Drug Delivery Technology®

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Delivering Therapeutic siRNA

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

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THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

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Multiple Release Profiles
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Increased Profit Potential
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Multi-Phase System
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Faster Development
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Reduces unpleasant ingredient taste and odor commonly found with tablets and traditional capsules. And, liquids provide less irritation than traditional delivery methods.

Tamper Proof Sealing
Band sealing reduces tampering and provides a non-permeable barrier to retard oxidation and increase shelf-life.

Unique Appearance
This new delivery system stands apart from look-alike products that crowd retail shelves.

Compounds
Deliver Pharmaceutical, bio-pharmaceutical and nutraceuticals in a single dosage form.

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MicroDose Technologies


The MicroDose Dry Powder Inhaler (DPI)

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MicroDose Technologies is a specialty pharmaceutical company successfully pioneering the creation of next-generation products utilizing its proprietary drug delivery technologies. MicroDose's Dry Powder Inhaler (DPI) and PolyCap™ combination oral dose capsule system promise to dramatically improve efficacy and compliance. Our multidisciplinary team is dedicated to delivering these innovative products to help transform the lives of atients suffering from a wide range of debilitating diseases.

MicroDose's next-generation DPI is a state-of-the-art electronic inhaler providing superior delivery for both small and large molecules to the lungs.

Advantages

- Highly efficient piezo driven action
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The MicroDose PolyCap™ System

MicroDose's PolyCap™ System is a proprietary approach that enables the rapid development of FDC therapies in a single dose, but separated by a physical barrier. Utilizing the proven strengths of capsules and the advantages of a barrier system, it allows for more rapid development timelines and lower regulatory requirements. Applications are broad, from products targeting the same indication (polypharmacy) to combination products addressing the growing patient populations suffering from multiple ailments (co-morbidity), such as hypertension, hyperlipidemia, and type II diabetes.


The MicroDose PolyCap™

Advantages

- Potential for FDA exclusivity
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- Shorter time-to-market (potentially less than 2 years)
- Lower development costs
- Easier manufacture
- Provides a barrier to generic competition

With the PolyCap™ System, the MicroDose FDC approachsupplies an effective means to implement life-cycle management strategies, minimize technical and regulatory risk, and enable new product development at a fraction of the cost it takes to bring a traditional combination product to market.

MicroDose Technologies' Commitment

- Creating superior products utilizing its revolutionary drug delivery technologies
- Collaborating with top-tier pharmaceutical and biotechnological partners to develop innovative products.

Please contact us to see how the MicroDose portfolio of products can benefit you.

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Therapeutic siRNA

"Compared to the local siRNA deliveries that were used in many early siRNA clinical trials, systemic siRNA delivery faces more challenges and hurdles that have slowed down the expansion of siRNA therapeutics. With increasing efforts dedicated to the development of more efficient systemic siRNA delivery technologies, it is conceivable the key delivery hurdles could be overcome and the potential of RNAi-based therapeutics may be realized in a not too distant future."

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Our proprietary AcuForm™ delivery system retains orally administered medications in the stomach to create a "launching platform" for controlled drug release. By targeting drug delivery to the upper GI tract, we can help reduce the potential for certain side effects associated with many medications.

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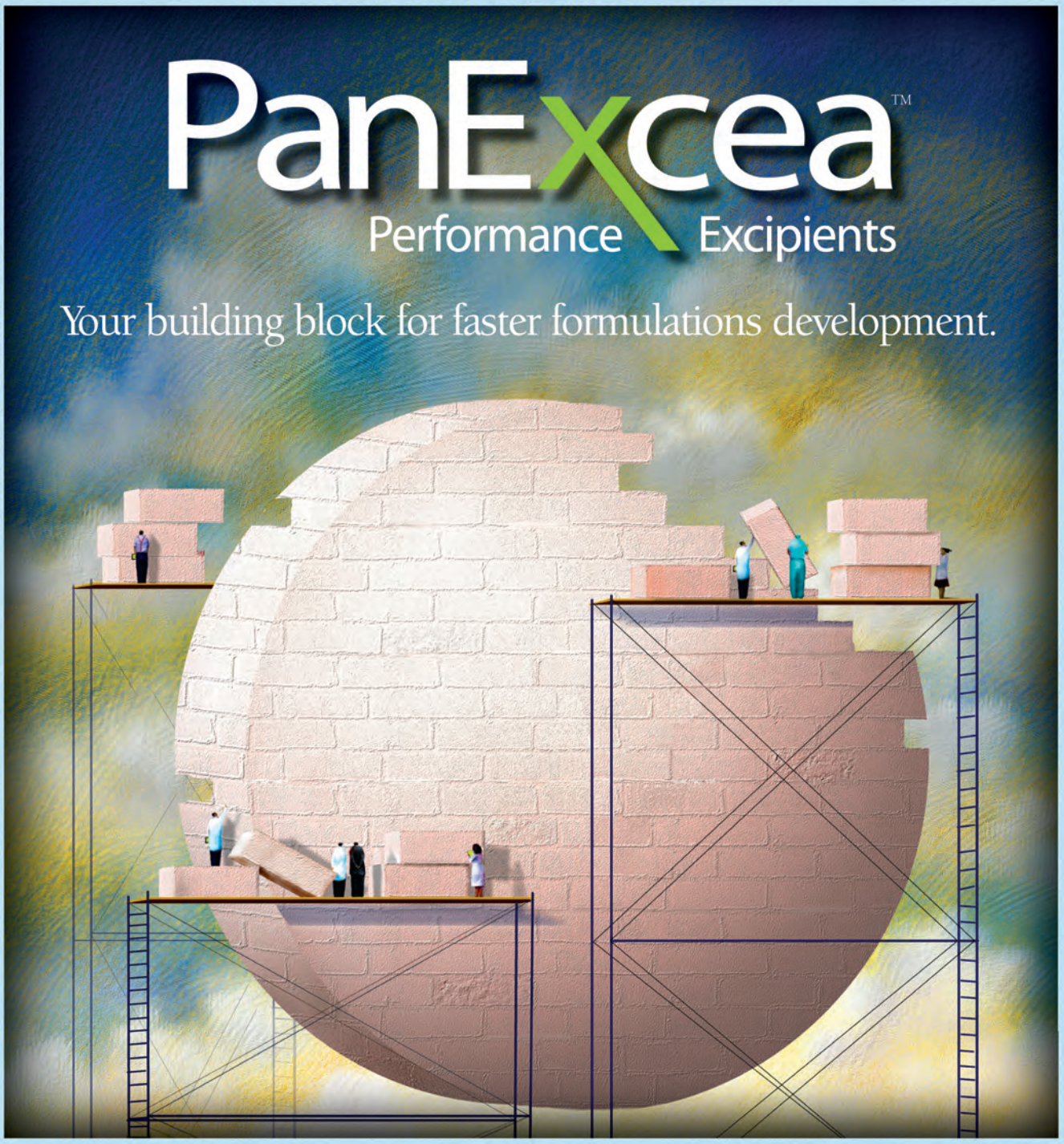

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MARKET NEWS AND TRENDS

PII Enters Strategic Collaboration With NexMed; Launches Drug Delivery Solutions Initiative

PII, (Pharmaceutics International, Inc.) and NexMed, Inc. recently announced they have signed a Memorandum of Understanding (MOU) for a strategic product development collaboration utilizing NexMed's NexACT drug delivery platform. Pursuant to the MOU, PII will promote the NexACT technology to its clients and may independently identify new product development opportunities for this collaboration with NexMed. PII will be responsible for the research and development of the new pharmaceutical products with technical guidance and oversight from NexMed, and will also assume responsibility for clinical trial material manufacturing and commercial manufacturing of the new products.

"We are very pleased to enter into this collaboration with PII," said Hem Pandya, NexMed's COO. "The strategic goal of this agreement is to broaden the promotion of the NexACT technology platform and permit us access to PII's research and development and commercial manufacturing infrastructure. We will also be able to continue with our current product development efforts at significantly reduced monthly overhead expenses."

"The collaboration between the companies will offer PII's customers opportunities for product development without having to move their compounds elsewhere," added Steve King, PII's Senior Vice President. "This technology fits well with PII's Drug Delivery Solutions initiative."

NexMed, Inc. is leveraging its proprietary NexACT drug delivery technology to develop innovative topical pharmaceutical products that address unmet medical needs. NexMed's novel, onychomycosis treatment, licensed to Novartis, is currently in pivotal Phase III trials in the US and Europe. In September 2007, NexMed filed a New Drug Application with the FDA for its alprostadil treatment for erectile dysfunction. NexMed's pipeline also includes a Phase II treatment for female sexual arousal disorder and an early stage treatment for psoriasis.

PII also announced the formal launch of a new business initiative, PII Drug Delivery Solutions. In response to demand from its clients for product development tools that meet the challenges of problematic new chemical entities (NCEs) and of product life cycle management (LCM), PII has put together a strategy and dedicated resources focused on drug delivery. This new initiative, named PII Drug Delivery Solutions, builds on the PII's proven track-record in formulation development and pharmaceutical manufacturing to help its clients bring new products to market with optimized clinical profiles and higher commercial value. Since its inception, PII has built considerable expertise in drug delivery, including conventional controlled-release formulation approaches, a portfolio of PII-developed technologies, and programs involving third-party platforms. Its alliance with Penwest Pharmaceuticals for TIMERx technology being an example.

The strategy for PII Drug Delivery Solutions is to provide dedicated business development, centers of technical excellence, proactive partnering, and integrated support from PII core resources. PII believes its exciting portfolio of in-house and partnered drug delivery technologies can be put to work to assist clients with their product development needs, be they early stage drug candidate optimization through to the revitalization of a marketed compound.

"Our dedicated business development team lead by Robin Mitchell and Susan Wiggins has extensive experience in drug delivery and contract services," said Mr. King. "We aim to proactively bring creative problem-solving solutions and product concepts to our clients. PII already has a very powerful portfolio of technology platforms at our disposal and intends to build on this during 2009. PII has quietly developed some impressive technologies of its own (nanoparticle formulations and MedCrystalForms' mixed phase co-crystals for enhanced drug bioavailability for example)."

"Through our partnerships with companies like Penwest, we can tackle a broad range of controlled-release challenges too," added Robin Mitchell, Senior Director Drug Delivery Solutions. "Susan Wiggins and I are very excited about the role we can play to strengthen our clients' business success in today's very competitive markets."

A privately held company, Pharmaceutics International, Inc. is a leading multinational contract formulation development, Clinical Trial Materials (CTM), and commercial manufacturing company with corporate headquarters in Hunt Valley, Maryland. Founded in 1994, PII can manufacture a wide range of dosage forms covering solid, semi-solid, and aseptic filling. This service is complemented by full analytical and regulatory support.

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MicroDose & Nexus6 Announce Collaboration to Evaluate Application of Remote Patient Compliance Monitoring Technology With MicroDose's Electronic DPI

MicroDose Technologies, Inc. and Nexus6 recently announced they have entered into a collaboration to investigate the application of Nexus6's SmartinhalerLive technology with MicroDose's next-generation electronic dry powder inhaler (DPI). Under the terms of the agreement, MicroDose will fund the development of prototypes based upon MicroDose's inhaler platform and incorporating Nexus6's SmartinhalerLive technology. MicroDose will receive an option for an exclusive license to the SmartinhalerLive platform for certain fields of use.

The aim of the investigation is to demonstrate the ability to wirelessly upload dosing and compliance information from the inhaler to a web-based server for data management and reporting. The SmartinhalerLive technology, providing global roaming wireless, is a natural extension of MicroDose's electronic inhaler features and will facilitate better communication between the physician, patient, and pharmaceutical company to improve all aspects of care.

The combined system would have benefits in both the clinical trials setting and with in-market products. By improving compliance through reminder features and through real-time tracking of compliance, patient safety, and clinical trial data management are improved. Improved control and monitoring of compliance can significantly reduce the number of patients enrolled per Phase II or Phase III clinical studies. In marketed products, the system represents a move to more personalized care, giving a better understanding of drug usage and patient response to therapy, and improved compliance and adherence.

"The combination of Nexus6 Technology and MicroDose's dry powder inhaler will ensure a continuous flow of real time clinical information, which will benefit physicians, patients, and pharmaceutical companies," said Mr. Michael J. Martin, VP of Business Development and Licensing of MicroDose.

"This partnership between Nexus6 and MicroDose will enable the drug delivery marketplace to access leading edge data collection and transmission capabilities, thereby increasing pharmaceutical adherence, improving patient well-being, and reducing overall health care costs," added David Evans, CEO of Nexus6.

The MicroDose DPI is among a number of key proprietary drug delivery platforms developed by MicroDose. By employing piezo electronics, the MicroDose DPI has the potential to deliver enhanced performance versus other inhalers, for efficient and reproducible delivery independent of patient coordination, inhalation rate, and posture. Microdose believes that the flexibility of the inhaler makes it a true platform technology, able to support a broad pipeline of products across the spectrum of patient populations and therapeutic categories.

MicroDose Technologies, Inc., based in Monmouth Junction, New Jersey, is a leading privately held drug delivery and specialty pharmaceuticals company, developing advanced pulmonary, fixed-dose-combination oral dosage, and other technologies and products for the pharmaceutical and biotechnology industries.

MicroDose's partnered programs include multi-product development and licensing agreements with Merck and Co. and Novartis, the development of an inhaled insulin product through MicroDose's QDose joint venture, and an inhaler for the systemic delivery of a nerve agent antidote for the US Department of Defense, in collaboration with the University of Pittsburgh. MicroDose is also conducting internal development programs for products employing its inhaler technology, and for combination oral dosage products employing its PolyCap technology in the areas of diabetes, hypertension, and hyperlipidemia.

Nexus6 Limited is a privately held New Zealand-based developer and manufacturer of solutions to increase patient adherence to respiratory medications, leading to improved disease management and reduced healthcare costs. Nexus6 SmartinhalerLive devices monitor and report patients' medication usage to their healthcare partners and are used in pharmaceutical clinical trials and respiratory disease management applications for chronic obstructive pulmonary disease, asthma, and cystic fibrosis. SmartinhalerLive uses wireless communications technology to provide real time data collection and reporting from drug delivery devices.

Wyeth Pharmaceuticals & Santaris Pharma A/S Announce Strategic Alliance to Develop RNA-Based Medicines

Wyeth Pharmaceuticals, a division of Wyeth, and Santaris Pharma recently announced they have entered into a worldwide strategic alliance to discover, develop, and commercialize new medicines based on Santaris Pharma's proprietary Locked Nucleic Acid (LNA) drug platform, which allows specific targeting and regulation of microRNAs (miRNAs) and messenger RNAs (mRNAs) as a means to affect gene expression mediated by the targeted RNAs.

Under the terms of the agreement, Santaris Pharma will receive an up-front payment of $7 million in cash, and Wyeth will make a $10-million equity investment in Santaris Pharma. Santaris Pharma may receive further milestone payments of up to $83 million for each of 10 potential targets. In addition, Santaris Pharma would receive royalties on the worldwide sales of all products arising from the alliance. The term of the research portion of the collaboration is 3 years. Wyeth has the right to extend the research portion up to 2 additional years.

Wyeth will select the RNA targets against which Santaris Pharma will use their proprietary LNA drug platform to generate unique drug candidates. Wyeth will be responsible for the development and commercialization of products arising from the alliance.

"With this alliance, Wyeth explores a fourth platform technology targeting RNAs, which complements our expertise in small molecules, vaccines, and protein-based therapeutics," says Mikael Dolsten, President, Wyeth Research. "This will increase our ability to develop and bring to market innovative, high-value medicines that have the potential to address significant unmet needs in critical therapeutic areas."

"We are delighted to welcome Wyeth as a new major partner," says Soren Tulstrup, President and CEO of Santaris Pharma. "This strategic alliance further consolidates Santaris Pharma's leading position in the rapidly evolving RNA-based therapeutic field. The scope of this collaboration demonstrates the utility of Santaris Pharma's proprietary LNA Drug Platform for developing new therapies targeting RNAs."

There are two major classes of RNA targets for this collaboration: messengerRNAs and microRNAs. miRNAs are recognized as important elements in regulation of gene expression in both normal and diseased cells, whereas mRNAs are translated into the proteins that determine all aspects of cell identity and behavior. Santaris Pharma's proprietary technology allows for the discovery of molecules that specifically and potently inhibit the function of either of these classes of RNA.

The Locked Nucleic Acid-based technology developed by Santaris Pharma creates synthetic chemical versions (LNAs) of the normal nucleic acid building blocks of RNAs. These LNAs improve the drug-like qualities of resulting therapeutics, called oligonucleotides, by increasing resistance to metabolism, increasing half-life, and improving tissue uptake. The LNA-based therapeutics also demonstrate improved binding affinity to their target RNA, which increases potency many-fold over other nucleotide therapeutics.

Santaris Pharma is a privately held biopharmaceutical company with exclusive pharmaceutical rights to the LNA Drug Platform used to develop new classes of RNA medicines targeting mRNAs and miRNAs associated with disease. Santaris Pharma's drug discovery engine provides fast and efficient generation of lead LNA drug candidates. The company's own research and development activities focus on microRNAs, infectious diseases, and metabolic disorders. Santaris Pharma has repeatedly validated the LNA Drug Platform through partnerships with major pharmaceutical companies. Santaris Pharma was founded in 2003, is based in Denmark, and the company and its partners currently have three compounds in clinical development and two more in late preclinical development. Since 2006, the company has raised more than 60 million Euros through private financing and corporate partnerships.

Merrion Announces License Agreement With Novo Nordisk to Develop Oral Formulation of GLP-1 Receptor Agonist(s)

Merrion Pharmaceuticals and Novo Nordisk A/S, a world leader in diabetes, have entered into a development and license agreement to develop and commercialize oral formulations of a Novo Nordisk proprietary GLP-1 receptor agonist using Merrion's proprietary GIPET technology. This is the second license agreement between the two companies concerning Merrion's GIPET technology. The first agreement for the development of oral insulin analogues was signed in November 2008.

Under this new license agreement, Merrion will receive up to $58 million for the first product developed under the agreement to reach the market based on achievement of certain development, regulatory, and sales milestones as well as royalties on sales. Novo Nordisk is responsible and will pay for the development and commercialization of the product candidates. Merrion is responsible for the development and manufacture of the initial clinical batches, with the work overseen by a joint development committee. Novo Nordisk and Merrion have collaborated since 2007 to test the utility of Merrion's GIPET technology in preclinical models.

The agreement also provides Novo Nordisk with the ability to develop additional oral formulations of Novo Nordisk GLP-1 receptor agonist compounds using Merrion's proprietary absorption enhancing GIPET technology. Merrion will be due additional milestone payments for any additional products developed under the agreement.

"This second partnership with Novo Nordisk builds on the first oral insulin analogue agreement signed in November 2008," said John Lynch, Chief Executive Officer of Merrion. "We believe this development further demonstrates the potential for long-term partnership between our two companies and also enhances our capacity to develop our other products and technologies."

"We are happy to have signed this partnership agreement with Merrion to use the GIPET technology in developing potential oral formulations of Novo Nordisk's proprietary GLP-1 receptor agonists. This partnership is another step in Novo Nordisk's research efforts in developing new treatments for people with diabetes," added Peter Kurtzhals, Senior Vice President, Novo Nordisk's Diabetes Research Unit.

Micromet Enters Agreement for Solid Tumor BiTE Antibody With Bayer Schering Pharma

Micromet, Inc., a biopharmaceutical company developing novel, proprietary antibodies for the treatment of cancer, inflammation, and autoimmune diseases, recently announced the signing of an option, collaboration, and license agreement with Bayer Schering Pharma AG, Germany, under which Bayer Schering Pharma has the exclusive option to obtain a license to one of Micromet's preclinical BiTE antibodies against an undisclosed oncology target.

Under the terms of the agreement, Bayer Schering Pharma will pay Micromet a Euro 4.5 million fee (approx. $6 million) to secure a 1-year option on a specific BiTE antibody. Bayer Schering Pharma may exercise this option prior to January 5, 2010, through the additional payment of an option exercise fee. The exercise of the option would trigger a formal collaboration between Micromet and Bayer Schering Pharma on the development of the BiTE antibody through the completion of Phase I clinical trials, at which point Bayer Schering Pharma would assume full control of the further development and commercialization of the BiTE antibody.

Micromet would be eligible for an option exercise fee and milestone payments of up to Euro 290 million (approx. $390 million) in total and up to double-digit royalties based on tiered net sales of the product. In addition, Micromet would be reimbursed for its R&D expenses incurred in connection with the development of the BiTE antibody in the collaboration with Bayer Schering Pharma.

"We are very pleased with Bayer Schering Pharma's interest in this preclinical BiTE antibody program and their financial commitment to secure exclusive access for the next 12 months. This deal represents further validation of our BiTE antibody technology by a major oncology company," said Christian Itin, Micromet's Chief Executive Officer.

"Oncology is one of our core growth areas, and biologicals are a key focus of our strategy. We are excited about Micromet's BiTE antibody technology and believe BiTE antibodies represent a novel and promising approach to cancer therapy," said Prof. Andreas Busch, Member of the Board of Management of Bayer Schering Pharma AG responsible for Global Drug Discovery.

BiTE antibodies are designed to direct the body's cytotoxic, or cell-destroying, T cells against tumor cells, and represent a new therapeutic approach to cancer therapy. Typically antibodies cannot engage T cells because T cells lack the appropriate receptors for binding antibodies. Previous attempts have shown the potential of T cells to treat cancer, but the therapeutic approaches tested to date have been hampered by cancer cells' ability to escape recognition by T cells. The use of BiTE antibodies that are specifically designed to engage T cells for attacking cancer cells may provide a more effective anti-tumor approach than conventional monoclonal antibodies.

Micromet, Inc. is a biopharmaceutical company with offices in Bethesda, MD, and Munich, Germany. The company is focused on developing novel, proprietary antibodies for the treatment of cancer, inflammation, and autoimmune diseases. The company's novel antibody technology is based on its proprietary BiTE antibody platform, representing a new class of antibodies that specifically activate T cells from the patient's own immune system to eliminate cancer cells or other disease related cells. Four of the company's antibodies are currently in clinical trials, with the remainder of its product pipeline in preclinical development.

New Interferon Formulations Promise to Eliminate Injections in Multiple Sclerosis Treatment

Nerveda Inc. and Aegis Therapeutics LLC recently announced preclinical results from their joint collaboration aimed at developing non-injectable formulations of the beta-interferons. The beta interferons, beta-1a (tradename Rebif), and beta 1b (tradenames Betaseron and Betaferon) are closely related injectable protein drugs in the interferon family that are used to treat both the relapsing-remitting and secondary-progressive forms of multiple sclerosis (MS). The beta interferons are currently administered by subcutaneous injection and have been proven clinically to slow the advance of multiple sclerosis and reduce the frequency of attacks. Current worldwide combined annual sales of Rebif, Betaseron and Betaferon are approximately $4 Billion.

