior anti-tumor immune response. With Oncothyreon Inc., we are combining ONT-10 with DepoVax and evaluating the ability of this combined vaccine formulation to elicit strong and long-lasting immune response. Our agreement with OncoTherapy Science will also explore enhancing the immunogenicity of their novel peptide cancer antigens in our DepoVax platform. ■

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Where's The Money?

By: John A. Bermingham

Happy New Year! With the advent of 2012, I thought that it might be timely to briefly discuss new company investment money (and their differences) because 2012 may just be the year of the start-up, and too often, I hear so many stories from entrepreneurs who wish they knew the difference before accepting a penny!

Seed Capital

Seed capital, or seed money, is money that is invested in very early stage start-ups and typically comes from savings, family, friends, or angel investors. The company is generally not producing revenue at this time but requires preliminary money for R&D, market research, and other overhead costs. Seed capital ensures there are enough funds to sustain the company for a period of time until it reaches either a state at which it is able to fund itself, or has created something in value so that it is worthy of future rounds of funding. Many entrepreneurs mistakenly believe that venture capital is the place to go for start-up money. In fact, most venture capital companies look for a revenue stream and an interesting or proven technology or service prior to investing. You can expect a seed capital investor to require equity in the company but not at the level of a venture capital company.

Venture Capital

The venture capital investment round occurs after the seed capital round and should be viewed as a growth capital round (also referred to as a series A round). Venture capital is appealing for start-up companies with limited operating history that are too small to raise capital in the public markets, through a bank loan, or a debt instrument. Because an investment in a start-up company is high risk, a venture capital company will expect to receive significant control over company decisions and a significant portion of the company's equity. You should keep in mind that you are much better off owning 30% to 50% of your company with the venture capitalist owning the remainder rather than owning 100% of a company that failed to come to market due to a lack of funding. Venture capital is a subset of private equity and therefore, all venture capital is private equity but not all private equity is venture capital. This is because private equity investments can also be leveraged buy-outs, distressed company acquisitions, and mezzanine capital investments.

Private Equity

Private equity firms generally look for more mature companies that have been producing revenue, often for a number of years. The acquisition can be a company of which the owner wants to cash out and retire or do something else. It can also be a strategic acquisition the private equity firm wants to absorb into one of its portfolio companies. Certain private equity firms focus on distressed companies so they can acquire the company on the cheap, many times through a bankruptcy. Private equity firms take majority control of the company and control the Board even if not occupying the Chairman position, but do give up to 10% of the equity to the senior management team as a long-term incentive. The owner of the company being acquired may stay in position as the CEO and continue to run the company or may be released, will have his or her equity acquired by the private equity firm, may be asked to reinvest part of the proceeds back into the company for new equity, or be given an earn-out provision whereby not all of the owner's equity is acquired but instead left in the company to be acquired at a later date based on future profits. Thus, the original owner has an incentive to ensure the value of the company and its profits increase over time. A private equity firm will usually hold onto a company for 5 to 7 years, sometimes longer, before selling the company, hopefully at a profit.

Whichever investment route you take (seed, venture, private equity, or all three), there is always plenty of money available for investment purposes for the right company. Next issue we will discuss how to prepare for it. The best of luck to you in 2012. ◆

Biography

John A. Bermingham is currently the Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc). He was the President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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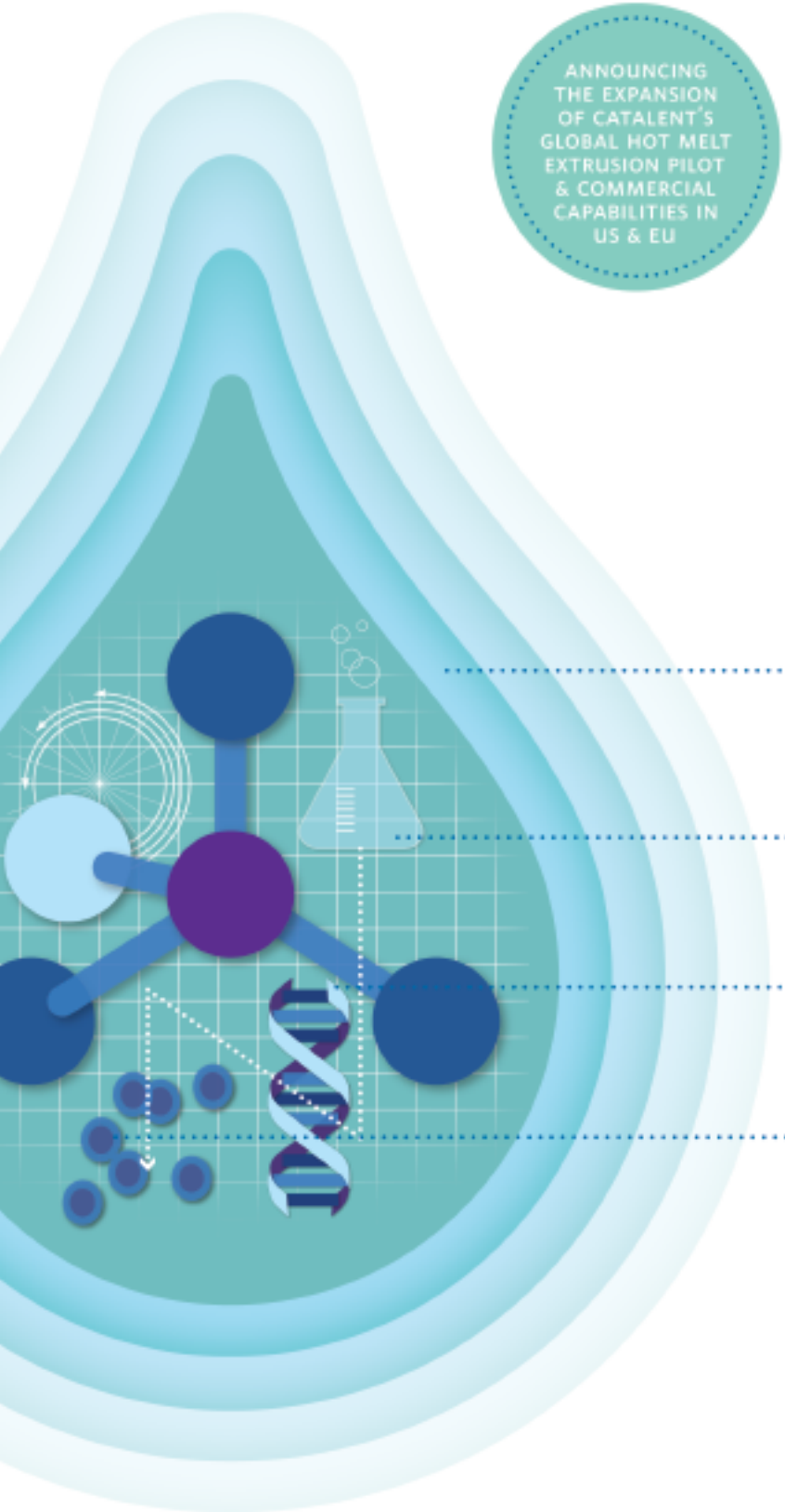

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