Because proteins are large and fragile molecules, they cannot be administered orally and are typically administered by injection. They are often subject to instability due to aggregation of the protein molecules - particularly upon storage and handling at non-refrigerated temperatures. The resulting protein aggregates are more poorly absorbed into the bloodstream upon injection due to their increased size, and induce development of circulating antibodies to interferon in patients that reduce the effectiveness of the drug over time.

Leading medical scientists at Johns Hopkins University, experts in the treatment of neurological diseases, in collaboration with Nerveda and Aegis have applied Aegis' Intravail transmucosal absorption enhancement, and ProTek protein stabilization technologies to address these problems and have demonstrated for the first time that the beta interferons can be administered intranasally to prevent nerve damage in preclinical animal models of MS. In addition, the new formulations were shown to reduce or eliminate the immunogenicity of Betaseron and Rebif, administered either by injection or intranasally, while substantially increasing stability in a stress test involving constant agitation at elevated temperatures for extended periods of time.

"Since interferons will continue to be the foundation of MS therapy, it is critical that non-invasive delivery options for patients be developed," said Dr. Edward Maggio, CEO of Aegis Therapeutics, who participated in the research. "The reduction in immunogenicity and the increase in stability also address a significant unmet need of the currently available beta-interferon therapies."

Nerveda plans to begin testing the new formulation in clinical trials in early 2009 in collaboration with clinicians and scientists at John Hopkins University Medical Center and other sites.

Nerveda is a privately funded specialty pharmaceutical and diagnostic company focused on improving the quality of life for patients suffering from neurodegenerative diseases and their caregivers. Nerveda supports the clinical development of products licensed from Johns Hopkins University, including neuroprotective compounds and stem cell therapeutics that show promise in treating auto-immune disorders.

Aegis Therapeutics is a drug delivery technology company commercializing its patented or proprietary drug delivery and drug formulation technologies through product-specific licenses. Its patented Intravail drug delivery technology enables the non-invasive delivery of a broad range of protein, peptide, and non-peptide macromolecular therapeutics that can currently only be administered by injection. Aegis' Intravail absorption enhancement agents provide exceptionally high and unmatched bioavailability performance, comparable in efficiency to subcutaneous injection, via the intranasal administration route.

A Spring-Powered Device for Subcutaneous, Intramuscular & Intradermal Injections Using an Auto-Disable Syringe

By: Maria J. Gutierrez, MD; Richard R. Stout, MD; Dan Williamson; Maria Bermudez, MD; William Gerson, DO; McKenzie B; Turner P; Innocent N; Rivera D; Castaneda R; Quiroz R; Correa O; Fumero D; Aversa D; Hermitt C; Baker A; Leano S; Richard K; and Carabali F

The Bioject research and development team has developed a new spring-powered injector known as the Zetajet™, which is based on the design of the Biojector® 2000 (B2000) for performance but uses a spring for its power source. The pressure profile of the Zetajet has been documented by in vitro testing to be virtually the same as that of the B2000, which has given millions of injections. The B2000 is a needle-free jet injection device that provides up-to-date jet injection technology and eliminates or reduces complications associated with others previous devices (eg, cross-contamination from patient to patient, lacerations at the injection site, difficult device cleaning, cumbersome tanks, etc).[1-12] The intended use of this device is to provide a low-cost, needle-free injection system that delivers SC, IM, or ID injections via a simple change of the syringe. There is no need to adjust the device or technique for different injection types.

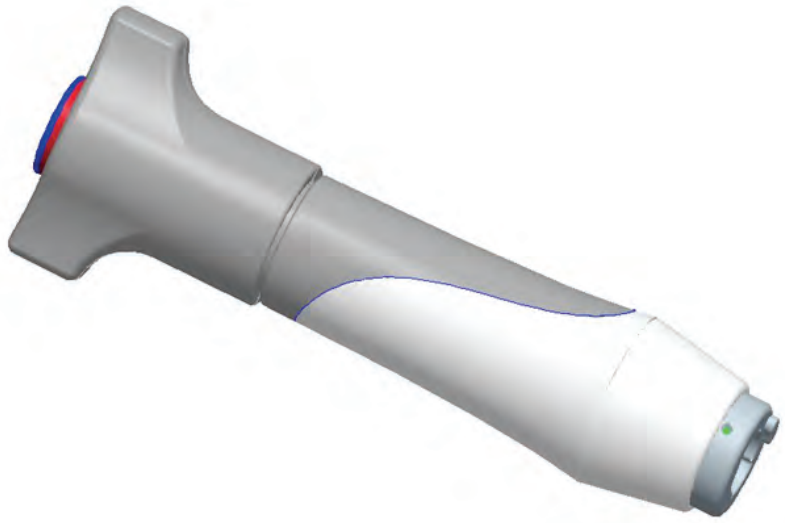
This new needle-free system offers an additional feature - an auto-disable syringe that prevents re-use of the syringe. The syringe may be used to perform reconstitution with manual movement of the syringe plunger; however, once the injection is given, the syringe is disabled with the plunger tip remaining in the syringe to prevent any possible re-use.

DEVICE DESCRIPTION

The Zetajet device is configured to administer between 0.05- and 0.5-ml SC and IM injections and 0.1-ml ID injections. The device is complete as packaged and requires no additional parts or modifications for function.

A great deal of attention was paid to making the device easy to use. Winding effort has been a major focus. Engineered plastic materials have been used to reduce friction. Ball

FIGURE 1



The Zetajet™ in one of many ergonomic designs

FIGURE 2

Syringe with volume graduations on the body for easier viewing while filling.

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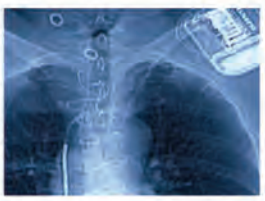


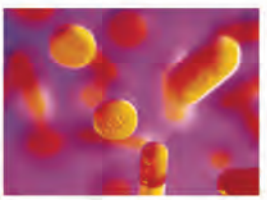

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bearings are used to keep friction low and extend the life of the device. The extra attention to design and the use of robust materials reduce noise and make the device solid and comfortable to handle.

The device is designed to be a platform technology to meet the requirements of multiple users. The interior core of the device is built within a stainless steel design using high-quality materials. Custom molded exterior components can be added to achieve specific design attributes needed for different clinical applications. For instance, devices built for geriatric or arthritic users can have features added to the exterior of the core device that make the device even easier to handle, reduce winding effort, easier to grasp, and require less activation force without actually changing the core device.

The spring is custom designed to have the power required to achieve IM injection depth together with long service life. The spring is compressed by winding the device, which has special proprietary features to reduce the energy needed to perform the winding maneuver. Shallow depths are achievable by using the appropriate nozzle orifice size based on Bioject's syringe expertise and capability.

The Syringe/Plunger Assembly has a unique auto-disable feature (patent pending) that prevents re-use of the syringe. The plunger is pre-assembled into the syringe and can be used for reconstitution and other pre-injection tasks. Once the device is activated, the mid-section of the plunger shears apart to prevent re-use of the plunger. The plunger tip remains in the end of the syringe, rendering the syringe inoperable. Figure 4 shows a device being prepared for use and giving an injection. The system is easy to use with three simple steps as shown.

METHODS

The Zetajet study was a three treatment, single blind, Phase I study, which was conducted at a single clinical center. After meeting all eligibility criteria, a total of 60 healthy subjects equally divided between males and females whose ages ranged from 18 to 55 were enrolled in this study comparing ID, SC, and IM injections of Zetajet. All subjects were given three injections: ID injection of 0.1-ml sterile 0.9% sodium chloride in the deltoid region of one arm, a 0.5-ml SC injection in the triceps region of the same arm, and a 0.5-ml IM injection in the deltoid region of the other arm with the order of the three injection methods done per the randomization schedule. After each injection, a subjective evaluation was made related to the injection site, and questions were asked regarding the patients' perceptions of the injection. After 5 minutes, the next injection was given.

This study consisted of an Injection Phase (Day 1) and Follow-up (Day 2). Immediately after each injection, the injection sites were evaluated by a trained healthcare professional (who had not given the injections) for surface wetness using a three-point scale, with 0 corresponding to no visible moisture, 1 corresponding to

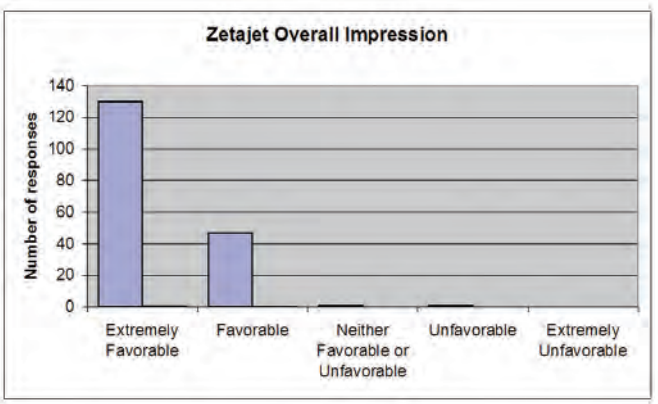
FIGURE 3

Samples of just some of the potential ergonomic designs that can be applied to the Zetajet™ for different clinical needs.

FIGURE 4

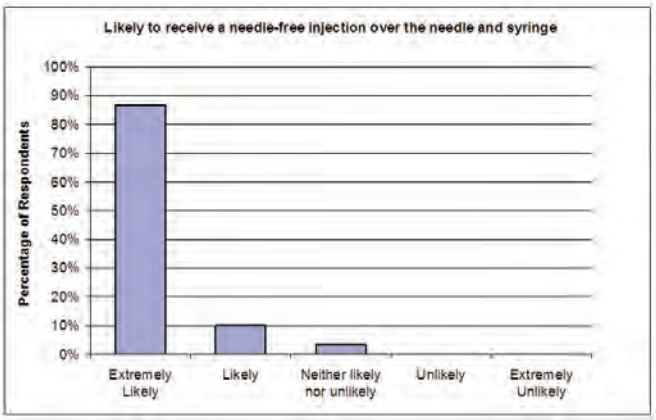
Wind the device - Fill the syringe - Give the injection.

FIGURE 5



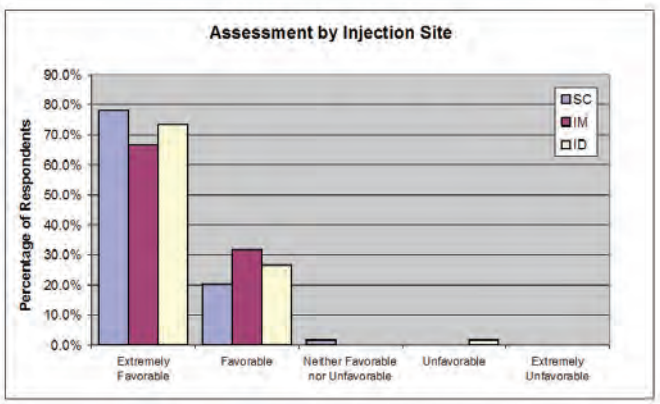
Overall impression 30 minutes after all injections were completed.

FIGURE 6



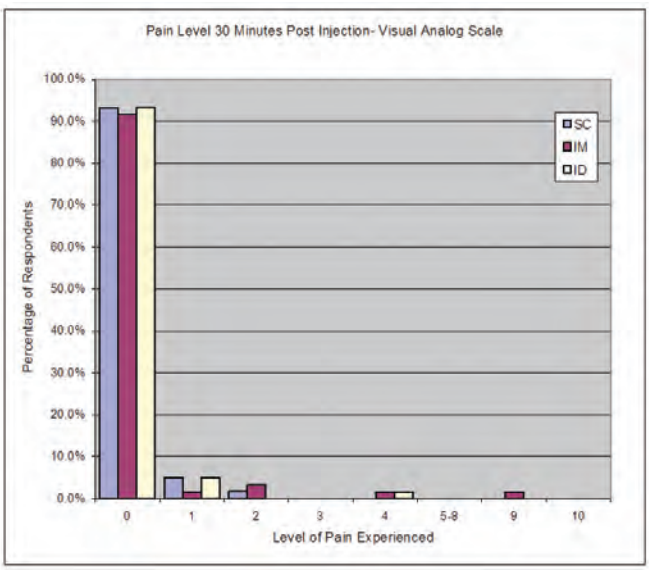
Patient preference, 24-hour assessment post injections.

FIGURE 7



Subject response for each type of injection 30 minutes post injection.

FIGURE 8



30-minute assessment post injections using the Visual Analog Scale.

visible moisture without flow, and 2 corresponding to moisture with visible flow. Within 5 minutes after the injections, the degree of pain with each injection was elicited from the subjects via a Visual Analog Scale (VAS) as well as a Verbal Scale. The injection sites were also evaluated immediately following for local reactions (bruising, redness, and wheal formation). The follow-up was completed 24 hours after the initial injection and consisted of injection site evaluations.

The injection sites were evaluated again 30 minutes after the third injection for local reactions (bruising, redness, and wheal formation). At this 30-minute post injection evaluation, the degree of pain for each of the injections was again elicited from the subjects via a VAS as well as a Verbal Scale. Subjects also answered questions on their opinions regarding needle-free injections. Subjects returned to the clinical site 24 hours after the injections, where healthcare personnel evaluated the injection site for local site reactions.

Patient Preference

A total of 179 injections were administered. Because of an unrelated vasovagal syncope by one subject, a response for the IM injection was not elicited. Immediately following the injections, 177 of 179 total responses reported an Extremely Favorable (n = 135) or Favorable (n = 42) impression of Zetajet injections with only one response each for Neither Favorable or Unfavorable or Unfavorable (Figure 5). There were no Extremely Unfavorable responses. The one report of Unfavorable occurred with the IM injection on a female subject who reported Extremely Favorable for ID and Favorable for her SC injection. There was an overwhelming positive response to the Zetajet injections. Following the injection on Day 1, 97% of the respondents stated they were Extremely Likely (87%) or Likely (10%) to request to receive a needle-free injection over the needle and syringe (Figure 6).

Regarding various types of injections (IM, SC, and ID), subjects had a positive impression of Zetajet. While subjects slightly preferred the SC injection, which received the highest percentage of Extremely Favorable assessments, both the IM and ID injections were highly rated with 100% and 98.3% of total assessments as Extremely Favorable or Favorable, respectively (Figure 7).

Pain Assessment

Data presented in Figure 8 indicate that by 30 minutes post injection, using the VAS, all three Zetajet injection methods reported to be significantly free of pain with more than 98% of responses reporting 2 or less on the VAS. Only one report of VAS pain > 4 was reported at 30 minutes post injection, and this was

with the IM injection in one female subject who reported a VAS pain score of 9.

At 30 minutes post injections using the verbal response, subjects continued to report a positive experience with the pain level of the Zetajet Injection System as seen in Figure 9. At 30 minutes post injection, 100% of ID injections received verbal pain scores of 2 or less, with 97% of SC injections receiving pain scores of 2 or less, and 93% of IM injections receiving pain scores of 2 or less. A verbal pain score of 2 was compared to a mild sting with a score of 3 as a bee sting. Only the IM injection had a significant report of pain at the 30-minute post injection assessment, with one subject reporting severe pain. When comparing the pain data from a previously published study using a needle and syringe for SC injections in Figure 10, it is apparent that the pain scores are much lower with the Zetajet SC injections.[12] There was as much as a 60% reduction in number of patients reporting no pain with needle-free versus needle and syringe at the 30-minute post-injection assessment.

INJECTION ASSESSMENT POST INJECTIONS

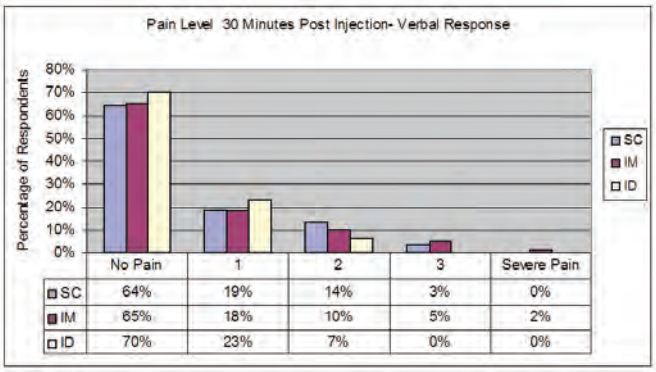
Intradermal injections were very well received with the lowest cumulative pain scores. The ID injections were also very consistent with 100% wheal formation. More moisture was seen with the intradermal injection than with the other types of injections, which is to be expected, and has been seen previously. This is the result of the use of the spacer, which sometimes produces a very small drop at the injection site after the injection. Visible moisture without flow was seen at 23% of the ID injection sites. The driest site was the IM injection site with a dry injection site reported 97% of the time (Figure 11).

DISCUSSION

The present investigation was undertaken to subjectively and objectively compare the SC, ID, and IM injection capability of Zetajet, Bioject's new, advanced spring-powered injector system. The study reconfirmed the capability of a spring-powered device to successfully provide three types of injection (SC, ID, IM) that was originally proven using the Vitavax, a precursor device that led to the development of the Zetajet.[13]

The device was well received by the clinical investigators and clinicians who used the device during the study. Comments received throughout the trial regarding the ease of winding,

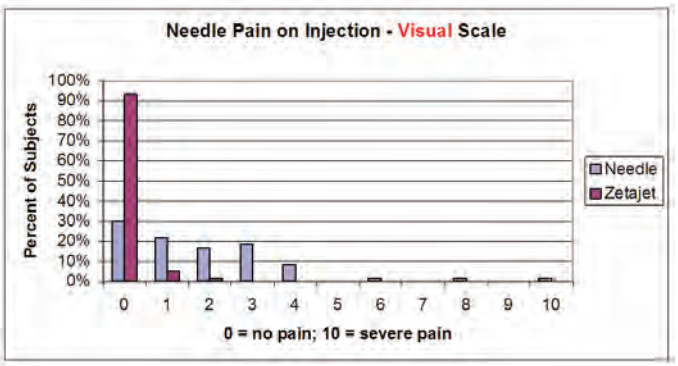
FIGURE 9



	No Pain	1	2	3	Severe Pain
SC	64%	19%	14%	3%	0%
IM	65%	18%	10%	5%	2%
ID	70%	23%	7%	0%	0%

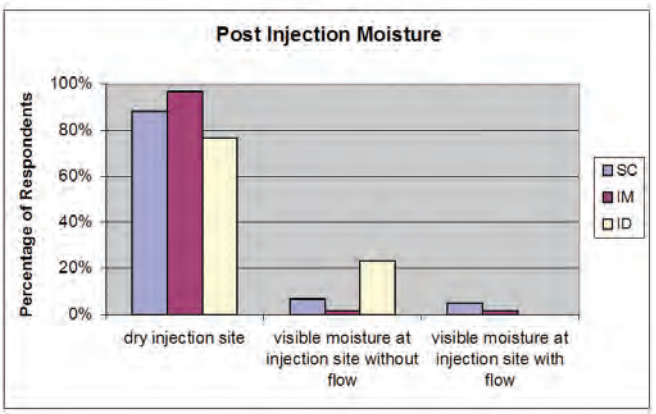
30-minute assessment post injections using the Verbal Pain Response.

FIGURE 10



Pain scores from a previous subcutaneous needle and syringe pain assessment study as compared to subcutaneous Zetajet pain assessment scores.

FIGURE 11



Post injection moisture.

loading, and administering the injection by the clinical investigators was very positive.

On the assessments by injection type, all three injection methods with Zetajet received very positive ratings with more than 96% overall receiving Extremely Favorable and Favorable ratings. Assessment of pain using a VAS and a Verbal Scale are considered to be more objective than responses to questions posed by a coordinator. Using the VAS at 5 minutes post injection, 43% of the ID, 37% of the SC, and 22% of the IM injections were assessed by the subjects to be free of pain with another significant percentage of subjects rating the pain using a VAS as less than 3 across all injection methods. Similar results were seen when reviewing the responses to the Verbal Scale, 47% felt no pain when given the ID injection, compared with 34% with the SC and 22% with the IM injection.

There was very little to no moisture reported at the injection sites for the SC and IM injections and 23% of ID injection sites showing visible moisture at injection site without flow.

CONCLUSION

Using a self-powered spring that has an auto-disable syringe makes this device very accessible for worldwide usage for mass immunization programs, where it eliminates the spread of disease from accidental needle-stick injuries and eliminates any possible re-use of a syringe or needle. The auto-disable syringe prevents possible contamination of syringes and vials. The multitudes of ergonomic options offer ideal flexibility for self-injection therapies. The durable nature of the device and reduced winding effort also gives the caregiver/home user a positive experience using the device. In conclusion, the results of this clinical trial indicate that the Zetajet needle-free injection system is preferred compared to a traditional needle and syringe system. It also demonstrated the subjective injection effectiveness of the Zetajet jet injection system for SC, ID, and IM injections. With these unique advances in delivery technology, the Zetajet is anticipated to provide the optimal injection therapy system for both developed and developing countries to provide a safer and more effective method for delivering their parenteral injectables.

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BIOGRAPHIES

Dr. Maria J. Gutierrez is the Principal Investigator of Comprehensive Phase One, a Division of Comprehensive NeuroScience, Inc. Born in Cuba, Dr. Gutierrez came to the US in 1979. She studied medicine in Cuba and in the Dominican Republic and completed her residency in NEOUCOM at Canton, Ohio. Dr. Gutierrez completed a fellowship in Rheumatology at the University of Florida in Gainesville and is board certified in Internal Medicine and Rheumatology. Since 1999, she has served as Principal Investigator of Comprehensive Phase One, a research unit specializing in Phase I and early Phase II clinical trials. She became a Certified Physician Investigator in 2006.

Dr. Richard Stout joined Bioject in April 1994 as Director of Clinical and Regulatory Affairs. He was promoted to Vice President of Clinical Affairs in December 1994 and to Executive Vice President and Chief Medical Officer in March 2007. In March 2007, Dr. Stout became a member of the Executive Committee. From 1992 to 1993, he was the Director of Clinical and Regulatory Affairs at EndoVascular Instruments, Inc., a developer of surgical devices and methods for endarterectomy and intraluminal graft placement. Dr. Stout acted as the Manager of Tachycardia Clinical Studies at Telectronics Pacing Systems, an international medical device company involved in manufacturing and distributing cardiac pacemakers and implantable defibrillators, from 1990 to 1992. From 1987 to 1989, Dr. Stout was Director of Medical Programs at Biotronik Inc., also a manufacturer and distributor of implantable cardiac pacemakers.

THIN FILM TECHNOLOGY

Orally Dissolving Film Strips (ODFS): The Final Evolution of Orally Dissolving Dosage Forms

By: Madhu Hariharan, PhD; B. Arlie Bogue, PhD

INTRODUCTION

In recent years, an entirely new class of pharmaceutical dosage form commonly called film strips or what will hereinafter be referred to as Orally Dissolving Film Strips (ODFS) has begun to appear in the OTC market space and has elicited the interest of consumers and healthcare professionals. Product development scientists and decision-makers within the pharmaceutical industry are working to expand the applicability of the technology and bring the obvious benefits of these novel products to the prescription drug marketplace.[1,2]

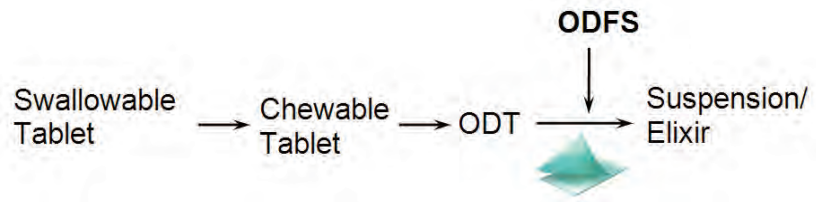
ODFS are postage stamp-sized rectangular strips of thin polymeric film formulated to disintegrate practically instantaneously when placed on the tongue. The term "thin film" is a broad term because these dosage forms also have applications for other routes of administration simply by modifying disintegration characteristics, mucoadhesion, and residence times at the site of use. This discussion will focus mainly on films for oral delivery of drug to the gastrointestinal (GI) tract, which is currently the most commonly available product class. In addition to ODFS, the other prospective manifestations of this dosage form will be addressed.

DEFINITION, HISTORY & ATTRIBUTES OF ODFS

Definition

It is not feasible for a single definition to encompass all types of films due to the widely different characteristics, routes of administration, and uses of these versatile dosage forms. However, for the instant purpose, the following simple

FIGURE 1



Evolution of Oral Dosage Forms

FIGURE 2

Preparation of Coating Dispersion

practical definition for ODFS is proposed: A thin, flexible, non-friable polymeric film strip containing one or more dispersed APIs, which is intended to be placed on the tongue for rapid disintegration/dissolution in the saliva prior to swallowing for delivery into the GI tract.

History

When ODTs were first introduced in the pharmaceutical marketplace, public acceptance came slowly because consumers had to be educated on the correct method of using the product. Consumers were specifically instructed not to swallow, chew, or co-administer with water, but to break up the tablet by gentle manipulation in the oral cavity. In contrast, ODFS were originally introduced into the marketplace as popular breath- freshening strips. The novelty of the product, the prominent promotional campaigns, and the intuitiveness of the concept (the product couldn't be swallowed like a tablet even if one tried) were largely responsible for its rapid uptake in the marketplace. Consumer familiarity with the concept meant that no re-education was necessary when OTC pharmaceuticals were first offered in this format. A consequence of the original success of breath-freshening strip products in the US market was the frenzied introduction of a slew of unregulated vitamin, mineral, and supplement (VMS) products in the ODFS format. Practically any company with expertise in polymeric web casting and handling entered the business of producing and marketing VMS thin film products of varying and questionable quality. It was almost 5 years after the first breath-freshening strips arrived that OTC monograph pharmaceutical ODFS products were introduced. A list of several ODFS products available in the US market place is shown in Table 1. Only a handful of companies have the technical and compliance infrastructure for producing strips in a pharmaceutical cGMP environment with the requisite level of aesthetic and physicochemical quality control. Furthermore, only very few companies have been able to produce commercial-scale ODFS containing bitter medications because the technology for manufacturing these films is complex and proprietary.

Advantages & Attributes

There are many distinct advantages and attributes of the film strip that make it unique compared to other dosage forms, including the following:

1. The polymeric films are very thin (typically 50 to 150 microns), which ensures rapid disintegration/dissolution due to the larger surface area available for wetting and eventual dissolution. It is practically impossible for a film strip to be intentionally swallowed intact because the quick wetting of the film generally causes adhesion to the tongue for a few seconds until dissolved and ingested along with the saliva to enter the

TABLE 1

Product/Brand Name	Drug Substance/Doses	Marketed By	Package Configuration
Theraflu Thin Strips	Diphenhydramine HCl 25 mg	Novartis Consumer Health	Foil-Foil CR Pouch
Theraflu Thin Strips	Dextromethorphan HBr 15 mg	Novartis Consumer Health	Foil-Foil CR Pouch
Triaminic Thin Strips	Diphenhydramine HCl 12.5 mg	Novartis Consumer Health	Foil-Foil CR Pouch
Triaminic Thin Strips	Dextromethorphan HBr 5.5 mg	Novartis Consumer Health	Foil-Foil CR Pouch
Triaminic Thin Strips	Phenylephrine HCl 2.5 mg	Novartis Consumer Health	Foil-Foil CR Pouch
Triaminic Thin Strips	Dextromethorphan HBr/ Phenylephrine HCl 5 mg/2.5 mg	Novartis Consumer Health	Foil-Foil CR Pouch
Triaminic Thin Strips	Diphenhydramine HCl/ Phenylephrine HCl 12.5 mg/5 mg	Novartis Consumer Health	Foil-Foil CR Pouch
Gas-X Thin Strips	Simethicone 62.5 mg	Novartis Consumer Health	Foil-Foil Peelable Non-CR Pouch
Chloraseptic Sore Throat Relief Strips*	Benzocaine 3 mg/2 mg	Prestige Brands	Cassette
Benadryl Quick Dissolve Strips	Diphenhydramine HCl 25 mg/12.5 mg	Pfizer Consumer Health	Foil-Foil CR Pouch
Sudafed PE Quick Dissolve Strips	Phenylephrine HCl 10 mg	Pfizer Consumer Health	Foil-Foil CR Pouch
Store Brand Antihistamine Medicated Strips*	Diphenhydramine Citrate 19 mg	Leiner Healthcare (Meijer, CVS, Longs, Duane Reade, etc)	Foil-Foil CR Pouch
Store Brand Cough Suppressant Medicated Strips*	Dextromethorphan HBr 7.5 mg/15mg	Leiner Healthcare (Meijer, CVS, Longs, Duane Reade, etc)	Foil-Foil CR Pouch
Pedia-Lax Quick Dissolve Strips*	Sennosides A&B 8.6/mg	CB Fleet, Inc	Foil-Foil CR Pouch

* Developed and manufactured by MonoSolRx LLC

Examples of Currently Marketed ODFS Products

gastrointestinal tract. The speed of disintegration/dissolution of the film can be modulated for applications, such as buccal or sublingual delivery for systemic and local effects, as well as for other routes of administration, such as ocular, vaginal, and even topical delivery.

2. The films are flexible and can be bent or folded. This prevents inadvertent breakage of the film and distinguishes films from tablets (especially ODTs), which are friable and can easily break during transportation or handling by the consumer. Furthermore, unlike some ODTs, films are not likely to experience moisture sorption, hardening, and slowing down of disintegration time over the course of shelf-life due to its properties and packaging configuration.[3]

3. The films are not friable. This attribute prevents fragmenting during transportation and handling and reduces the possibility of residue remaining in the blister or foil pouch as is often observed for some types of ODTs (eg, lyophilized or effervescent ODTs). The lack of friability means the entire intended dose can be accurately consumed by the user, and an individually packaged unit dose can be conveniently carried around without risk of product damage.

4. The films can be consumed without water. This obvious advantage is shared with ODTs along with other factors, such as ease of swallowing. These advantages have clearly gone a long way toward meeting the need for improved patient compliance especially in pediatric, geriatric, and dysphagic patient populations.

Additionally, ODFS have several unique and novel advantages that make them the natural and final evolution of orally disintegrating dosage forms. The ODFS dosage form allows discreet consumption of the dose, and the smaller size of the dosage form allows for shorter residence time within the oral cavity and potentially more effective avoidance of unpleasant taste. In a healthcare provider setting, there is potential for reduced dosing errors because the dosage forms are usually supplied in printed, individual pouches. Almost as importantly, the technology for making these fast-disintegrating film dosage forms is simple and pharmaceutically elegant compared to relatively complex ODT technologies, such as lyophilized, compression molded, effervescent, and sugar floss dosage forms. Innovative drug delivery firms are undoubtedly very close to delivering prescription pharmaceuticals to the marketplace in these next-generation dosage forms to meet the clinical need for enhanced patient compliance and efficacy.

FORMULATION & PROCESSING OF ODFS

Drug Considerations & Taste-Masking

The drug may be present in the ODFS as discrete particles of unmilled, micronized, or nano-sized drug crystals. Alternatively, the drug may be molecularly dispersed in the polymers of the ODFS as a solid dispersion. Many pharmaceutically active molecules exhibit a bitter taste response and typically require some level or type of taste-masking. The following are the four primary approaches for modulating the taste of bitter medication to improve their palatability:

1. Obscuration is the simplest method, which involves co-formulating a product with pleasant-tasting ingredients that mask or distract from the unpleasant taste of the active ingredient. The use of sweet and/or sour substances to disguise bitterness, combined with olfactory stimulants, such as artificial and natural flavors, can significantly improve the palatability of many drugs. This approach is easy enough to practice readily but may be insufficient by itself to obtain an acceptable tasting product, especially if the pharmaceutical active is extremely bitter.

2. Barrier or occlusion methods involve the creation of a molecular or microscopic barrier, which

TABLE 2

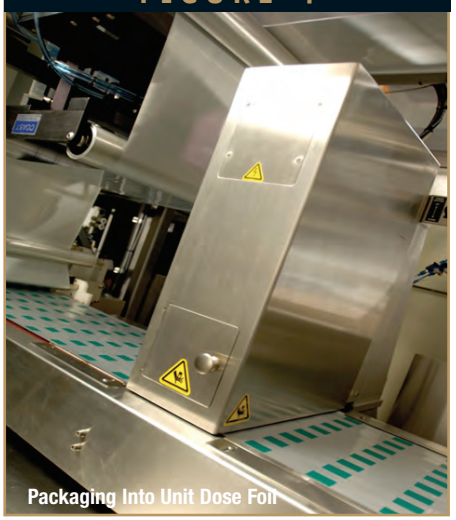
Testing Method
-Tensile Strength -Elongation -Puncture Resistance -Peel strength (from substrate) -Tear Resistance -Fold/Bend Resistance -Curl Resistance -Hygroscopicity -Film Disintegration Time -Film Dissolution time (not drug release)

Tests for Evaluating Thin Films During Development

FIGURE 3

Wet Casting of Film Onto Substrate

FIGURE 4



Packaging Into Unit Dose Foil

eliminates or reduces contact between the bitter actives and the taste receptors on the tongue. Molecular occlusion of drugs within the cage-like molecular structure of cyclodextrins has been claimed to provide some measure of taste-masking. At the microscopic particulate level, individual grains/crystals of the active drug may be physically occluded within matrix microspheres, microcapsules, coated crystals, or granules. An example of this approach is the coated particles of dextromethorphan hydrobromide in a film strip formulation developed and manufactured by MonosolRx. The problem of residual particles in the mouth is minimized in ODFS because of the shorter residence time and smaller overall quantity of material to dissolve and swallow. On the other hand, the maximum drug loading is lower compared to tablets due to the weight limitation discussed further.

FIGURE 5

Finished Product & Primary Pouch Package

3. Chemical modulation of API involves modifying the solubility of a drug in saliva to reduce the availability of free drug molecules to stimulate taste receptors. The simplest manifestation of this may be the use of a free base instead of a salt of the drug substance (as exemplified by the use of ondansetron free base in the GSK's ODT versus the HCl salt in the IR tablet). Another approach might be the use of a buffering excipient within an orally dissolving formulation to transiently alter the salivary pH to reduce the solubility of the active. Yet another strategy that has been used in a commercial ODFS is the creation of drug complexes with ion-exchange resins. These drug resinates do not release the drug in an ion-free media but readily do so within the GI tract. For a prescription drug, however, they would be considered as new salt forms and could not be pharmaceutical equivalents to the reference listed drug.

4. Physiological methods involve blocking of taste receptors by specific molecules, such as adenosine monophosphate and phosphatidic acid and other proprietary bitter-masking compounds.

Taste-Masking by Coating for ODFS

The two main subsets of ODFS formulations that are generally developed separately but concomitantly are the polymeric film matrix and the taste-masked drug particles embedded within the film matrix. Because the ODFS manufacturing process involves suspending these taste-masked particles in water prior to wet casting of the film, the taste-masking coating may erode/dissolve or become increasingly porous during processing, thereby exposing free drug. Appropriate coating polymers and excipients combined with specialized aliquot-mixing processes/equipment to minimize the contact time of the particles with water/solvent are used to prevent leaching of the drug from the particles prior to creation of the dried bulk film. Appropriate selection of polymer type and grade and percentage of solid ingredients provides the ideal viscosity to allow for adequate flow of the suspension while maintaining the suspended particles in the coating solution.

Dosage Size & Drug Loading

The formulation of ODFS presents distinct challenges that are not typically encountered by pharmaceutical scientists working on other types of solid dosage forms. The upper limit of the piece weight of each individual ODFS unit is much lower than that for a tablet or capsule. ODFS have a larger overall surface area because they are typically 25 to 40 mm in length and about 20 to 30 mm in width, and it is this larger surface area combined with the thinness of the film that allows its rapid dissolution. The films can have a dry thickness of between 50 and 200 microns, and the piece weight of these strips rarely exceeds 150 mg. For a given compositional formula, the time for oral dissolution varies directly with the film thickness. Formulations intended for slower dissolution in the buccal or sublingual cavity can be formulated with specific polymers at greater thicknesses to provide a wide range of oral dissolution times. In general for an ODFS, there is a practical weight and/or thickness above which the film is perceptibly gummy and slow and not particularly suitable as a quick dissolving product.

The upper limit for drug loading in ODF can be roughly estimated to be about 120 mg. More typically, the practical upper limit of drug loading is in the range of 60 to 80 mg of neat drug substance. If a taste-masking or other functional coating is applied, the maximum drug loading can be significantly lower.

Composition

ODFS formulations almost always use more than one polymer to achieve the right balance of desirable film properties. The properties of the film may be further modulated by selecting the appropriate molecular weight (MW) grades of the polymers.[4] The polymers are generally water soluble, such as various molecular weight grades of cellulose ethers, polysaccharides, polyvinyl alcohol (PVA), polyvinylpyrolidone (PVP), copolyvidone, polyethylene oxide, polyethylene glycols etc. Smaller proportions of swellable, water-

insoluble polymers may be used at times to impart desired functionality. The MW grade and polymer composition are also dictated to some extent by the processing conditions.

The piece weight of these dosage forms is relatively low, which leaves little room for superfluous formulation components. Invariably, the major components in the film formulation are the polymers and the drug, and the proportion of these relative to each other is dictated by two factors: 1) the minimum amount (% w/w) of polymer required to create a matrix that can accommodate the drug and all other non-polymeric components while maintaining sufficient mechanical strength and 2) the % w/v of polymers in the coating suspension, which is limited by the desired viscosity range. Viscosity must be high enough to prevent suspended solids from settling during the coating operation to allow for the creation of a uniform product but not too high to cause mixing problems and film defects from poor spreadability (ie, high contact angle).

Adjuvants & Flavor Considerations

In addition to the major components, other additives in the film have specific purposes, such as lubricants and anti-tacking agents to modify adherence of the films to each other as well as to the substrate or pouching material, and also to the roof of the mouth. Other ingredients like preservatives, colors, and opacifiers are usually included at their typical usage levels. Flavoring agents are key components of ODFS not only because they play the role of masking any residual unpleasantness of the active substance but also for their potential impact on film characteristics. The proportion of flavors in ODFS are generally somewhat higher compared to traditional chewable or ODT tablets. It is generally not advisable to use spray-dried or encapsulated flavors in these formulations as they may result in settling, poor film texture, streaking, and disruption of particles during drying of the film. It is more common to use liquid flavor oils (with or without liquid carriers) that are well dispersed within the final formulation prior to coating. Careful selection of the flavor source, type, and concentration is important because it impacts organoleptic perception as well as mechanical properties of the film.

Substrate

The adherence between the dried film and the substrate on which the web is formed must be optimal so that it does not spontaneously delaminate during handling but also allows for easy separation from the substrate prior to packaging. The substrate must be pharmaceutically acceptable and must withstand heating during the drying process without warping or softening.

Characterization of ODFS - Attributes Measured During Development

During development of ODFS, certain specialized types of physical testing are generally advisable because they are important from the perspective of the packaging operations and patient acceptability. These tests often center around attributes such as speed of disintegration/dissolution and mechanical strength testing. Often, these tests do not have formally specified acceptance values or ranges but are useful in a development setting to compare between formulations and optimize product quality and performance. At times, there may be a need for empirically established acceptance limits for certain mechanical attributes to enable trouble-free processability and performance in production settings. Examples of these types of test measurements are shown in the Table 2.

Manufacturing of ODFS by Wet Film Casting

The manufacturing of film strips involves the following three major stages:

1. PREPARATION OF STOCK SOLUTION & FINAL DISPERSION: This step involves high intensity mixing of the predominantly soluble inactive ingredients in water to dissolve them and produce a viscous, homogeneous stock solution, which contains all ingredients except the active(s). The actives are typically added in the final step to produce the final solution or suspension followed by homogenization if necessary and a final degassing step under vacuum to remove dissolved air prior to the subsequent coating step. Typical in-process checks in this manufacturing step are viscosity, pH, and percentage solids.
2. COATING OF THE DISPERSION ONTO A SUBSTRATE TO CREATE BULK FILM PRODUCT: In a continuous operation, the final dispersion is applied as a thin, wet film onto a flexible substrate and conveyed through an oven at a constant rate to dry the film and produce the bulk final product “master” film rolls. The width of the coated film on the substrate can vary from about 8 to 30 inches or even more for larger commercial-scale batches. Manufacturing parameters that are often controlled are solution temperature, wet coat thickness, oven temperature, and airflow rates. Typical in-process checks in this manufacturing step are appearance, coat weight per unit area, moisture, water activity, and assay per unit weight. The coating process is amenable to batch-wise or continuous operation and is also particularly suited for Process Analytical Techniques for continuous measurement of a variety of desired attributes.
3. CUTTING OF THE BULK FILM PRODUCT INTO INDIVIDUAL STRIPS & FOIL-FOIL POUCHING: The bulk roll product is first processed through a slitting machine resulting in a film roll width suitably sized for the pouching machine. This operation does not have any impact on the final size/content of the strip and may be regarded as an intermediate preparatory and non-critical step.

In the pouching operation, the film is unrolled, gang-printed across the width of the roll using a rotogravure printer, and then separated from the substrate. It is then imparted a primary cut in the machine (length) direction to separate into narrow “ribbons” (~ 22 mm wide). Each ribbon is cut to a preset length into individual film strips. The film strips are transferred between two layers of the aluminum foil pouching material and sealed at the edges using heated platens. These steps occur in a continuous operation on a high-speed pouching machine often fitted with a vision system that performs 100% inspection of a variety of visible attributes. Piece weight variation and dimension measurements are typical off-line in-process checks during packaging.

Bulk Film & Packaging of Individual Film Strips

The film produced in the coating process may be considered as the bulk product in which the drug particles are essentially uniformly immobilized within the polymer web. If uniformity of content is achieved in the bulk film, the individual units will also be uniform because no segregation can occur during the final pouching operation in which the final dosage unit is created. In practice, the uniformity of the blend is ascertained in both the liquid state as well as the dry final film prior to pouching. The high degree of precision in the cutting/pouching operation ensures excellent weight and content uniformity.

For prescription drugs in a unit dose pouch, child-resistance is often a desired feature and may be easily achieved by appropriate selection of foil material and opening method.[5] Additionally, a hermetic seal coupled with practically non-existent headspace in these flat foil pouches often improves chemical and physical stability. Secondary packaging is most often performed in cardboard cartons containing multiple pouched strips.

Finished Product Specifications

ODFS are generally subjected to release tests similar to those for typical solid oral dosage forms, such as weight, assay, related substances, content uniformity, moisture, drug release by dissolution, and microbial testing. Dissolution testing often requires the use of a sinker to prevent floating on the surface of dissolution media.[6] Depending on the water activity of the final dosage form, microbiological testing may be eliminated with proper justification.

Future Applications of Thin Film

ODFS formulations are generally intended for per oral administration of drugs to the GIT; however, other routes of administration are easily conceivable. Drugs with significant transmucosal flux rates can be administered via thin films specially formulated to dissolve slowly in the buccal or sublingual cavities. Drugs can also be administered vaginally or topically for local or systemic effects. Drug particles coated with controlled-release coatings may also be incorporated within thin films to produce dosage forms with any desired drug release profile married with the convenience of dosing as an ODFS.

Incompatible combination drugs may also be included within a single dosage form using multilayer films laminated together. A separating inactive film layer may also be introduced to prevent contact between incompatible actives.

SUMMARY

The growing success and popularity of ODT and ODFS in recent years is testament to the need for effective taste-modulated, "without water" pharmaceutical formulations. Another compelling motivation for these dosage forms is the global movement in the public and private sectors for more pediatric-friendly drug delivery systems and more pediatric labeling for drug products.[7] Examples of the actions taken by government include mandated (eg, US legislation - Best Pharmaceuticals for Children Act) and voluntary programs (eg, FDA Modernization Act of 1997) that require a drug firm show safety and/or efficacy of a drug product in pediatric age groups.

ODFS are the natural evolution of rapidly dissolving dosage forms for administration of pharmaceuticals. They are ideal not only for pediatric and geriatric populations but also for active adults desiring a portable dosage form with the ability for discreet use. A promising future can easily be envisioned for this robust, elegant, and convenient product.

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BIOGRAPHIES

Dr. Madhu Hariharan has over 12 years of experience in product development in the pharmaceutical industry. He currently leads Regulatory Affairs at MonosolRx in Portage, IN, with ancillary responsibilities in the area of Business Development. In his previous position as Director of Pharmaceutical Development at MonosolRx, he was responsible for the pharmaceutical and clinical development of several prescription and OTC thin film drug products for oral, buccal, sublingual, and vaginal applications, several of which were successfully commercialized or are currently awaiting marketing authorization. Dr. Hariharan's main experience has been in the area of traditional and novel oral dosage forms, including IR, chewable, ODT, and thin films as well as various modified-release technologies. He has also been extensively involved in the development of fast onset products using nanoparticulates and lipidic self-emulsifying dosage forms. Previous to MonosolRx, he has served in various scientific and technical management positions within R&D and Operations at Fuisz Technologies, Searle/Pharmacia, and Abbott Laboratories. Dr. Hariharan has 12 research and general articles, several pending patent applications, and conference presentations to his credit. He earned his BS in Pharmacy at the University of Pune, India, and his PhD in Pharmaceutics from the University of Georgia in Athens, GA. He is a member of the American Association of Pharmaceutical Scientists. Dr. Hariharan can be reached at mhariharan@monosolrx.com

Dr. B. Arlie Bogue is currently the Senior Director of Manufacturing Technology at MonosolRx in Portage, IN. His responsibilities include process development and scale up of new ODFS products. Dr. Bogue has over 20 years of experience in pharmaceutical process development, technology transfer, and scale up. His primary experience has been in the manufacturing of oral dosage forms, including IR, CR, combination IR/CR, chewable, ODT, and thin films. Previous to MonosolRx, he has served in various technical management positions within Operations at Kos Pharmaceuticals (Abbott Laboratories), Capricorn Pharma, Fuisz Technologies, Warner Lambert, and Sandoz. Dr. Bogue has written 14 research articles, given numerous technical presentations, obtained 22 US and multiple foreign patents, and has several pending patent applications. He earned his BS in Physical Chemistry at Colorado State University and his PhD in Chemical and Bio Engineering at Arizona State University. He also completed Post-doctoral studies in the Biochemical Engineering Department at the University of Virginia.

DELIVERY OPPORTUNITIES

Continued Drug Delivery Opportunities in Diabetes Management

By: Daniel Ruppar, Frost & Sullivan

INTRODUCTION

Pharmaceutical drug development is often a game of chance. There will be plenty of failure before success at all stages of the process - from an initial high-throughput screen to issues with approved drugs. As the industry continues to right and transition itself to maintain future growth, the utilization of and innovation through drug delivery technologies is top-of-mind in many disease areas. With interest in biotech, specialty pharma, lifecycle management, and other new product development, companies are incorporating new types of drug delivery technologies into their product designs as they seek to provide new solutions to patients. In diabetes, the "failure" of the first marketed inhaled insulin, Exubera (Pfizer), led to other late-stage inhaled insulin pipeline compounds to also be pulled from development. Currently, MannKind Corporation stands as the leading prospect to deliver a successful inhaled insulin product to the market. The question many may ask is whether there is still an opportunity for an inhaled diabetes drug.

INHALED PRODUCT FAILURES DO NOT MEAN THE OPPORTUNITY ISN'T THERE

The failure of inhaled insulin thus far does not mean the approach of inhaled delivery of diabetes drugs is something to eliminate. Many of the adverse points with the device or side effects of Exubera are really failures for that specific drug. Many of the pulled products in late-stage development would have also had similar hurdles if they made it to the market. Novo Nordisk was already leaning toward a second-generation version of their pipeline product as the one to have better prospects in the market. Therefore, those that have left development may not have had a product with the characteristics and benefit profile to perform well in an area of now heightened scrutiny. In the end, as big pharmaceutical companies are realigning their portfolios and objectives for future growth, it made sense for them to stop these programs.

However, for inhaled delivery in diabetes, this does not reflect the willingness in the market to use a good drug with that delivery approach. The onus is still on the industry to

FIGURE 1

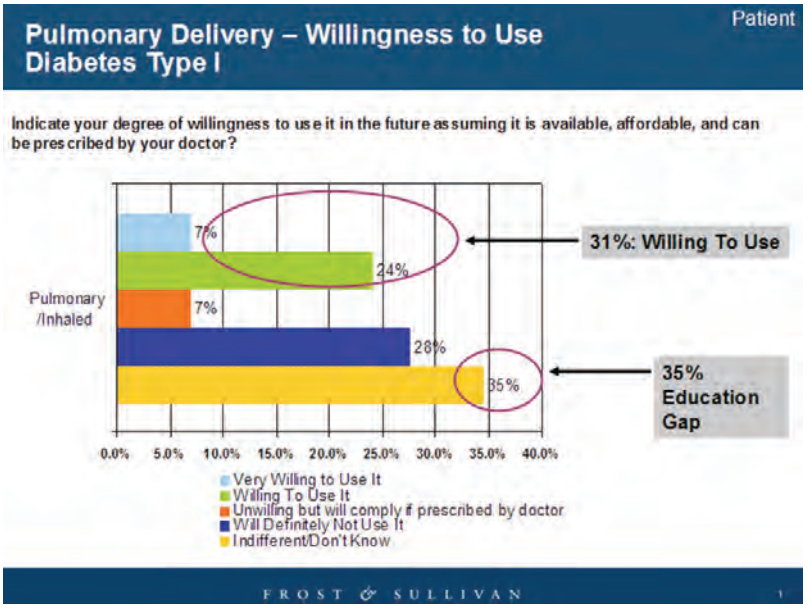
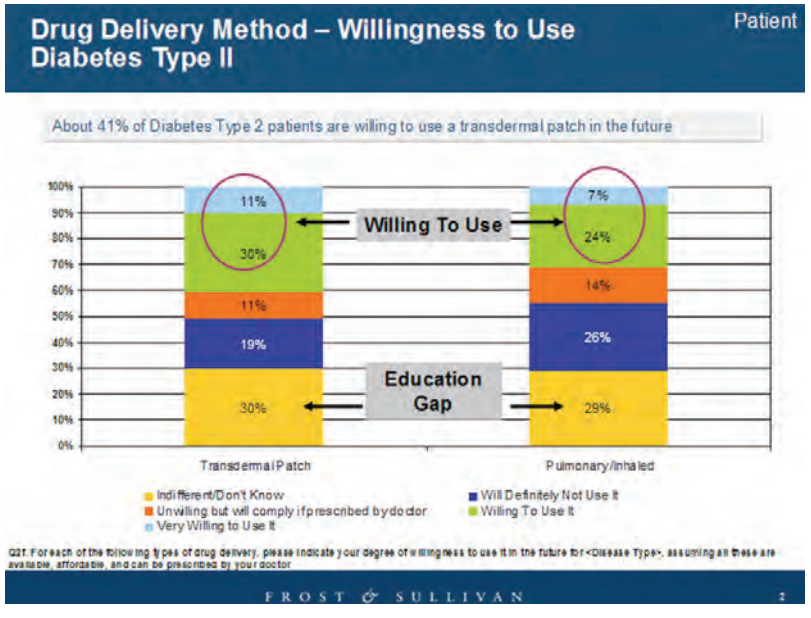


FIGURE 2



provide the market with a medicine that lives up to the hype. For example, in Frost & Sullivan research with type 1 diabetics, only 28% of patients expressed they would definitely not use an inhaled diabetes medication (Figure 1).

Conversely, 31% of patients stated they were willing or very willing to use inhaled delivery for their diabetes medication. Seven percent were unwilling but would take the inhaled medicine if prescribed by their physician. An additional 35% were indifferent to the approach, which yields developers with an "Education Gap" in terms of bringing patients to their drug and educating them about the benefits. Overall, this presents developers with a majority who would already use an inhaled diabetes drug, or could be educated on the benefits of these drugs. The problem is developing an effective, safe, and low-barrier inhaled product and getting it into the market. Perhaps MannKind's AFRESA (Technosphere Insulin System) will fit this need better than Exubera was able to.

For the type 1 diabetes patient who is unwilling to use an inhaled diabetes drug, the question to understand is why. If those points can be addressed and improved upon by technology, then that could bring additional patient willingness potential to bear. When barriers for inhaled delivery were posed to type 1 diabetic patients, the leading key barriers were adverse side effects, and they believed it was very inconvenient. The "very inconvenient" issue may be harder to modify, but the adverse side effect point (lead choice, 30% of respondents) is more product dependent than delivery dependent. In the end, both barriers could be tied more to the exposure of the patients to Pfizer's product while it was in the market and are probably not totally indicative of things that are impenetrable blockades for future product development.

GLP-1: INSULIN ISN'T THE ONLY NEED

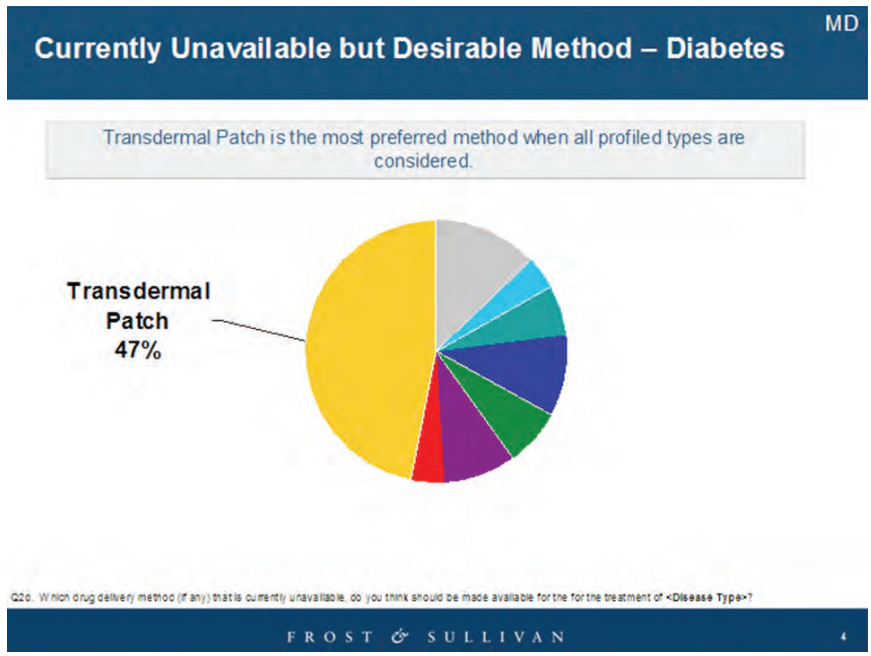
In terms of inhaled diabetes medications, more than inhaled insulin is currently in the works. For example, MannKind Corporation's MKC 253 pipeline compound is an inhaled GLP-1 agonist. This class is one of the leading new pipeline areas in diabetes drug development and is also tied to a syringe, like insulin. Even though diabetes patients in general are more familiar with needles than those with most other chronic diseases, it is still critical to push the frontiers of drug delivery in the area. With GLP-1 compounds showing added benefits to patients, such as weight loss, a non-syringe GLP-1 with that added benefit could be of interest to patients.

OTHER OPPORTUNITIES: TRANSDERMAL

There are other areas of value for future diabetes drug development. A transdermal patch approach is one in which there is current work (Altea Therapeutics/Insulin Patch), but it does not have the heightened awareness that surrounded inhaled products. A key question to understand is if physicians and patients are interested in a transdermal patch as a diabetes product. When type II diabetics were asked about this, the willingness of patients to use a transdermal patch was greater than that for an inhaled drug, 41% to 31% comparatively (Figure 2). There is an additional "Education Gap" opportunity, but also the negative "unwillingness to use" for transdermal was lower than that for inhaled, 19% versus 26%.

If a transdermal diabetes product were brought to the market, would that particular form be of interest in the treatment of diabetes to MDs? When asked about this issue, it was found that MDs would also have an interest in transdermal delivery of diabetes medication. Transdermal was the leading response (47%) in terms of a method desired by physicians and was of far greater interest to them than an inhaled product (Figure 3).

FIGURE 3



SUMMARY

For drugs that are utilizing a "new form" of delivery, breaking into the market can be hard. Not only do patients provide an audience that needs convincing, but physicians must also be brought on board. When physician attitude toward new delivery forms was explored, Frost & Sullivan found that a majority of doctors are willing to prescribe them. Therefore, with patients and physicians interested in new delivery forms, the burden is on R&D. For a transdermal patch in diabetes, whether it is for insulin, GLP-1, or some other drug class, there must be both successful technology development and product development to meet that need and see potential market success.

Hopefully, the problems with bringing inhaled insulin to market won't stymie the development of new diabetes drugs utilizing innovative drug delivery technologies. Patients in this area need new drug types and options in their treatment. If MannKind Corporation is able to bring inhaled products to market with the company's Technosphere technology, then that may improve the outlook for that delivery type within the industry. Additionally, with an interest with patients and physicians around a transdermal patch, if a developer can bring a safe and differentiated product to the market, that may be received with even better fanfare than the excitement was for inhaled insulin.

BIOGRAPHY

Daniel Ruppar is the Manager of Frost & Sullivan's North American Pharmaceutical & Biotechnology analyst team. He focuses on monitoring and analyzing emerging trends, technologies, and market dynamics in the Pharmaceutical and Biotechnology Industry. His recent work has focused on a variety of areas, including specialty pharmaceuticals, drug delivery, diabetes, and thrombosis. He also has performed consulting duties for Venture Capital and Financial Services clients. Prior to this, Mr. Ruppar spent 9 years in the pharmaceutical industry as a medicinal chemist working on therapeutic/drug area targets, including oncology, metabolic disease/diabetes, interferon, thrombopoietin, and the androgen and estrogen receptors. Additionally, he is a co-author of multiple scientific publications in peer-reviewed journals for his work in chemistry, has authored multiple articles in Drug Delivery Technology, and is a co-inventor on 4 patents for his work in drug discovery. He also most recently has presented his work in Diabetes/Drug Delivery at Drug Delivery Partnerships 2008.

SIRNA THERAPEUTICS

Systemic Delivery of Therapeutic siRNA: Opportunities & Challenges

By: Frank Y. Xie, PhD; Qing Zhou, PhD; Ying Liu, MS; Samuel Zalipsky, PhD; and Xiaodong Yang, MD, PhD

INTRODUCTION

Discovered about a decade ago by Fire, Mello, and colleagues, RNA interference (RNAi) is a natural biological process in which a double-stranded RNA molecule activates the cellular RNAi machinery to specifically inhibit target gene expression by cleavage of target messenger RNA (mRNA).[1] Characterized subsequently by Tuschl and other scientists, the intermediate effector of RNAi is a 21-23 nucleotide (nt) double-stranded RNA molecule known as small interfering RNA (siRNA) that is generated through cleavage of the long double-stranded RNA in cytoplasm by the RNase III enzyme Dicer.[2,3] These siRNA intermediates were incorporated into the multi-protein complex, called RNA Induced Silencing Complex (RISC), which includes the endonuclease Argonaute 2 (Ago2).[4] The Ago2 within RISC uses the antisense strand (guide strand) of siRNA as a guide to find mRNA containing complementary sequences and cleaves the phosphodiester backbone of target mRNA at a specific site between 10-11 nt from the guide strand's 5 end.[5] Another class of non-coding RNAs, microRNAs (miRNA), also utilizes RNAi machinery to suppress the target gene expression in a sequence-specific manner.[6] Unlike RNAi induced by siRNAs, which leads to degradation of target mRNA complementary to siRNA, the RNAi induced by miRNAs results in translation suppression and eventually degradation of the target.

RNAi, with its high specificity and potency of gene silencing, not only has become a powerful tool in gene discovery and target validation, but also provides a novel therapeutic strategy, particularly for those non-druggable targets.[7,8] Although more classes of small non-coding RNAs, including miRNA, have been identified that play important regulatory roles in gene expression, the majority of efforts into the use of RNAi as a therapeutic modality has focused on siRNAs.[9,10] Rapid advances in RNAi research and development has resulted in a number of ongoing clinical trials, with many more expected to enter clinical trials soon (Table 1).

The following provides an overview of the critical steps in the development of siRNA therapeutics, from the selection of siRNA specific for the target of interest to the development of novel formulations for efficient in vivo systemic delivery of siRNA therapeutics. Also reviewed are the various approaches being explored and developed to address the key issues and challenges in systemic siRNA delivery.

SELECTION OF POTENT & SPECIFIC siRNA

Selection of a potent and specific siRNA as an active pharmaceutical ingredient (API) is the first step toward the successful development of siRNA therapeutics. During the process of selecting API siRNA, considerations should be given to siRNA potency in silencing target gene expression and chemical modification of siRNA sequence to increase silencing potency, avoid potential off-target effect, and minimize activation of the innate immune responses.

Design of siRNA Structure & Selection of Potent & Specific API siRNA

Chemically synthesized 21-nt siRNA duplexes with 2-nt 3' overhangs on both passenger and guide strands have been a standard form of siRNA molecule in mammalian cells. Other structures have been explored to increase siRNA potency. By introducing mismatched base-pair or DNA/RNA hybrid base-pair into a perfect pairing siRNA at a certain region, Zamore and colleagues were able to enhance siRNA potency by up to 10-fold.[11] They also demonstrated an enhanced knock-down efficacy by creating a wobble base-pair between the guide strand of siRNA and its target mRNA, probably due to increasing the recycle rate of RISC.[11] It was reported that asymmetric siRNA with one 2-nt 3' overhang and one blunt-end is a potent RNAi trigger, which mediated a strong target gene Apolipoprotein B (ApoB) silencing in non-human primates.[12] Rossi and colleagues found that longer blunt-ended siRNA (27-nt) is up to 100-fold more potent than conventional 21-nt siRNA with 2-nt overhangs. They hypothesized that longer siRNAs serve as a substrate of Dicer,

and Dicer and TAR (trans-activating region) RNA-binding protein (TRBP)-protein activator of the interferon-induced protein kinase (PACT) might comprise a loading platform for RISC formation that enhances silencing potency.[13] The potency can be further enhanced by modification of the 27-nt siRNA into an asymmetric structure with 2-nt 3'overhang on the guide strand and blunt-ended on the other terminal with two DNA/RNA hybrid pairings.[14]

Potency and specificity are the major concerns for design and selection of siRNA. Many web-based siRNA design algorisms are available, and most siRNA manufactures also provide their own siRNA design algorisms. These algorisms allow for effective identification of siRNA sequences that are a perfect complement to target mRNA in coding or non-coding regions, based on a combination of target mRNA sequence and its secondary structures. However, prediction of siRNA potency solely relying on our in silico siRNA design algorism is still far from perfect as illustrated by the observations that shifting a 21-nt siRNA by a few bases along the mRNA sequence can change its potency by more than 10-fold.[15] Thus, for selection of API siRNA, combination of siRNA design algorism and in vitro knock-down potency screening of siRNA candidates has become a common practice.

At Intradigm, a similar approach is applied for API siRNA selection. Starting with 100-200 siRNA candidates for a given target gene generated through usage of a proven web-based siRNA design algorism, we further reduce the number of siRNA candidates based on bioinformactic analysis and additional stringent parameters of selection. Priority is given to those siRNA candidates that are complementary to human gene homologous mRNA sequences in mouse and monkey. A high-throughput in vitro siRNA screening platform was established that includes 2-3 rounds of potency screening of the siRNA candidates. siRNA silencing potency was measured at the mRNA level using a quantitative real-time PCR assay and/or at the protein level using an ELISA assay. The final API siRNA sequences are determined based on target gene knock-down potency. Our selected API siRNAs are extremely potent with IC50 in the range of subnanomolar.

TABLE 1

Compound	siRNA Target	Sponsor	Delivery	Indication/ Status
Bevasiranib	VEGF	Opko (Acuity)	Local	AMD/Phase III
Bevasiranib	VEGF	Opko (Acuity)	Local	DME/Phase II
siRNA-027	VEGFR1	Merck(Sirna)/Allergan	Local	AMD/Phase II
ALN-RSV01	Respiratory Syncytical Virus	Alnylam	Local/Chemical Modified siRNA	RSV/Phase II
PF4523655/RTP801i-14	RTP801	Quark/Pfizer	Local	DME/Phase I/II
I5NP/AKIi-5	p53	Quark	Systemic/Chemical Modified siRNA	AKI/Phase I
DGFi	p53	Quark	Systemic/Chemically Modified	DGF/Phase I/II
CALAA-01	Ribonucleotide Reductase M2	Calando	Systemic/Cationic Polymer	Solid Tumors
TD101	Keratin 6a (K6a) N171K Mutant	TransDerm	Local/Intradermal Injection	PC/Phase IB
sidrzT	HIV/AIDS Lymphoma	City of Hope-Benitec	Lentiviral Vector/Ex Vivo	HIV/AIDS Phase I
NUC B1000	Hepatitis B virus	Nucleonics	Plasmid/Cationic Lipids	Hep B /Phase I

*** AMD (Age Related Macular Degeneration) - DME (Diabetic Macular Edema) - RSV (Respiratory Syncytical Virus) - AKI (Acute Kidney Injury in Kidney Transplantation) - DGF (Delayed Graft Function in Kidney Transplantation) - PC (Pachyonychia Congenita) - HIV/AIDS (Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome) - Hep B (Hepatitis B Virus)**

RNAi-based therapeutics in development

Chemical Modification of siRNA to Enhance its Performance

Certain types of chemical modifications to the siRNA duplexes may be considered to enhance the performance of siRNA, including increase of siRNA stability, decrease of off-target effect, and reduction of cytokine activation.

Chemical modification to improve siRNA serum stability against nuclease degradation is critical for in vivo siRNA delivery. Integration of a phosphorotioate (P=S) backbone linkage at the 3' end of siRNA provides exonuclease resistance, and 2' modifications (2'-O-methyl and 2'-fluoro nucleotides and related) provides endonuclease resistance.[16,17] Modifications of siRNA with 2'-O-

TABLE 2

Solutions	Examples	Pros	Cons
Local Delivery	Ocular (AMD), Lung (RSV)	Simple, low dose, and less side effects	Limited applications, innate immune response
Chemical Modification/Conjugation	Several Modifications Described in Text	Protect siRNA from degradation, reduce off-target effect	Poor cellular internalization, may alter siRNA potency
Gene Delivery	Viral Vector, Plasmid	Long duration of RNAi effect	Nuclear transportation, immunogenicity, potential toxicity from saturation of endogenous silencing pathways
Synthetic Vectors	Liposomal, Polymer-Based Nanoplex	Better PK profile, targeted delivery, improved endosomal release, payload interchangeable	Liver accumulation, safety, immunogenicity, biodegradability

Delivery solutions for RNA therapeutics

methyl and 2'-fluoro nucleotides not only enhanced plasma stability of siRNA, but in some cases, these modifications also improved potency of siRNA by over 500-fold compared to unmodified siRNA.[18] Modification of siRNA with 4'-thioribose increased siRNA stability by 600-fold compared to unmodified siRNA.[19-23] Other chemical modifications for improvement of siRNA stability have also been reported.[24]

The off-target effect of siRNA was found to be sequence-dependent due to sharing a complementary sequence between off-targeted mRNAs and one of the two strands of siRNA.[25,26] Further studies indicated that the complementary regions are most often found in the 3'-UTRs of the off-targeted gene, which suggests that siRNA may silence off-target gene through the mechanism of miRNA mediated RNAi.[27] Chemical modifications of the 5' of passenger strand of certain siRNA were found to reduce the off-target effect by inhibiting the loading of the passenger strand into the RISC.[24]

Another chemical modification proven to be effective in reducing the off-target effect is to modify the 5' region of guide strand siRNA with 2'-OMe, the region usually regarded as the active "seed" region of miRNA.[28] The complementary sequence between the "seed" region of the guide strand and the off-targeted mRNAs is the molecular basis of off-target silencing.[29]

One of the undesired effects of siRNA for therapeutic applications is the stimulation of the innate immune response that results in rapid production of interferon and pro-inflammatory cytokines.[30-32] Certain specific sequences in siRNA duplexes, the so-called "immune stimulatory sequence," can engage with Toll-like receptors (TLRs) in dendritic cells, most likely the TLR7/8 expressed in endosome, and increase the production of type I interferon.[33] Recently, "naked" siRNA has been shown to activate TLR3 on the surface of vascular endothelial cells and trigger the release of IFN-gamma and IL-12 that mediate non-specific antiangiogenic effects in in vivo models.[34] Cytokine production stimulated by siRNA can be reduced by chemical modification, such as selective incorporation of 2'-O-Methyl (2'OMe) nucleotides, in particular, guanosine or uridine residues in the constituent RNA oligonucleotides.[35] The hypothesis for the cytokine inhibition effect is that 2'-O-methyl-modified RNAs may act as TLR antagonists.[36]

SYSTEMIC DELIVERY OF siRNA

Having selected potent and specific siRNAs is only the first step toward successful development of siRNA therapeutics. The effective delivery of siRNA to the appropriate target cells remains the major hurdle. A number of delivery solutions have been explored for siRNA delivery (Table 2). Local delivery of siRNA avoids many of the hurdles that systemic siRNA delivery encounters, such as serum instability, urine excretion, and inefficient delivery to target tissues. Using a murine model of herpetic stromal ketatitis that develops from herpes simplex virus corneal infection, we found that subconjunctival administration of siRNAs targeting genes in the VEGF pathway specifically silenced expression of these target genes and significantly inhibited the corneal angiogenesis and disease severity.[37] Direct intravitreal injection of non-formulated VEGF siRNA in a mouse model of retinal neovascularization resulted in a significant reduction of angiogenesis in the eye.[38] This paved the path to ongoing Phase III trials for age-related macular degeneration (AMD) conducted by Opko Corporation (formerly Acuity). Other ongoing clinical trials utilizing the local siRNA delivery approach include a Phase II evaluation of Sirna-027 (VEGFR1-siRNA) in AMD patients by Merck (Sirna)/Allergan, a Phase II evaluation of RSV01 (RSV-siRNA) for RSV infectious disease by Alnylam Pharmaceuticals, and a Phase II of PF4523655/RTP801i-14 for diabetic macular edema by Pfizer/Quark Pharmaceuticals (Table 1).

Despite the advances of local siRNA delivery, its applications are limited by its inadequate accessibility of tissue types. In contrast, systemic delivery of siRNA has much broader therapeutic applications, but encounters some significant challenges. For instance, systemic siRNA delivery has to avoid urine excretion and serum instability, enhance siRNA delivery to target tissues, and mediate efficient target gene silencing.

A number of systemic RNAi delivery approaches, including viral and non-viral vector systems, have been extensively studied. Viral vectors can effectively deliver expression-based target-complementary short hairpin RNA (shRNA) to induce RNAi in vivo. However, they have some limitations and drawbacks found in gene therapy, as well as additional potential undesired effects from saturation of endogenous RNAi-silencing pathways.[39] Many non-viral carriers used for gene therapy have been adopted for siRNA delivery. The cationic lipids and cationic polymers are the two main classes of non-viral siRNA delivery carriers. Both cationic lipid- and polymer-based carriers are positively charged and form nano-sized particles (nanoparticles) or complex (nanoplex) when mixed with negatively charged siRNA.[11,40-44] Other approaches also demonstrated promising potentials, such as direct conjugation of siRNA with cholesterol, PEG-siRNA conjugate, and antibody-protamine coupled siRNA polyplex.[45-48]

Liposomes for Systemic siRNA Delivery

Liposomes consist of phospholipid bilayers with an encapsulated aqueous compartment. Liposomes have been successfully applied for formulation of small molecule drugs to improve drug's pharmacokinetic properties and reduce toxicity profiles. In vivo knock-down of target gene was achieved in rodents and non-human primates by systemic administration of chemically modified siRNA encapsulated in stable nucleic acid-lipid particles (SNALP) that consist of cationic and neutral lipids and an outer coating of PEG.[11] A single dose of SNALP-formulated apoB siRNA at 2.5 mg/kg reduced apoB mRNA by more than 90%, accompanied by more than 65% reduction of serum cholesterol and more than 85% reduction of low-density lipoprotein. Similar liposome formulations have also demonstrated successful siRNA delivery to the liver, such as anti-viral efficacy against HBV and Ebola virus infection.[49,50]

Liposome-based siRNA delivery has also demonstrated anti-tumor efficacy in the xenograft models. Systemic delivery of Raf-1 siRNA formulated with novel cationic cardiolipin liposomes resulted in silencing of Raf-1 gene expression and inhibition of tumor growth in human prostate tumor models.[51] The pegylated liposomes were capable of increasing plasma concentrations of siRNA, and thus improving accumulation of siRNA in tumors by the enhanced permeability and retention effect. An siRNA sequence-specific anti-tumor activity was observed when pegylated liposomes carrying Bcl-2 siRNA were administrated intravenously into a mouse model of human prostate cancer.[52]

Polymer-Based Nanoplexes/ Nanoparticles for Systemic siRNA Delivery

Different cationic polymers that are capable of condensing siRNA and facilitating cellular uptake have been investigated as carriers for systemic siRNA delivery. One of the most advanced polymer-based nanoparticle systems is a cyclodextrin-based nanoparticle delivery platform developed by Calando Pharmaceuticals. This self-assembly nanoparticle system contains cationic polymer cyclodextrin, PEG, and PEG conjugated with targeting ligand, transferrin, for specific delivery to transferrin receptor-expressing tumor cells.[42,43] Systemic delivery of siRNA against the EWS-FLI1 gene formulated in the cyclodextrin-containing nanoparticles significantly inhibited tumor growth in a murine model of metastatic Ewing's sarcoma.[42] Removal of the targeting ligand or the use of a control siRNA sequence eliminated the anti-tumor effects. The same nanoparticles carrying siRNA targeting the M2 subunit of ribonucleotide reductase (CALAA-01) were evaluated in a non-human primate safety study. Multi-doses of CALAA-01 were well tolerated in cynomolgus monkeys suggesting that systemic delivery of polymer-based siRNA nanoparticles can be safely administered to non-human primates.[43] CALAA-01 is currently being evaluated clinically for its safety and efficacy in patients with solid tumors.

A novel polymer-based nanoplex, the siRNA Dynamic PolyConjugate technology, was developed to deliver siRNA specifically to hepatocytes.[41] The polyconjugate was constructed by linking the siRNA to the PBAVE polymer through a disulfide linkage; the siRNA-polymer conjugate was then reversibly modified with maleic anhydride derivatives synthesized from carboxy

dimethylmaleic anhydride containing PEG (for reduction of non-specific interactions) or NAG groups (allowing hepatocyte targeting). The resulting siRNA polyconjugate was 10 ± 2 nm in diameter, negatively charged, soluble, and non-aggregating under physiological conditions. Systemic delivery of siRNA formulated in the Dynamic PolyConjugate in mice effectively knocked down the expression of two endogenous genes, apoB and peroxisome proliferator-activated receptor alpha.[41]

At Intradigm, we developed PolyTran technology for systemic siRNA delivery. PolyTran is a family of branched poly histidine-lysine biodegradable polypeptides. The cationic PolyTran peptide serves as a condenser for anionic siRNA to form nanoplex when mixed together with siRNA. PolyTran nanoplex protects siRNA from nuclease degradation and facilitates endosomal escape of siRNA.[53,54]

PolyTran nanoplex (PT-NPX) carrying VEGF-siRNA were internalized efficiently by tumor cells leading to silencing of target expression in vitro. To test the in vivo efficacy of this delivery method, nude mice bearing human epidermoid carcinoma A431 were treated intravenously with PT-NPX carrying siRNAs against human VEGF, mouse VEGFR2, or human EGFR at 2 mg/kg dose twice a week for 3 weeks. Bevacizumab and Erlotinib were given as the positive control. All cohorts treated with PT-NPX carrying active siRNAs demonstrated a significant anti-tumor effect similar to the positive control treated animals. Significant anti-tumor efficacy was also observed a human non-small cell lung cancer A549 model.[55] In addition, systemic tissue distribution of siRNA to the tumor was confirmed using fluorescent-labeled siRNA PT-NPX. These results provided the preclinical validation of PolyTran technology for systemic delivery of potential therapeutic siRNAs for cancer treatment.

Our observations were further confirmed by recent publications in that intravenous administration of PolyTran nanoplex, carrying siRNA against human rhomboid family-1 (RHBDF1) gene or Raf-1 gene, silenced the expression of the target genes and resulted in a marked inhibition of tumor growth in MDA-MB-435 and 1483 xenograft models.[56,57]

SUMMARY & FUTURE PERSPECTIVES

Significant progress has been made recently in the development of siRNA therapeutics, with a few ongoing clinical trials and many more to enter clinical testing. Compared to the local siRNA deliveries that were used in many early siRNA clinical trials, systemic siRNA delivery faces more challenges and hurdles that have slowed down the expansion of siRNA therapeutics. With increasing efforts dedicated to the development of more efficient systemic siRNA delivery technologies, it is conceivable that the key delivery hurdles could be overcome and the potential of RNAi-based therapeutics may be realized in a not too distant future.

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BIOGRAPHIES

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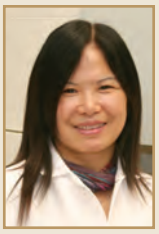
Dr. Qing Zhou is a Director of Pharmacology and Assay Development at Intradigm, focusing on development of targeted siRNA delivery. Previously, he was a Senior Scientist in Abgenix specializing in antibody drug discovery and preclinical research for cancer therapy. He earnned his PhD in Pharmacology from Temple University and completed Post-doctoral training at the University of Southern California in Biochemistry and Molecular Biology.



Ms. Ying Liu is the Head of In Vivo Pharmacology Group at Intradigm Corporation. Before Intradigm, she worked for 6 years at Abgenix, now Amgen, in the Preclinical Department, and 10 years in DNAX Biopharma, Schering-Plough. She earned her MS from SUNY Albany and her BS from Shan Dong University in China.

Dr. Samuel Zalipsky has 2 decades of experience after completion of his PhD work in Chemistry at the University of Minnesota. Except a short stay at Rutgers University as a visiting professor, he spent his career in the biopharma industry, contributing to several commercialized technologies. His areas of expertise include carrier mediated drug delivery, liposomes, bioconjugates, and biocompatible polymers. He authored over 80 papers and has 45 US patents. He currently serves as a VP of Technology at Intradigm. Previously, he was Senior Research Fellow at ALZA/Johnson & Johnson, where he was engaged in development of peptide/protein delivery methods and in targeted liposomal delivery of oncologics. Earlier positions include Senior Research Investigator at SEQUUS Pharmaceuticals and Director of Chemistry Research at ENZON.

Dr. Xiaodong Yang is Vice President of Research and Preclinical Development at Intradigm Corporation, where he is in charge of research and development of RNAi-based therapeutics. Dr. Yang was the Oncology Program Team Leader and Senior Director of Cancer Pharmacology at Abgenix, responsible for setting strategy and managing oncology project portfolio and corporate partnerships. Dr. Yang earned his MD from Peking University and was awarded his Doctorate in Immunology from the University of Bern. He completed his Post-doctoral training at Novartis and Stanford University.

DEVELOPMENT STRATEGIES

Speeding Drugs With Non-Traditional Delivery Mechanisms to Market

By: Robert R. Andrews, MS, MBA, and Russell L. Newton, MS

INTRODUCTION

With the impending 2012 expiration of numerous long-held, extremely profitable patents and intense competition from generic drug manufacturers, the pressure is on Big Pharma to fill the pipeline with high-margin breakthrough drugs.[1] Due to pain, inconvenience, incomplete absorption, and other well-known drawbacks of drugs delivered orally and by injection, significant research resources are being dedicated to develop novel delivery systems for highly demanded drugs. Whether incorporating a liquid drug into a transdermal patch or converting a tablet into a powder form for inhalation, developing non-traditional delivery methods for drugs can provide a new path to a profitable product.

While most drug development processes are plagued by high costs (now exceeding $1.2 billion according to the Tufts Center for the Study of Drug Development), long development cycles (typically 7 to 12 years), and intense regulation, these issues can be complicated when developing drugs with non-traditional delivery mechanisms.[2] The inability of many top-notch companies to bring an inhalable insulin product to market is evidence of the significant challenges.

The following provides guidance on how to overcome the most commonly encountered issues in developing non-traditionally delivered drugs. Evaluating critical drug development parameters early in the process can avoid costly late-stage revamping and speed drugs to market.

DESIGNING THE DELIVERY DEVICE

A fundamental ingredient in a successful non-traditionally delivered drug is the design of the delivery device itself, which is essential to ensure consistent delivery over time. Unfortunately, firms often do not test the delivery mechanism of the drug until the last few years of the development process. By this point, if certain conditions are preventing the device from adequately delivering the dosage stated in clinical data and the FDA submission and from being effective, serious delays will result. At this point, changes with regard to formulation, particle size, and other drug characteristics will be extremely costly and time-consuming because extensive testing has been completed. It is therefore critical to plan for the drug delivery mechanism and establish requirements for the delivery device in the early stages of drug development.

The first step in designing the delivery device is identifying the key drivers for reliable delivery at all user conditions and designing for these characteristics. It is important to consider the characteristics of the drug itself and the effects of the delivery system on the drug.

The requirements specification needs to be developed to ensure that the device meets the intended use. Extensive program and product risk analysis, including hazards, FMEA, and FMECA analyses throughout the development program are important factors for a successful product introduction.

Drug Characteristics

For inhaled therapies, the drug's particle size distribution is one characteristic that will dictate the design of the delivery device in terms of its orifice size. Drugs with larger particle sizes will require larger orifices. The orifice size should accommodate the particulate sizes at the upper end of the particle distribution curve to avoid clogging or caking, which can cause variability in the dosage.

The drug's molecular weight and particle size in addition to the

viscosity of the generated aerosol will dictate the amount of pressure and temperature required for effective delivery. The higher the viscosity of a given aerosol, the higher the delivery pressure must be.

Delivery System's Effect on Drug

The delivery device should be designed so that it does not alter the drug's characteristics. Pressure must be controlled through proper design of the device's orifices and device geometry. While adequate pressure is essential for consistent delivery, extreme pressure can cause higher temperatures, which can alter drug particles and affect the drug's efficacy.

Additionally, the device must protect against a significant change in the bulk viscosity of the delivery aerosol in the anticipated temperature range of use. If significant bulk viscosity change takes place in the temperature range of 65° F and 75° F, for example, there will be variability in the amount of drug delivered depending on whether the user is indoors or outdoors. In such a case, the delivery device must isolate the aerosol from changes in ambient temperature.

Lastly, the drug's residence time, or the time that it will be present in the delivery system, should be evaluated, especially for heat-sensitive drugs. Residence time may need to be minimized to prevent alteration of the drug's characteristics.

REVIEWING PACKAGING MATERIALS

Special attention must be paid to selecting materials for single-dose packaging for drugs with non-traditional delivery mechanisms. For example, static-dissipative packaging materials are not as essential for liquid-based drugs as they are for powder-based drugs. Powdered pharmaceuticals must be packaged in environments with some level of humidity in order to control static, typically in the 20% to 40% range. In addition, static dissipation mechanisms may need to be built into the bulk packaging to prevent accumulation of static charge in individual packages. Options include integrating conductive surfaces on the inside of the bulk packaging to prevent static electric charges from accumulating on individual doses.

Another critical consideration is the surface tension of the drug. For tablet-form drugs, surface tension is a non-issue, while for liquid and suspension-form drugs, surface tension is one of the most important factors in selecting a packaging material.

Retention of drug in the package can also be affected by the wettability of the packaging material, with non-wettable materials more prone to retain the drug. Studies should be conducted to ensure that there is no interaction between the drug and the packaging material throughout the life of the package. In addition, adhesion of the drug to the package must be tested, and materials that do not retain drug or do so consistently in a predictable manner should be selected.

Packaging must be designed to be opened in a manner that will not disrupt the delivery process. Difficult-to-open packages can lead to loss of drug. Lastly, drug packaging materials must maintain their integrity throughout shipping and storage.

EFFECTS OF THE SUPPLY CHAIN ON DRUG DELIVERY

The entire supply chain must be assessed when developing a drug for non-traditional delivery. For quality drug consistency and consistent delivery, it is important to consider the environmental conditions the pharmaceutical will encounter from packaging at the plant through shipping and storage at the pharmacy until final consumption by the patient.

In terms of variability caused by conditions such as temperature, humidity, and vibration, not all drug formats are equally affected. As one example, drugs delivered in tablet form are typically not as affected by supply chain conditions as are powdered drugs that are inhaled. When adopting a non-traditional delivery mechanism, drug efficacy must be re-evaluated after exposure to all possible environmental conditions that may be experienced in the warehouse, during shipping and in storage at the customer use site. Otherwise there is risk of variability in the drug performance and delivery that was never indicated during clinical trials.

Storage

During storage, whether in warehouse facilities or at the customer site, it is important to consider how environmental conditions may affect the drug. The effects of temperature on drug efficacy and delivery have been widely studied. However, drugs using new delivery mechanisms may subject the drug to more stress. Therefore, the product needs to be tested for shelf-life and proven to maintain performance.

Shipping

As during storage, the temperature and humidity during transit must be controlled to avoid altering a drug's efficacy or delivery efficiency. It is important to test the product's sensitivity to temperature and humidity while in its shipping container by subjecting it to appropriate extremes that may be encountered and identifying if there is

any resulting variation in drug efficacy.

Vibration can also cause differing effects on drugs in various formats. For inhaled powdered drugs, exposure to vibration during shipping can alter distribution inside the individual drug containment system and erode the ability of the delivery device to provide uniform delivery during patient use. It should be noted that the goal is not to necessarily deliver 100% of the drug from a dose package. The goal, rather, is to have each individual package reliably deliver the same amount of drug so the patient receives consistent dosages over time.

To identify vibration-caused delivery variation, tests should be conducted to evaluate a drug's delivery mechanism after exposure to vibration at different orientations for different periods of time. Testing should uncover how much drug is delivered by the delivery mechanism and if there is variability dose-to-dose.

If delivery variation is occurring, several steps can be taken to correct the issue. First, packing the individual drug containment systems at the same orientation inside the bulk package will ensure that all doses are affected uniformly during transport, leading to consistent delivery. Shipping containers can be designed with isolating devices and padding to dampen the effects of vibration. They can also include devices that indicate when a product has been subjected to vibration severe enough to cause product damage. Drug containment systems can be pre-conditioned by subjecting them to vibration using a controlled system before shipping to ensure the effects of vibration during shipping are negligible (see Side Bar).

Barometric pressure drops experienced during air transportation can affect the distribution of powdered drugs within a package and affect dosage. They can also affect the integrity of packaging materials and compromise sterility. Environmental chambers can be used to simulate conditions during air transportation to test how the drug might be affected.

Other important aspects to consider are the length of time the pharmaceutical is able to be exposed to the temperature conditions experienced in shipping and the strength of the shipping container.

SUMMARY

Drugs with novel delivery systems offer many advantages to patients in terms of ease-of-use, convenience, and efficacy. They also offer great promise to those pharmaceutical companies that can bring them to market most quickly. To rapidly and efficiently develop successful drugs with non-traditional delivery mechanisms, planning for and testing the delivery mechanism is crucial. When new drug delivery systems are used, the delivery device needs to be developed with attention to product and project risk analysis to ensure a successful development program. In addition, nothing can be assumed based on prior experience, and all materials and components need to be reevaluated for that specific system.

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SIDEBAR

Conditioning as a Late-Stage Solution

If after accounting for all of the issues described thus far, it is discovered late in the development cycle that the tested drug-delivery device combination is not performing well, it appears that the only option is the extremely burdensome process of altering drug particle size or formulation. However, to ensure adequate delivery of the pharmaceutical and reduce dosage variability, conditioning processes can be used. First, conditioning the actual compound, for example through a drying step that does not alter its composition, can serve to avoid retention of the drug in the package. This method will avoid the need to conduct costly retesting due to revision of the drug's composition. Additionally, the drug's packaging material can be conditioned, for example by coating the surfaces of the container. Coating can reduce variability in the amount of drug retained in the package to facilitate a more consistent dosage over time.

BIOGRAPHIES

Mr. Robert R. Andrews is Medical Division Manager for the Commercial Equipment Group at Foster-Miller Inc., part of the Technology Solutions Group of QinetiQ North America. He has more than 30 years of medical device experience managing product development and operations. He has 11 issued US medical device patents and has written and published numerous articles for various medical and academic publications. He earned his MBA from Bryant College and his BS and MS in Plastics Engineering from The University of Lowell. He can be contacted at (781) 684-4639 or randrews@foster-miller.com.

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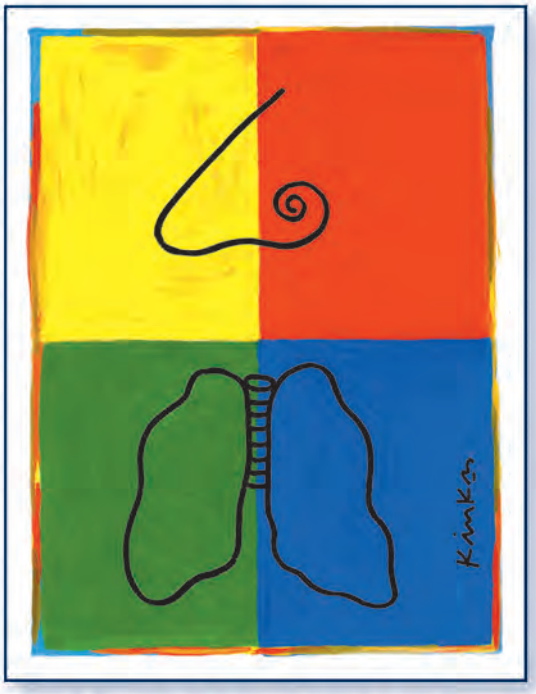

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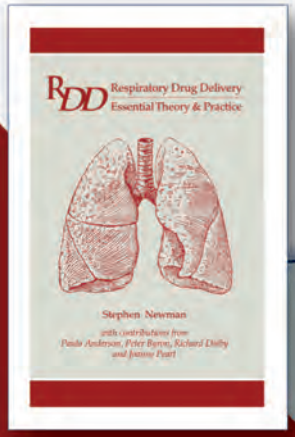

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PREFILLED SYRINGES

A Rational Approach to Determining the Maximum Allowable Gas Bubble Inside a Prefilled Syringe to Minimize Stopper Movement & Protect Product Sterility

By: Shawn Kinney, PhD; Andrea Wagner, PhD; and Christian W. Phillips

ABSTRACT

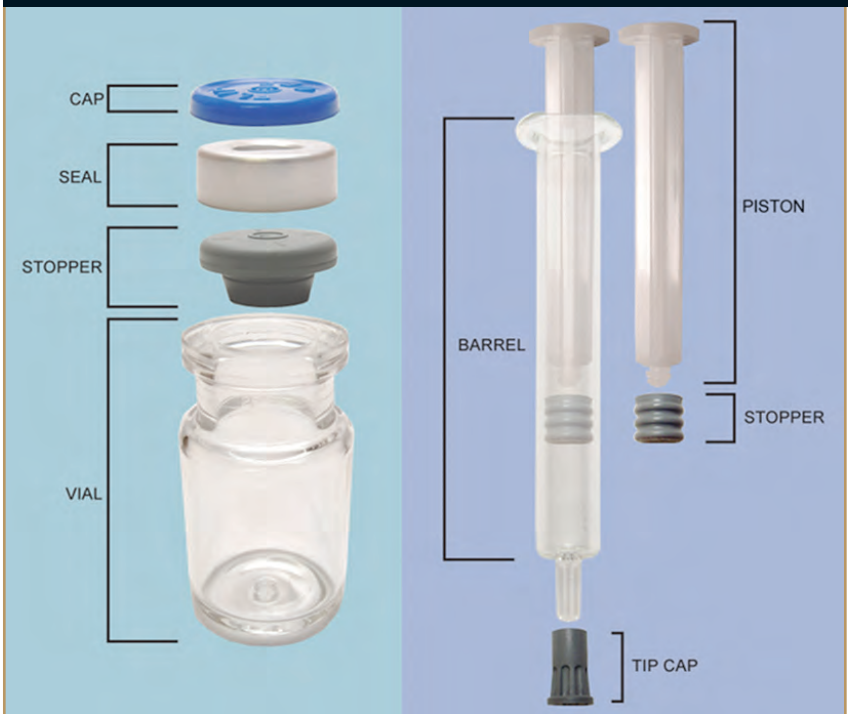
Prefilled syringes are a fast-growing alternative to vials in the parenteral product market due to the many advantages they offer relative to vials. These include reduced overfill requirements, ease of use, more accurate dosing, decreased waste, and enhanced product differentiation.

Conventional syringe-filling processes typically leave a large air bubble in a syringe that can negatively impact product sterility and package integrity. Using a series of equations and hypothetical scenarios, this article will demonstrate the potential impact of a bubble on stopper movement during periods of reduced atmospheric pressure. It will also propose a rational approach for determining the maximum allowable size of a gas bubble inside a prefilled syringe taking into account several critical factors. After weighing some of the alternatives for limiting stopper movement during shipping as well as one additional benefit of bubble-free filling, this article will make the case that reducing or eliminating the bubble inside a prefilled syringe is a preferred means for ensuring product sterility while enhancing the benefits of a prefilled syringe.

INTRODUCTION

The internal environments of a glass vial and a glass syringe have a number of features in common, as shown in Figure 1. Both presentations are essentially glass cylinders that are sealed by an elastomeric closure, or stopper, and both contain a gaseous headspace, or bubble. However, there is one noteworthy difference. A vial's stopper is held in place by a crimp, while a syringe's stopper is designed to move in order to allow injection of the drug product. This freedom of movement, when coupled with a gas bubble (which is not intrinsic to a syringe but is a byproduct of sub-optimal filling processes) can potentially cause significant challenges with regard to package integrity and product sterility, particularly when the syringe is exposed to repeated changes in atmospheric pressure, such as during shipping. Reducing or eliminating the

FIGURE 1



Comparison of a vial and a syringe. Both are essentially glass tubes sealed with an elastomeric closure and contain a gas headspace.

bubble inside the syringe would limit stopper movement, potentially enhancing sterility assurance of the product.[1]

In a preliminary study of the impact of a bubble on stopper movement in a prefilled syringe, three syringes were placed inside a Hypak vacuum chamber. One syringe contained a 2.5-mm bubble, one a 5.0-mm bubble, and yet another contained no bubble at all. Next, a vacuum was pulled at 8 inches of mercury and then again at 15 inches while the syringes were closely monitored for signs of stopper movement. The procedure was then repeated five more times, with a new set of syringes each time, to substantiate the initial findings, which included the following:

- In the syringes containing a bubble, the stopper was seen rising into non-sterile areas of the syringe barrel each time the vacuum was pulled.
- In the syringes containing no gas bubble, however, the stopper was not seen rising at all.
- The size of the bubble inside the syringe made a difference in the amount of stopper movement. The syringes filled with a 2.5-mm bubble experienced less movement than the syringes filled with a 5.0-mm bubble. When the vacuum was released and the pressure returned to original levels, the stoppers in the syringes containing a bubble returned to their original position with no indication that they had moved.

Due to the difficulty of controlling for all of the variables that affect stopper movement in a prefilled syringe, a series of equations were devised to show, on a theoretical level, the relationship between the size of the gas bubble and stopper movement. Using Boyle's Law, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to changes in pressure, and the amount of stopper movement that occurs as a result of that expansion and contraction was calculated.

TABLE 1

Gas Bubble Size	H_{sb} = 6.2 mm Approximate Elevation (1,000s ft)	H_{sb} = 4.3 mm Approximate Elevation (1,000's ft)
0.5 mm	21	19
1.0 mm	16	14
2.5 mm	13	7
5.0 mm	7	<5

Approximate elevation (in feet above sea level) at which a stopper will have moved 1/5 H_{sb}.

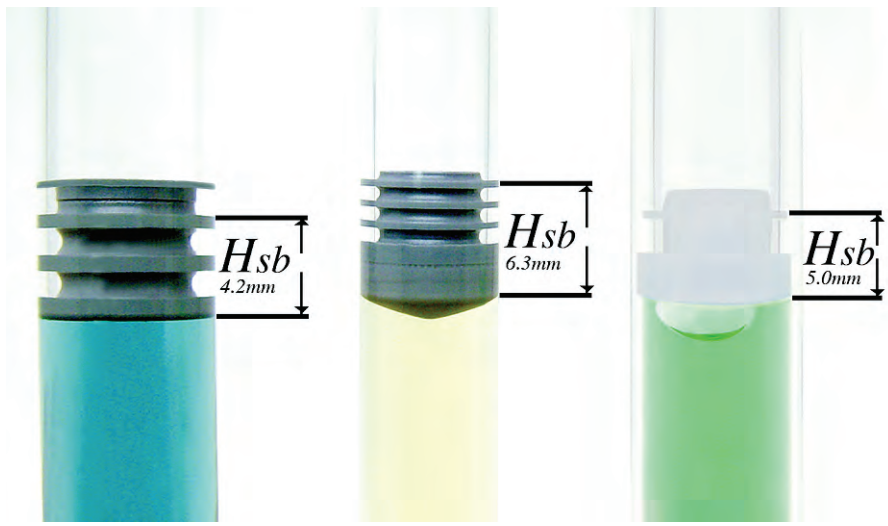
Plugging these calculations into a hypothetical situation in which a syringe is shipped multiple times from the manufacturer to the end-user, a rational approach was developed for determining the maximum allowable size of a gas bubble inside a prefilled syringe. Among the factors taken into account were stopper height, the elevations to which a syringe will likely be exposed and the consequent changes in pressure which it will undergo, as well as the number of times a syringe will be subjected to reduced atmospheric pressure.

STERILE BARRIER HEIGHT: H_{SB}

In a prefilled syringe, a sterile barrier is created in which the stopper is in intimate contact with the glass barrel of the syringe, as shown in Figure 2. The sterile barrier height, or H_{sb}, spans the entire distance from the uppermost to the lowermost point of stopper contact and represents the limit of upward stopper movement, which the stopper can undergo before product sterility is potentially compromised.

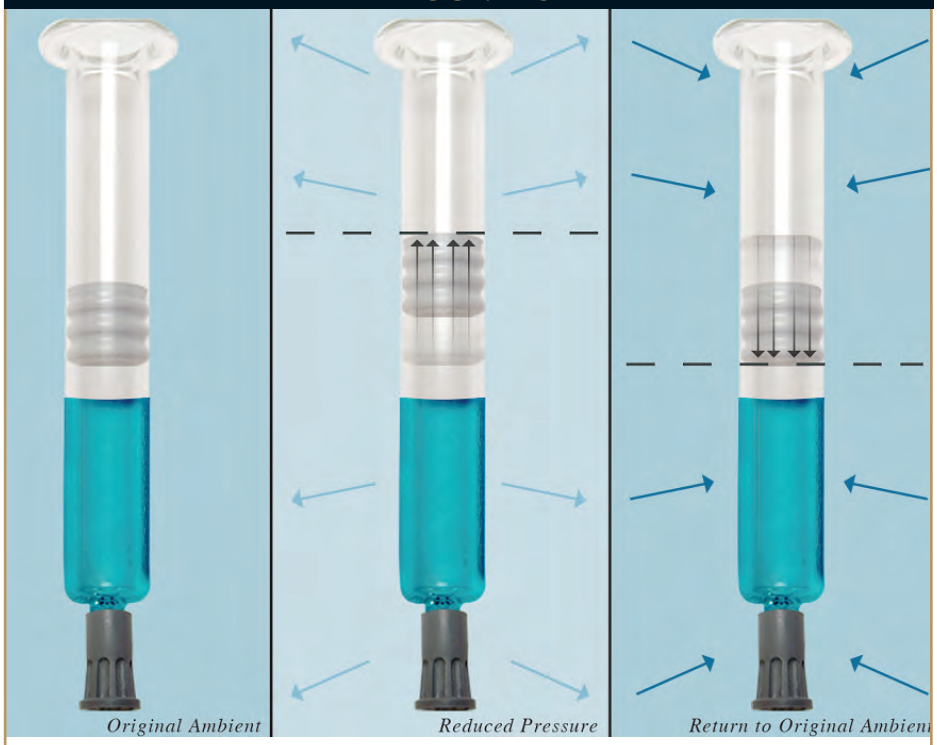
A gas bubble sealed inside a prefilled syringe acts like a spring, expanding and contracting with changes in temperature or external ambient pressure. If the external ambient temperature increases or pressure decreases, the gas bubble expands, pushing the stopper up until the pressure in the syringe is equivalent to the external pressure. When the external ambient pressure and/or temperature return to their original levels, the gas bubble in the syringe contracts until the pressure in the syringe is equal to the external pressure. This causes the stopper to return to its

FIGURE 2



Syringes and stoppers. The distance from the uppermost to the lowermost point of contact between the stopper and the syringe is known as the sterile barrier height or H_{sb}.

FIGURE 3



A gas bubble will expand or contract under changes in ambient pressure. This expansion/contraction will cause stopper movement in a syringe with no visible evidence that the stopper has moved when external conditions are returned to their original levels.

original position, leaving no visible evidence that the stopper has moved (Figure 3).[2]

If the stopper in a syringe moves more than the distance of H_{sb}, it can pull microorganisms or contaminants from the non-sterile portion of the syringe into the drug product, potentially causing a sterility failure. This same phenomenon could occur when a stopper moves less than the distance of H_{sb} if it moves multiple times and the sum of all stopper movements exceeds H_{sb}, as demonstrated in Figure 4.

PRESSURE & THE VOLUME OF A GAS BUBBLE

The amount of change in the volume of a gas bubble is relatively small over the reasonable temperatures to which a syringe might be exposed (total range of approximately 40ºC); however, the volume change due to pressure changes alone can be significant, as demonstrated in the calculations that appear further on.

Assuming that temperature remains constant, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to pressure changes can be calculated using Boyle's Law (Equation 1).

Equation 1.

$$P_1V_1 = P_2V_2$$

Where P_1 = pressure condition 1, V_1 = volume condition 1, P_2 = pressure condition 2, and V_2 = volume condition 2. The volume (V) of a cylinder, such as a syringe, is given by Equation 2.

Equation 2.

$$V = \pi r^2 h$$

Where r = internal radius of the syringe barrel, and h = height of the gas bubble/air gap (assuming the bubble spans the entire diameter of the syringe). If Equation 2 is substituted for V in Equation 1, and both sides are divided by πr^2, the result is as Equation 3.

Equation 3.

$$P_1h_1 = P_2h_2$$

Where P_1 = pressure condition 1, h_1 = height condition 1, P_2 = pressure condition 2, and h_2 = height condition 2. Thus in Equation 4, the theoretical height of the gas space in the syringe at a given external pressure can be determined based on the initial conditions (condition 1).[2]

Equation 4.

$$h_2 = P_1h_1/P_2$$

The percentage of total stopper movement beyond the initial sterility barrier (H_{sb}) can be calculated by subtracting the initial height (H_1) from the height calculated in Equation 4 (H_2) and dividing the result by Hsb, as shown in Equation 5.

Equation 5.

$$\text{Percent } H_{sb} = 100*(H_2 - H_1)/H_{sb}$$

Figures 5b and 5c show the percentage of H_{sb} that a stopper will move in syringes with an H_{sb} of 6.2 and 4.3 mm, respectively, and initial bubble sizes ranging from 0.5 mm to 5 mm, the most common size range for a bubble. The points on the x axis in Figures 5b and 5c represent feet of elevation rather than absolute pressure to demonstrate the effect that reduced pressure (due to changes in elevation) will have on a syringe. These points were determined using a conversion of 1 inch Hg vacuum equal to 1000 feet of elevation (Figure 5a).

The *y* axis in Figures 5b and 5c represents the percentage of H_{sb}, which the stopper in a syringe will move, while the red line at 100% shows the point at which the stopper will enter a non-sterile area of the syringe, potentially compromising product sterility.

In the example in Figure 5b, in which H_{sb} is 6.2 mm and the initial bubble size is 2.5 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 23,000 feet. When the initial bubble is 5.0 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 20,000 feet.[2]

Because the cargo hold of an airplane is generally maintained at a pressure equal to 8,000 feet of elevation, and ground elevations during shipment do not often exceed 10,000 feet, a stopper is not likely to move more than H_{sb} in a single exposure. However, during shipment, a syringe could possibly be exposed to reduced pressure on several occasions which, taken together, increases the potential for total stopper movement to exceed H_{sb}.

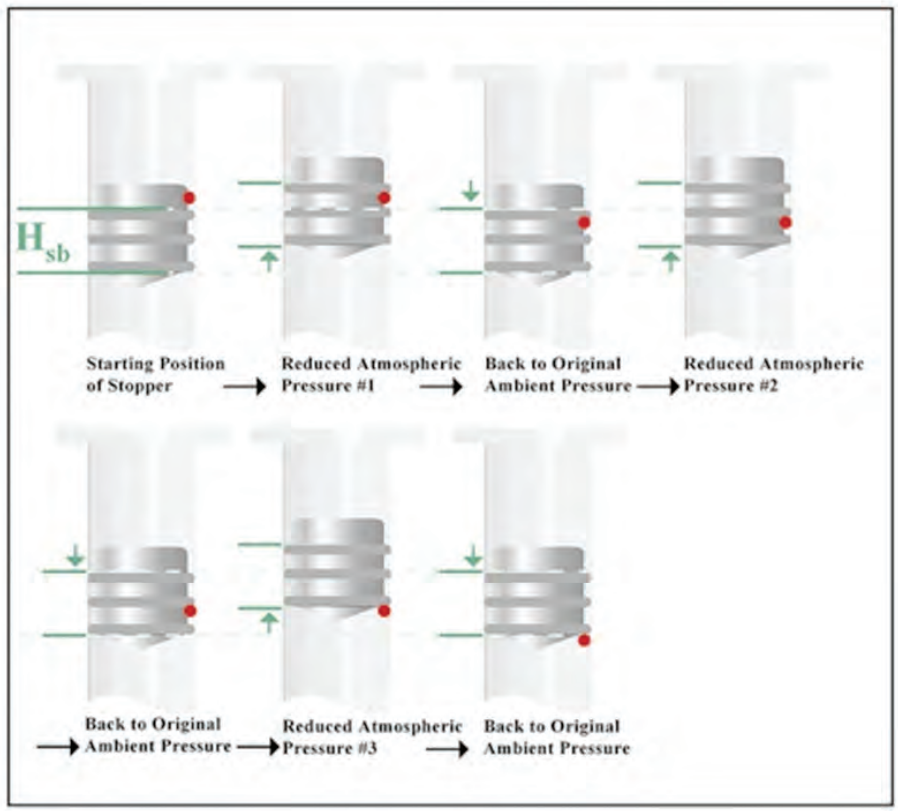
Consider, for example, a syringe that is shipped from a CMO's manufacturing site to the sponsor company's facility to a distribution center and finally to the end-user's site, for a total of three shipments. It is possible that one or more legs of the product's journey could involve more than one flight, creating additional opportunities for the stopper to rise and fall. Under those conditions, it is conceivable that a syringe could be exposed to changes in pressure on five occasions, resulting in five up and down stopper movements. In that case, a stopper would only need to rise 1/5 H_{sb} each time to potentially pull non-sterile material, such as silicon, or other contaminants into the product causing a sterility failure.

Table 1 shows the approximate elevations at which the stopper would exceed 1/5 of H_{sb} given several different sized bubbles. To prevent stopper movement as a result of changes in ambient pressure, syringes should ideally be filled without any gas bubbles. However, in practice, most syringe filling equipment does not have the capability to remove all of the gas in a syringe. When that is the case, the maximum acceptable size of a gas bubble for a given stopper in a prefilled syringe should be determined. This can be done by factoring in the differential pressure changes to which a syringe will likely be exposed, the number of times it will be subjected to reduced pressure, and the height of the sterile barrier.

DETERMINING THE MAXIMUM SIZE OF A GAS BUBBLE

Using the aforementioned equations, the size of the bubble that will lead to a movement of the stopper equal to 1/5 of H_{sb} can be calculated at a number of different elevations. For example, Figure 6 shows the results of calculations performed using elevations of 8,000 and 12,000 feet with a range of H_{sb} from 1 to 15 mm. In situations where H_{sb} is 4.0 and elevation is 8,000 feet, the maximum acceptable size of the gas bubble is approximately 2.0 mm. When the elevation reaches 12,000 feet, however, the maximum acceptable size of the gas bubble decreases to approximately 1.6 mm.[2] The aforementioned analysis is a worst-case scenario and does not take into account frictional forces and break loose forces. Frictional forces caused by the stopper rubbing against the syringe, and the break loose force, which is required to start the stopper moving, should reduce stopper movement. Break loose forces, which increase over the life of the syringe, would improve resistance to stopper movement the longer the product was in transit, requiring greater force to initiate the movement of the stopper. However, it is not unreasonable to assume that a newly filled prefilled glass syringe with silicon has very little break loose force. In fact, we have confirmed in our laboratories that standard, commercially available glass syringes and elastomeric stoppers with silicon show actual stopper movement that is approximately 75% of that which has been theoretically calculated in this article. We did not perform an extensive study of all factors that could affect glide and breakloose forces; therefore, we have used theoretical calculations to demonstrate

FIGURE 4



If the stopper moves more than H_{sb}, contaminants may be pulled into the sterile liquid. This effect can occur with multiple movements if the sum of all stopper movements exceeds H_{sb}.

several worst-case scenarios for stopper movement.

The aforementioned analysis is also based on the assumption that pressures are controlled at consistent levels throughout shipment when, in fact, the actual magnitude of reduced/increased pressure to which syringes are exposed is generally not known. Cargo is shipped by a variety of carriers, many of whom may not consistently control, measure, or report changes in pressure. Atmospheric pressure in a cargo hold could rise and fall during flight, and the drug manufacturer would not be aware of it upon inspection at the final destination.

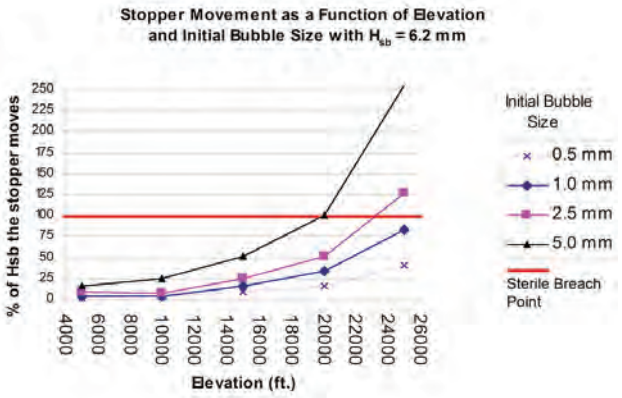
There are alternative means to prevent contamination due to stopper movement other than reducing the size of the gas bubble or increasing H_{sb}. For example, the stopper can be locked in place with a device placed inside the barrel, or the entire syringe can be sealed inside a sterile container (protecting the sterility of the barrel above the stopper), or the syringe can be placed in a holder that secures the plunger rod in place. However, each of these approaches adds cost and requires additional packaging and does not provide the added benefits of a bubble-free syringe.

FIGURE 5A

Elevation	" Hg Vac.	psi	torr
0	0	14.7	760
8,000	8"	10.7	555
10,000	10"	9.8	506
12,000	12"	8.9	455
15,000	15"	7.3	379
18,000	18"	5.9	302
25,000	25"	2.4	125
27,000	27"	1.4	74

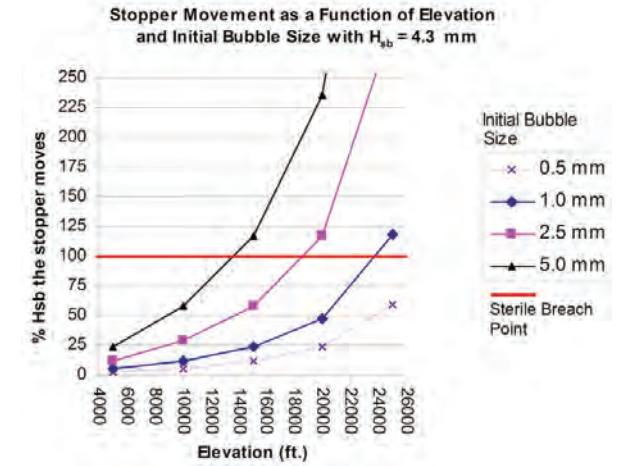
Conversion of 1-inch Hg vacuum equal to 1000 feet of elevation.

FIGURE 5B



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 6.2 mm.

FIGURE 5C



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 4.3 mm.

ELIMINATING PRODUCT LOSS

One added benefit of a bubble-free syringe is the reduction in the amount of product inadvertently lost during use. In a side-by-side analysis, 15 syringes were filled with gas bubbles of varying sizes, while 15 syringes were filled with no bubble. As the tip caps on each set of syringes were removed, the needles were watched for any sign of dripping or product leaks. In the set that were filled with a bubble, product was observed leaking from needle over 75% of the time when the tip cap was removed. Conversely, in the needles that were bubble-free, no product was seen leaking from the needle any time the tip caps were removed (Figure 7).[2]

This is because in a bubble-free syringe, there is no expansion and contraction of the bubble as a result of the small vacuum that is created when the tip cap is removed. Without a drip, there is added assurance that the end-user will receive the entire deliverable dose. There is also less risk that the administrator or end-user will be exposed to cytotoxic or potent compounds, as well as a reduction in product wasted.

CONCLUSION

Although, on the surface, syringes may appear very similar to vials, the freedom of stopper movement in a prefilled syringe, coupled with a gas bubble, will result in challenges to package integrity and product sterility when the syringe is exposed to changes in atmospheric pressure. A gas bubble is not intrinsic to a syringe but is the result of a sub-optimal filling process and therefore, can be reduced or eliminated using alternative filling methods.

Manufacturers go to great lengths to monitor and control the temperature to which products are exposed during shipping. Yet the same attention has not been paid to changes in differential pressures to which a product is exposed. Given that a number of today's parenteral products are shipped several times before reaching the end-user, undergoing several changes in atmospheric pressure and several potential

movements of the stopper, such attention is warranted. Just as exposure to elevated temperatures may impact the shelf-life and efficacy of products, exposure to reduced pressure may potentially impact the sterility and safety of an injectable product in a prefilled syringe if one is not aware of the importance of reduced bubble size and stopper design.

In this discussion, we have proposed one way to determine the maximum acceptable size of a gas bubble that can be left inside a syringe based on stopper height as well as other variables. There are alternative ways to protect prefilled syringes from contamination due to stopper movement, but these require additional packaging and do not offer the added benefits of a bubble-free syringe, such as enhanced dosing accuracy and safety as well as reduced waste due to the elimination of a product drip at the needle when the tip cap is removed.[3]

As prefilled syringes continue to find favor as an alternative to vials for many of today's parenteral products, reduced gas bubble filling should likewise become increasingly popular as an alternative to traditional filling methods and may one day become the industry standard.

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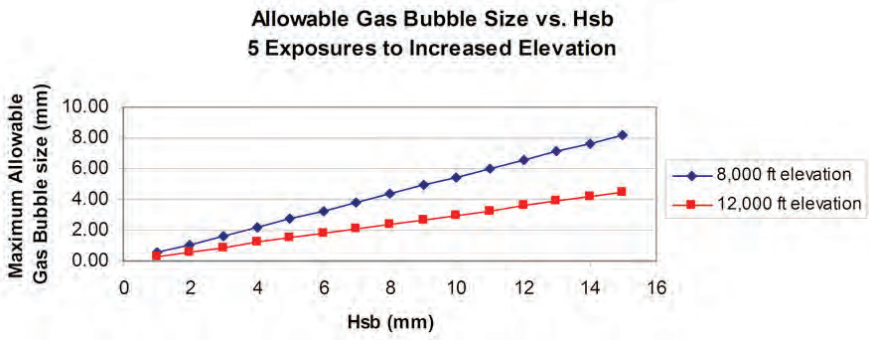
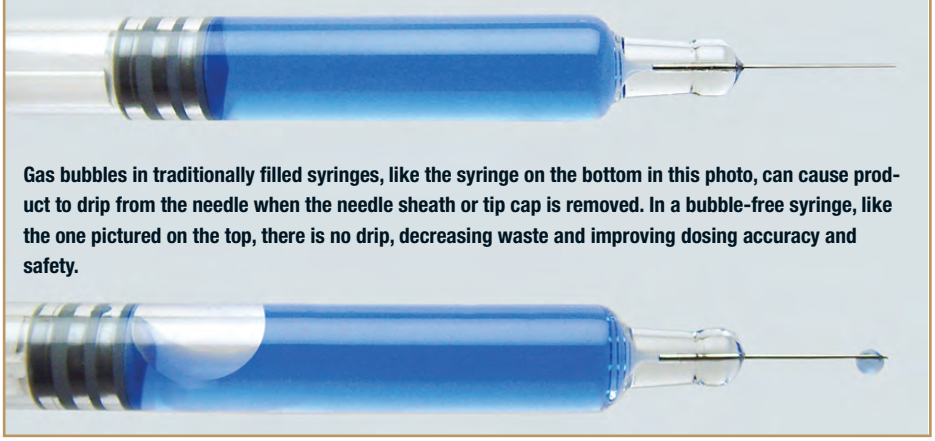
FIGURE 6



The data demonstrates that smaller gas bubbles and stoppers with larger H_{sb} reduce the risk of stopper movement exceeding 1/5 H_{sb}.

FIGURE 7



Gas bubbles in traditionally filled syringes, like the syringe on the bottom in this photo, can cause product to drip from the needle when the needle sheath or tip cap is removed. In a bubble-free syringe, like the one pictured on the top, there is no drip, decreasing waste and improving dosing accuracy and safety.

BIOGRAPHIES

Dr. Shawn D. Kinney, President of Hyaluron Contract Manufacturing (HCM), founded HCM in 1999 to provide aseptic manufacturing and filling services to the pharmaceutical, biotech, and medical device industries. Dr. Kinney earned his PhD in Chemistry from the University of Massachusetts at Amherst, a Masters in Medicinal Chemistry from Northeastern University, and a BS in Chemistry from the University of Massachusetts at North Dartmouth. Dr. Kinney has worked at Anika Therapeutics, Wyeth-Ayerst, and Millipore and has more than 20 years of experience in the pharmaceutical industry. He has extensive experience in the development of sterile formulation and filling processes, including viscous and difficult-to-fill products. Prior to founding HCM, he was responsible for the sterile formulation and filling of hyaluronate into prefilled syringes in his role as VP of Operations at Anika Therapeutics. Recently, Dr. Kinney has pioneered a new technology in online vacuum filling and stoppering (Bubble-Free Filling®) and has been granted a patent. He continues to oversee HCM's expansion and leadership in the aseptic contract manufacturing industry. He can be reached at shawn@hyaluron.com or (781) 270-7900, ext. 218.

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Christian W. Phillips is the Director of Process Engineering, at HCM. Mr. Phillips has 14 years of experience in R&D, Process Development, Tech Transfer, and Manufacturing environments suited for the introduction of novel biotherapeutics and generics, including fill/finish applications. Prior to HCM, Mr. Phillips was employed by Transkaryotic Therapies (now Shire HGS). Mr. Phillips earned his BS in Biology from St. Michael's College and is the co-inventor with Shawn Kinney of HCM's Bubble-Free Filling® technology. He can be reached at cphillips@hyaluron.com or (781) 270-7900, ext. 181.

NANOTECHNOLOGY

Nanoparticles in Cancer Research: A Novel Drug Delivery & Pharmacological Approach

By: Priyal Patel (PhD student), Maulik A. Acharya, and Jayvadan Patel, PhD

ABSTRACT

This review explores recent work directed toward more targeted treatment of cancer, whether through more specific anticancer agents or through methods of delivery. Nanoparticles are tiny materials (1000 nm) that have specific physico-chemical properties different to bulk materials of the same composition, and such properties make them very attractive for commercial and medical development. However, nanoparticles can act on living cells at the nano level, resulting not only in biologically desirable, but also undesirable effects. In contrast to many efforts aimed at exploiting desirable properties of nanoparticles for medicine, there are limited attempts to evaluate potentially undesirable effects of these particles when administered intentionally for medical purposes. Therefore, there is a pressing need for careful consideration of benefits and side effects of the use of nanoparticles in medicine. This review aims to provide a balanced update of these exciting pharmacological and potentially toxicological developments as well as discuss the classes of nanoparticles, the current status of nanoparticle use in pharmacology and therapeutics, and the demonstrated and potential toxicity of nanoparticles.

INTRODUCTION

Cancer was once considered an incurable disease, but today, most patients diagnosed with early stages of many cancers will survive their illness. Advances in cancer diagnostics and therapeutics throughout the past few decades are largely responsible for this significant improvement. Despite these advances, cancer remains the second leading cause of death in the world. The most common cancer treatments are limited to chemotherapy, radiation, and surgery. Limitations in cancer treatment are a result of current challenges seen in cancer therapies today, including lack of early disease detection, non-specific systemic distribution, inadequate drug concentrations reaching the tumor, and inability to monitor therapeutic responses. Poor drug delivery and residence at the target site leads to significant complications, such as multi-drug resistance. Nanotechnology has the potential to offer solutions to these current obstacles in cancer therapies because of its unique size (1 to 100 nm) and large surface-to-volume ratios.[1]

Nanoparticle size, toxicity, status, and applications are discussed in Table 1.

OVERVIEW OF DIFFERENT CLASS OF NANOPARTICLES

Liposomes

Liposomes are nanoparticles comprising lipid bilayer membranes surrounding an aqueous interior. The amphilic molecules used for the preparation of these compounds have similarities with biological membranes and have been used for improving the efficacy and safety of different drugs. Usually, liposomes are classified into three categories on the basis of their size and lamellarity (number of bilayers): small unilamellar vesicles or oligolamellar, large unilamellar vesicles, and multilamellar vesicles. The active compound can be located in the aqueous spaces (if it is water-soluble) or in the lipid membrane (if it is lipid-soluble). Recently, a new generation of liposomes called “stealth liposomes” have been developed. Stealth liposomes have the ability to evade interception by the immune system, resulting in a longer half-life.[2]

Emulsions

Emulsions comprise oil-in-water-type mixtures that are stabilized with surfactants to maintain size and shape. The lipophilic material can be dissolved in a water-organic solvent that is emulsified in an aqueous phase. Like liposomes, emulsions have been used for improving the efficacy and safety of diverse compounds.[3]

Polymers

Polymers, such as polysaccharide chitosan nanoparticles have been used for some time now as a drug delivery system. Recently, water-soluble polymer hybrid constructs have been developed. These are polymer-protein conjugates or polymer-drug conjugates. Polymer conjugation to proteins reduces

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immunogenicity, prolongs plasma half-life, and enhances protein stability. Polymer-drug conjugation promotes tumor targeting through the enhanced permeability and retention effect, and at the cellular level following endocytic capture, allows lysosomotropic drug delivery. Ceramic nanoparticles are inorganic systems with porous characteristics that have recently emerged as drug vehicles.[4]

Dendrimers

Dendrimers have emerged as an important class of drug-encapsulating nanoparticles as a result of their unique architecture and macromolecular characteristics. Dendrimers are synthetic, highly branched, spherical, monodispersed macromolecules with an average diameter of 1.5 to 14.5 nm. A typical dendrimer molecule consists of an initiator core, highly branched layers composed of repeating units, and multiple active terminal groups. The architectural design of dendrimers provides a high level of control over the dendrimer size, shape, branching length, and surface functionality.

Biodegradable polyester dendrimers based on 2,2-bis(hydroxymethyl)-propanoic acid monomers have been developed for intracellular release of doxorubicin after hydrolysis of the hydrazone linkage. The promising properties of polyester dendrimers as a drug delivery system has led to further studies based on tunable architectures and molecular weights to optimize tumor accumulation. In a comparative study with Doxilin C-26 colon carcinoma-bearing mice, the polyester dendrimer drug conjugate shows similar efficacy to the doxorubicin-liposome formulation.[5]

Nucleic Acid-Based Nanoparticles

In nucleic acid-based nanoparticles, DNA and RNA macromolecules can be used as substrates for developing therapeutic and imaging nanocarriers. A multivalent DNA delivery vehicle, with an average size of 100 nm, was recently reported for simultaneous targeted drug delivery, imaging, and gene therapy. Targeted multifunctional RNA nanoparticles (25 to 40 nm) have also been developed with a trivalent RNA core, RNA aptamers for targeting, and siRNAs for therapeutic effect.[6]

Polymeric Nanoshells

Polymeric nanoshells consist of diblock copolymers that can be assembled into a core/shell structure. In general, nanoshells are made by self-assembly of oppositely charged polymers covering the surface of the drug's nanoparticles. Therefore, the drug-release rate is controlled by the chemistry of the polymers and the diffusion coefficient through the polymeric layer. For example, nanoshells encapsulating doxorubicin have been synthesized using amphiphilic tercopolymer poly(N-isopropylacrylamide-co-N,N-dimethylacrylamide-co-10-undecenoicacid) that can trigger intracellular doxorubicin release at pH 6.6.

TABLE 1

Nanoparticle	Size	Toxicity	Status	Application
Liposome	100-200 nm	Low	Clinical use	Delivery
Small Polymer	~200 kDa	Low	Research	Delivery
Dendrimer	2-6 nm depending on generation number	Variable depending on cell type	Phase I	Delivery
Virus	30-100 nm	High	Phase II	Delivery
Hybrid System	-	-	-	-
QD-Virus	Variable	-	Research	Imaging Delivery
Metal Core Dendrimers	2-4 nm for gold	-	Research	Delivery
Nanoshells	60-400 nm	Non-toxic	Research	Imaging, Treatment
Quantum Dots	2-10 nm	Toxic	Commercial	Sensing, Imaging
Carbon Nanotubes		Expected to be non-toxic	Research	Delivery, Sensing
Single-Walled	1-2 nm diameter, variable length	-	-	-
Multi-Walled	20-25 nm diameter, variable length	-	-	-
Nanowires	Variable length/diameter	NA	Research	Sensing

Nanoparticle size, toxicity, status, and application.[6]

Metallic nanoshells, approximately 20 nm in diameter, are characterized by a dielectric core coated with a thin metallic shell to improve their biocompatibility and optical absorption. These particles possess a highly tunable plasmon resonance mediated by the size of the core and the thickness of the shell, which in turn determines their absorbing and scattering properties over a broad range of the spectrum from the near ultraviolet to the mid-infrared.[7]

Gold Shell Nanoparticles

Gold shell nanoparticles, other metal-based agents, are a novel category of spherical nanoparticles consisting of a dielectric core covered by a thin metallic shell, which is typically gold. These particles possess highly favorable optical and chemical properties for biomedical imaging and therapeutic applications.[8]

ROLE OF NANOTECHNOLOGY IN DIAGNOSTICS, PHARMACOLOGY & THERAPEUTICS

Discovery of biomarker nanotechnology is being applied to biomarker-based proteomics and genomics technologies. Nanoparticles can be used for qualitative or quantitative in vivo or ex vivo diagnosis by concentrating, amplifying, and protecting a biomarker from degradation in order to provide more sensitive analysis.[9] Initial studies with magnetic nanoparticle probes coated with antibodies and single "bar code" DNA fragments are able to amplify signals of small abundant biomolecules. This amplification is comparable to polymerase chain reaction (PCR) amplification of nucleotide sequences and can theoretically be used to detect hundreds of protein targets at a time in patient samples. Such analysis would enable physicians to properly diagnose disease at very early stages and begin treatment before severe cellular damage, improving patient prognosis. For instance, in vitro streptadivin-coated fluorescent polystyrene nanoparticles have been used to detect the epidermal growth factor receptor (EGFR) in human epidermoid carcinoma cells by flow cytometry.[10] These results were really successful as nanoparticles enhanced the sensitivity to detect EGFR compared to the conjugate streptadivin-fluorescein. In addition, a nanoparticle oligonucleotide bio-barcode assay has been used to detect small levels of the cancer marker prostate-specific antigen (PSA) in serum. The use of this new technique offers a high ratio of PCR-amplifiable DNA to labeling antibodies that can considerably enhance assay sensitivity.[11] Therefore, a low amount of free serum PSA could be detected in patients suffering from prostate cancer or even women suffering from breast cancer with a great improvement in tumor screening and diagnosis. Molecular diagnosis currently involves imaging diagnosis, which is not limited to a gross description of anatomic structures, but can also involve imaging of cellular signaling.[12]

EXPLORING NANOPARTICLE TOXICITY

Ensuring that nanoparticles are safe for use in humans will be a key factor in determining how big of an impact nanotechnology has on the detection and treatment of cancer. Wendelin Stark, PhD, of the Swiss Federal Institute of Technology in Zurich, and his colleagues used human mesothelioma cells and rodent fibroblast cells to characterize the toxicity of seven industrially important nanoparticles.[13] The investigators also used widely studied nontoxic silica particles and toxic asbestos fibers as reference materials. The investigators dosed each of the two cell lines with varying amounts of the nine materials and measured their effects on cells' metabolic activity and ability to proliferate.[14] One striking finding was that particle solubility strongly influenced toxicity. Low concentrations of soluble zinc oxide particles, for example, triggered a sharp drop in cell metabolism and proliferation. However, at higher concentrations, toxicity actually dropped, likely because zinc oxide particles clump together at the higher concentrations tested. Insoluble metal oxide particles showed virtually no effect on cell function at any concentration.[15] The investigators did observe that uncoated iron oxide particles were particularly toxic regardless of concentration.

In a second report, a team of investigators led by Barbara Rothen-Rutishauser, PhD, and Peter Gehr, PhD, both of the University of Bern, used a variety of advanced microscopic techniques to study how nanoparticles penetrate red blood cell membranes.[16] This team found that both gold and titanium nanoparticles did accumulate in red blood cells despite the absence of endocytosis receptors. This accumulation did not depend on the size or surface charge of the nanoparticles tested. These results, say the investigators, suggest that nanoparticles must cross the cell membrane by an as-yet undiscovered mechanism that needs further investigation. Stark and his colleagues tested compounds against human and rodent cells. They discovered the mildly soluble nanoparticles proved the most acute toxic response of those studied. For instance, the iron oxide nanoparticles appeared astonishingly toxic,

roughly as toxic as the crocidolite asbestos toward human cells. “That was very surprising,” said Stark. Moreover, the zinc oxide nanoparticles reduced cell proliferation more potently than asbestos did in rodent cells.[17] Overall, zinc oxide nanoparticles and asbestos significantly reduced human and rodent cell culture activity the most. The amount of iron oxide used in the nanoparticles for a toxic dose would itself not prove toxic if given in a completely dissolved form. This suggests there may be a toxic effect specific to nanoparticles, such as stress caused by the surface, size, or shape of the particles.[18]

SUMMARY

Nanotechnology is definitely a medical boon; it will radically change the way we diagnose, treat, and prevent cancer to help meet the goal of eliminating suffering and death. The development of engineered nanoparticles with substantial biomedical significance has posed new opportunities and challenges for pharmacology and therapeutics. Nanomaterials and nanoparticles are likely to be cornerstones of innovative nanomedical devices to be used for drug discovery and delivery, discovery of biomarkers, and molecular diagnostics. Although most of the technologies described are promising and fit well with the current methods of treatment, there are still safety concerns associated with the introduction of nanoparticles in the human body. These will require further studies before some of the products can be approved. The diversity of engineered nanoparticles and of several possible side effects represents one of the major challenges for nanopharmacology and therapeutics.[19]

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BIOGRAPHIES

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Achieving Optimal Particle Size Distribution in Inhalation Therapy

By: Thomai (Mimi) Panagiotou, PhD

INTRODUCTION

Inhalation therapy has proven to be an effective method of administering a number of pharmaceuticals for more than a century. However, achieving the optimal particle size for a treatment with particular pharmaceutical formulations has been a troublesome task. This article addresses many of the concerns medical device manufacturers and their pharmaceutical partners have when attempting to achieve the correct particle size for an inhalation device.

Until recently, aerosols were used primarily to deliver locally active drugs to the respiratory system as a means of treating asthma, cystic fibrosis, and other respiratory illnesses. During the past few years, significant advances have occurred in the use of inhalation technology for the administration of systemically active medicines such as insulin. For systemically active drugs, the aerosol particles must be small enough to reach the alveolar surface in peripheral areas of the lung. Pharmaceutical companies are currently developing methods for producing aerosolized formulations containing uniform, optimally sized particles.

BENEFITS OF INHALATION THERAPY

A principal benefit of inhalation therapy is the rapid onset of action, especially when compared to perorally

FIGURE 1

ingested medicine (oral dosages). The fast medicinal action produced by inhalation delivery results from the large absorption area of the lung. For locally acting drugs, the onset of action is immediate. Systemically active inhaled drugs reach the blood stream quickly, within seconds. Rapid onset of action is especially important for rescue medications (ie, asthma products), as well as pain medication and time-sensitive therapies, such as insulin. Patients cannot always afford to wait the 15 minutes or longer it often takes for a tablet to make its way though the gastrointestinal (GI) tract.

Avoiding the GI tract offers, through inhalation therapy, other advantages. Unlike perorally ingested medicine, inhaled drugs are not subjected to the first-pass metabolism effect that significantly reduces bioavailability. After a drug is swallowed, it is absorbed by the digestive system. The absorbed drug is then carried through the portal vein into the liver. Some drugs are so extensively metabolized by the liver that only a small amount of unaltered drug may enter systemic circulation. Further, stomach contents and variable absorption levels among patients add to the variability of bioavailability of the drug.

In addition to the problems of delayed onset of action and reduced bioavailability, perorally ingested medicines can also cause undesirable side-effects in the GI tract. In contrast, medicines that are inhaled are better tolerated by the body, and delivery via the respiratory system provides a friendlier chemical environment that is less destructive to the medicine.

Injected drugs also avoid the problems associated with the GI tract, but needles are invasive by definition. In some instances, the social environment or physical constraints affecting the patient may make it difficult or socially uncomfortable to affect self-injection. Inhaled drugs are perceived as being more user friendly than injections, resulting in better patient compliance for self-administered medications. Inhalation therapies also provide faster onset of action compared to intramuscular injection.

EFFECT OF PARTICLE SIZE

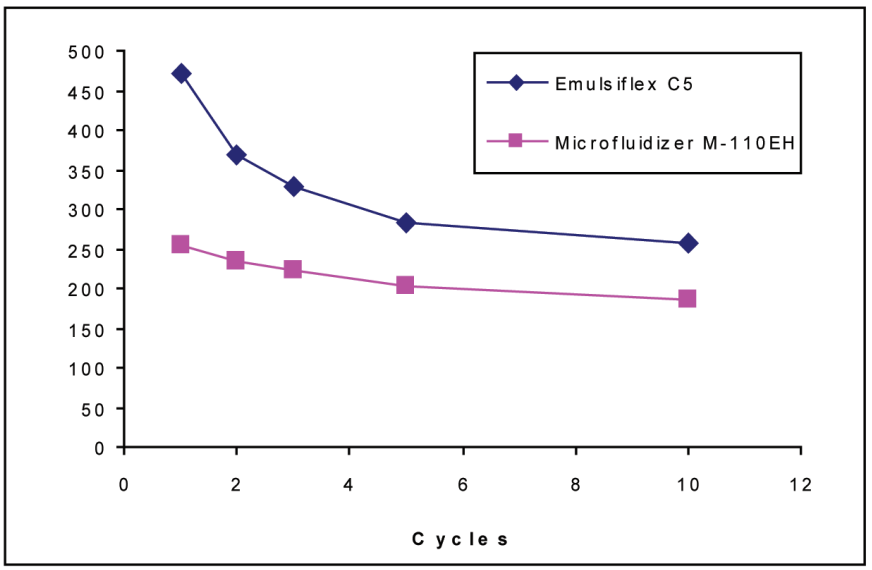
The destination of aerosol particles is critical to the efficaciousness of inhalation therapy. For locally acting drugs, the particles obviously need to be deposited in the area of the respiratory tract requiring treatment. The treatment of asthma, for example, requires that the inhaled drug reach the lower airways in order to achieve the desired therapeutic effect.

For systemically acting drugs, a high percentage of particles needs to reach the alveoli deep in the periphery of the lung. The lungs contain about 300 million pulmonary alveoli that serve as the primary sites of gas exchange with the blood and are the fastest and most efficient area for absorption of systemically active drugs.

The extent of deposition of the inhaled particles (as opposed to the portion that is exhaled) and the location of the deposition depends largely on the size of the particles and the velocity of inspiratory flow.

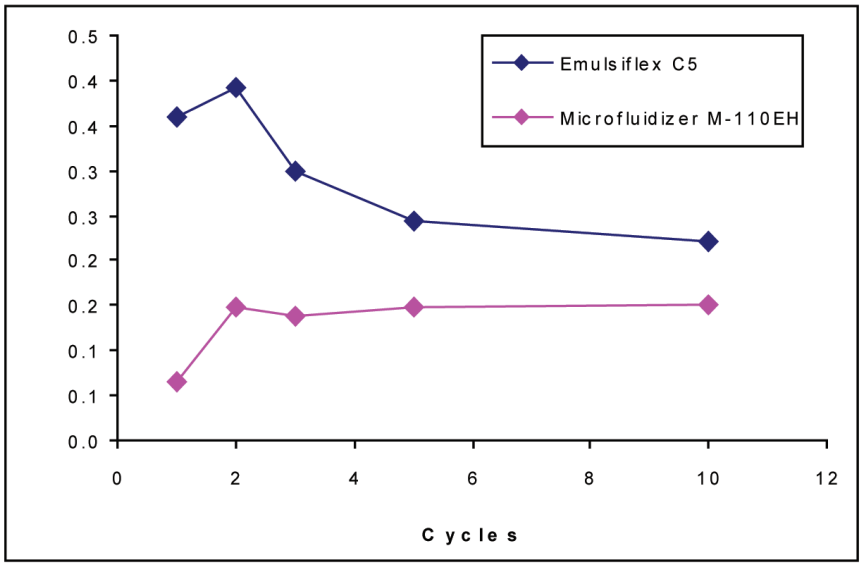
Large particles (5 to 10 microns) do not follow changes in the direction of air flow and have a tendency to be deposited by inertial impact; therefore, they tend to be deposited in the upper airways without reaching the site of action or reabsorption. Moreover, particles deposited in the mouth and throat can be swallowed and can lead to local or systemic side effects. This

FIGURE 2



Budesonide in emulsion. Smaller particle size.

FIGURE 3



Budesonide in emulsion. Narrower size distribution.

phenomenon is often observed with cortisone asthma medication, which can result in infections in the mouth.

Intermediate-sized particles (3 to 5 microns) can be carried further into the bifurcations and smaller airways of the bronchii and bronchioles. Small particles (1 to 3 microns) behave more like gas molecules and follow the airflow all the way to the alveoli.

The very smallest particles (1 to 0.5 microns) can fail to be deposited in the alveoli, and portions of the medicine can resultantly be exhaled therefore not achieving the desired therapeutic levels. Controlling the air velocity by slow inhalation will maximize the number of particles that reach the alveoli and minimize the number that are exhaled.

FORMULATIONS

The size of the aerosol particle entering the body is a function of the inhaler device and the formulation of the medication. Inhalers and nebulizers of different types each have the ability to generate aerosol particles of certain size range.

For liquid formulations containing soluble drugs, the size of the aerosol particle is largely a function of the design and operation of the delivery device the nebulizer or "atomizer" that converts the liquid into a vapor or mist.

However, for drugs in powder form and for insoluble drugs that are suspended or dispersed in emulsions, the particle size in the formulation of the drug product is critical. The formulation of the drug product and the design of the delivery device must be matched in order to produce uniform and optimally sized aerosol particles.

For example, if a pharmaceutical company is formulating liquid medication with suspended drugs and the goal is to deliver aerosol droplets with a mean particle size of 3 microns, the component drug suspended inside the liquid droplets must have a particle size smaller than 3 microns. Otherwise, the droplet would not be able to carry the drug and would remain "empty." Therefore, when formulating liquid inhalation medication with suspended drugs, the size distribution of particles must be carefully adjusted and controlled.

The actual size of the drug particle depends on the type of dispersed system (suspension, emulsion, liposome, or colloidal system). Studies performed by PARI GmbH, a worldwide leader in aerosol delivery and research, clearly indicate that the inhalation efficiency with suspended drug particles will significantly increase when the drug size falls below 1 micron. Aerosol droplets are typically not uniform in size but rather have a size distribution. More specifically, an aerosol with a mean particle size of 3 microns will contain some particles larger and smaller than the mean size. The goal is to achieve relatively uniform product with a limited particle size distribution, as represented by a low polydispersity index value or as plotted in a narrow bell curve.

PARTICLE SIZE REDUCTION METHODS

A number of methods of particle size reduction have been employed to develop and manufacture dispersed formulations of inhalation medicine. Precipitation, coacervation, and emulsion-based methods are employed in research environments. However, the solvents and other chemicals used in the process can remain as residue that can be toxic in the lungs. In fact, process chemicals and excipients that are approved for oral medication may not be acceptable for inhalation therapy. For these

reasons, several mechanical methods are frequently used, including conventional homogenization, ultrasonication, and high-shear fluid processing.

CONVENTIONAL HOMOGENIZATION

Historically, the most common mechanical process for particle size reduction is the conventional homogenization process. The process was originally designed for processing milk and other dairy products. Auguste Gaulin received a patent in 1899 for a milk homogenization mechanism that reduced the size of fat globules in order to prevent the formation of a cream layer. The process involves forcing milk through a tiny orifice under high pressure.

Over the past century, more than 100 additional patents have been awarded for improvements on Gaulin's original design to produce smaller average particle size and achieve higher levels of precision than traditionally required by the dairy industry. For advanced products, conventional homogenizers can be designed to perform a variety of cell disruption, particle size reduction, and emulsification operations by selecting or creating a particular orifice size and valve geometry and by adjusting the pressure.

However, for conventional homogenizers, the orifice size, valve geometry, and pressure settings apply only to a specific flow rate. When scaling up from a laboratory-size homogenizer to a pilot system, and from a pilot system to a full-scale production system, completely different valves are used, and the pressure may need to be raised or lowered considerably. Sometimes several iterations of equipment design must be tested before an acceptable product is produced, or until the specified flow rate is achieved.

Conventional homogenization has served the needs of the dairy industry for over a century. However, particle reduction applications in the pharmaceutical and biotechnology industries require a level of precision, uniformity, and predictability that is usually best achieved with newer particle reduction technology.

ULTRASONICATION

Sonic disruptors, or sonicators, break up particles in liquid media with powerful ultrasonic waves, ranging from about 15 kHz to 50 kHz. Ultrasonic waves in these frequencies are inaudible to the human ear, but they are capable of exerting pressures of more than 500 atmospheres and generating locally temperatures of up to 5,000°C. A probe or horn containing a piezo-electric generator amplifies the waves into an intense beam that creates the cutting or shearing effect on particles. This effect is called cavitation.

At a microscopic level, the pressure waves cause bubbles to form and then grow and collapse violently. This implosion generates a shock wave that reduces particle size. The process is so powerful that it can easily overprocess materials, excessively pulverizing the product. The locally high temperatures can also harm the drug or alter its chemistry. Sonicators are commonly found in the laboratory, but they can be prohibitively expensive for producing commercial production volumes.

HIGH SHEAR FLUID PROCESSING

A relatively new method of particle reduction high shear fluid processing is favored by many research laboratories, as well as pharmaceutical and biotechnology companies, because of its unparalleled ability to produce extremely small particles of uniform size and to scale up linearly from laboratory to production volume.

High shear fluid processing systems contain an electric-hydraulic system providing power to one or two single-acting intensifier pumps. The pump amplifies the hydraulic pressure to the selected level which, in turn, imparts that pressure to the product stream. Process pressures range from 100-3,000 atmospheres, resulting in high-velocity, high-shear process streams.

The intensifier pump supplies the desired pressure at a constant rate to the product stream. As the pump travels through its pressure stroke, it drives the product through precisely defined fixed-geometry microchannels within the interaction chamber. At the end of the power stroke, the intensifier pump reverses direction, and the new volume of product is drawn in. The intensifier pump again reverses direction and pressurizes the new volume of product, repeating the process.

As a result, the product stream accelerates to high velocities, creating shear rates within the product stream that are orders of magnitude greater than conventional means. The entire product experiences identical processing conditions, producing uniform particle and droplet size reduction.

The fixed geometry of the microchannels not only ensures that the processing conditions are identical for all product passing through a single machine, but that the processing conditions are also identical for all machines using a particular interaction chamber design and pressure setting regardless of flowrate

capacity. Therefore, once a high shear fluid processor achieves a successful result with a small laboratory system producing only a few hundred milliliters per minute, the same interaction chamber and pressure specifications can be used in the design of a full-scale production system that produces commercial larger volumes. Because of the ability to scale-up production seamlessly, many users of high shear fluid processors skip the usual pilot stage and move directly from the laboratory to full-scale commercial production capacity.

COMPARATIVE TESTING

PARI GmbH has conducted laboratory testing to evaluate the performance of various particle reduction methods for the formulation of inhalation medicine. The Microfluidizer® M-110EH high shear fluid processor (Figure 1) was evaluated in comparison to a conventional homogenizer. In the first set of tests, both pieces of equipment were used to create a suspension formulation of Budesonide, a glucocorticoid steroid used for the treatment of asthma, non-infectious rhinitis (including hay fever and other allergies), and for treatment and prevention of nasal polyposis. The drug also has efficacy for bowel and colon disease, but it has a high first-pass metabolism, making it an excellent candidate for systemic inhalation delivery.

In the side-by-side test of the Budesonide suspension formulation, the PARI laboratory found no significant difference in the average size of the particles between the Microfluidizer processor and the conventional homogenizer. However, the Microfluidizer processor produced a better size distribution (eg, a polydispersity index of 0.8 compared to 1.0 after one cycle).

The difference between the Microfluidizer processor and the conventional homogenizer were more pronounced for the production of emulsions that can be used to deliver Budesonide. With one cycle of processing, the Microfluidizer processor produced a smaller z-average particle size (250 nm) compared to 475 nm for the conventional homogenizer (Figure 2). Moreover, the conventional homogenizer required 5 cycles to come close to the results achieved by the Microfluidizer processor in a single cycle. The Microfluidizer processor also produced a significantly narrower particle size distribution (Figure 3), with a polydispersity index of only 1.3 after 1 cycle, compared to 4.0 for the conventional homogenizer.

The PARI researchers found that high shear fluid processing provides an excellent method of particle size reduction and production of dispersed system formulations for inhalation therapies. The system offers precise control over processing conditions, and the availability of different homogenization chambers provides flexibility in producing a variety of formulations with various particle sizes while maintaining a very narrow particle size distribution.

BIOGRAPHIES

Dr. Thomai "Mimi" Panagiotou, Ph.D., is the CTO of Microfluidics International Corporation. Microfluidics develops high shear fluid processors for processing multiphase fluids and nanomaterial formulations. Applications of the technology include drug delivery, electrode materials for batteries and fuel cells, nanoceramics for optical coatings and carbon nanotube dispersion. Dr. Panagiotou has responsibility for the overall direction of Microfluidics' technology and leads the development of Microfluidics Reaction Technology (MRT), an award winning process intensification technology to manufacture nanosuspensions "bottom up". Prior to Microfluidics, Dr. Panagiotou was a Manager at Arthur D. Little and a Principal Scientist at Physical Sciences. In her previous positions, Dr. Panagiotou was involved in the development of drug eluting, polymer coatings for stents, insulin inhalation devices and spectroscopy based sensors. Dr. Panagiotou holds a MS and Ph.D. in Mechanical Engineering from Northeastern University. She co-authored over 60 papers for journals and conference proceedings and is a co-inventor of two patents.

Technology Showcase

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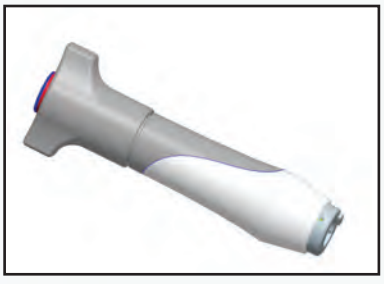
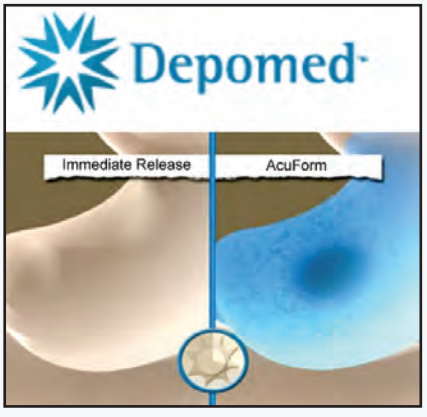
Spring-Powered Injector



Bioject has developed a new spring-powered injector known as the Zetajet, based on the design of the Biojector 2000 (B2000) for performance but uses a spring for its power source. The pressure profile of the Zetajet has been documented to be virtually the same as that of the B2000, which has given millions of injections. The B2000 is a needle-free jet injection device that provides up-to-date jet injection technology and eliminates or reduces complications associated with other previous devices (eg, cross-contamination from patient to patient, lacerations at the injection site, difficult device cleaning, cumbersome tanks, etc). The intended use of this device is to provide a low-cost, needle-free injection system that delivers SC, IM, or ID injections via a simple change of the syringe. For more information, contact Bioject at (800) 683-7221 or visit **www.bioject.com.**

Upper GI Delivery



AcuForm is Depomed's unique, patented, polymer-based technology designed to optimize drug delivery. AcuForm allows for targeted, controlled delivery of pharmaceutical ingredients to the upper GI tract, the preferential absorption site for many oral drugs. Unlike immediate- and some extended-release formulations that pass through the upper GI tract within approximately 3 hours following ingestion, AcuForm's unique swelling polymers allow the tablet to be retained in the stomach (gastric retention) for approximately 8 to 9 hours. During this time, the tablet's active ingredient is steadily delivered to the upper GI tract at the desired rate and time, without the potentially irritating burst of drug that often occurs with other formulations. For more information, visit Depomed, Inc. at **www.depomedinc.com.**

Technology Showcase

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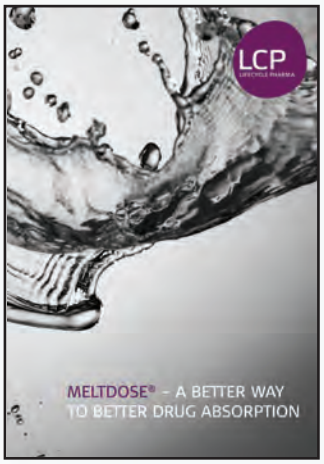
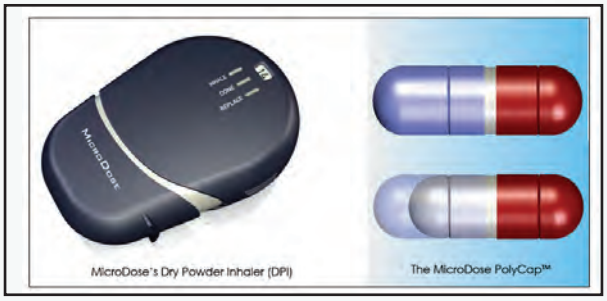
Hovione is an international group dedicated to the cGMP development and manufacture of APIs, serving exclusively the pharmaceutical industry. With FDA-inspected plants in Europe, the Far East, and the US, Hovione is committed to the highest levels of service and quality. With a 50-year track-record, Hovione offers advanced technologies as well as APIs for all drug delivery systems, from oral to injectable and from inhalation to topical applications. Specializing in complex chemistry and particle engineering, Hovione offers all services related to the development, manufacture, and preformulation of both NCEs and existing APIs for off-patent products. Our aim is to do well what is difficult, to give our customers what they cannot find elsewhere. For more information, visit Hovione at **www.hovione.com.**

Absorption Enhancement



LCP is an emerging specialty pharmaceutical company focused on certain cardiovascular indications and organ transplantation. It currently has one product on the market, seven clinical development programs covering five product candidates, and three product candidates in preclinical development. Its first commercialized product, LCP-FenoChol, has received FDA approval for sale in the US under the brand name FenoglideTM and is marketed in the US by Sciele Pharma. Fenoglide and its other development compounds are based upon its unique drug delivery technologies. The proprietary MeltDose® platform enhances the absorption of poorly soluble drugs. Applying MeltDose technology creates new versions of existing drugs with improved oral bioavailability, improving efficacy, allowing for lower dose, and in some cases, reducing food effect and/or potential side effects. For more information, visit LCP at **www.lcpharma.com.**

Next-Generation Products



MicroDose Technologies is pioneering the creation of next-generation products utilizing its proprietary technologies. MicroDose's Dry Powder Inhaler (DPI) and PolyCap™ combination oral dose capsule system promise to dramatically improve efficacy and compliance. MicroDose's next-generation DPI is a state-of-the-art electronic inhaler providing superior delivery for both small and large molecules to the lungs. It provides a platform technology that is low cost, reusable, and environmentally friendly, which can support a full pipeline of products. MicroDose's PolyCap System is a proprietary approach that enables the rapid development of FDC therapies in a single dose, but separated by a physical barrier. Utilizing the proven strengths of capsules and the advantages of a barrier system, it allows for more rapid development timelines and lower regulatory requirements. For more information, contact MicroDose Technologies, Inc. at (732) 355-2100 or visit **www.microdose-tech.com.**

Technology *Showcase*

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Founded in 1991, Particle Sciences is an integrated provider of both standard and nanotechnology approaches to drug development and delivery. Through a combination of preformulation, formulation, analytic, bioanalytic, and manufacturing services, Particle Sciences provides clients with a powerful, integrated solution to most efficiently take a drug from discovery to the clinic. Each project has a dedicated team and leader to manage the project from start to finish. With years of experience to draw upon, Particle Sciences can confidently handle difficult APIs, complicated intellectual property terrains, and challenging delivery goals to arrive at the simplest, most efficient solution to the client's needs. For more information, contact Particle Sciences at (610) 861-4701 or visit **www.particlesciences.com.**

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PharmaForm doesn't just provide its clients with creative solutions; it creates successful partnerships. As a pharmaceutical contract service provider, it offers a wide range of formulation, drug product development, manufacturing, analytical testing and stability services, patent litigation support services, and product platform licensing opportunities. Its formulation scientists have core expertise and experience in improving solubility of poorly soluble compounds. One such available technique to clients is Evaporative Precipitation into Aqueous Solutions (EPAS), a process that causes the formation of nano-sized particles that can help enhance bioavailability of a poorly soluble compound. PharmaForm's state-of-the-art facility is registered with the FDA and the DEA and is cGMP/GLP Compliant. For more information, contact PharmaForm at (512) 834-0449 or visit **www.pharmaform.com.**

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Executive Summary

David Platt
CEO
Pro-Pharmaceuticals

The Untapped Potential of Carbohydrates in Drug Discovery & Development

Pro-Pharmaceuticals Inc. is a development-stage company engaged in the discovery, development, and commercialization of first-in-class, targeted therapeutic compounds for advanced treatment of cancer, liver, microbial, and inflammatory diseases. The company's focus is the development of a new-generation of anti-cancer treatments using carbohydrate polymers to increase survival and improve the quality of life for cancer patients. The technical objective is to employ the sugar-specific receptors sites found on the cancer cell surface to facilitate the delivery of well-known, FDA-approved chemotherapy agents, whereby increasing their efficacy and reducing their toxicity. As a result of their structural complexity, carbohydrates have not received as much scientific attention as nucleic acids and proteins, and are not as well understood, David Platt, CEO of Pro-Pharmaceuticals, recently shared with *Specialty Pharma* magazine. He says carbohydrate molecules, which are essential to the transmission and recognition of cellular information, have been shown to play an important role in major diseases including cancer, cardiovascular disease, Alzheimer's disease, inflammatory disease, and viral infections. Mr. Platt believes this offers a largely untapped area for treatment of disease, including chemotherapeutics, infection treatment, vaccines, and antibiotics.

Q: ***Why do you believe that carbohydrates are under-used in the pharmaceutical industry?***

A: Every cell in the human body contains carbohydrate receptors, many of which mediate processes related to disease and health. In fact, nature uses carbohydrates everywhere: as nutrients, structural elements of cell walls, in energy storage, and in molecular signaling and recognition to name a few important areas. Considering the ubiquity of carbohydrates in biological systems, one would assume that a fair fraction of drugs in our pharmacopoeia would be carbohydrate-based or contain carbohydrates, but this has not occurred. Considering the nearly limitless combinatorial possibilities for polysaccharides, saying that carbohydrates are under-used in drug development is in fact a gross understatement. Only a few dozen carbohydrate-based compounds or conjugates have been approved. Heparin and related compounds, plus the antibiotics streptomycin and neomycin, are composed solely of sugars or amino sugars. Disaccharide-derived drugs include the anti-peptic sucralfate and lactulose, a colonic acidifier. Tobramycin, an anti-bacterial, is a trisaccharide. We also have a handful of macrolide or large-molecule antibiotics consisting of sugar

or aminosugar conjugates, and of course, there are the anti-cancer nucleotide and nucleoside analog drugs—fludarabine and gemcitabine, and the HIV agent stavudine. Still, other agents based on monosaccharide conjugates of polyenes, triazole, imidazole, and other simple heterocycles are prescribed to combat bacterial and fungal infections, cancer, and other conditions.

Q: *You have mentioned a "discovery gap" in drug development. How serious is the problem?*

A: What I call the "discovery gap" has plagued the pharmaceutical industry for the past decade. Since the early 1990s, companies have embarked on initiatives to improve the number of discovery-stage compounds that are promoted to clinical development, but most of these efforts have failed. For example, high-throughput screening, combinatorial chemistry, million-compound libraries, and automation have been largely unsuccessful in uncovering enough new molecules for Big Pharma to succeed and continue growing. Approvals of New Molecular Entities (NMEs) have been relatively flat for the past 12 years, hovering in the mid-20s per year.

At the same time, pharmaceutical R&D costs, on an approved-compound basis, have skyrocketed. Cost estimates for bringing a new compound to market range from $900 million to more than $2.5 billion. Add to this blockbuster patent expirations, which by 2012 are expected to wipe $55 billion in sales off the books of major companies, and you can see the magnitude of the problem. Some experts are beginning to talk about the end of the "blockbuster drug" economic model.

Q: *How can carbohydrates help?*

A: We believe carbohydrates hold the key to answering many of the questions facing drug developers. The fact that so many cells implicated in both disease and health possess carbohydrate receptors is the first clue that this class of molecule might play an important future role in drug discovery. The other is our ability to create novel carbohydrates of almost any size and composition. Theoretically, one could discover, through ordinary receptor binding studies, which of these molecules bind to cells implicated in disease. By digging a bit deeper, it is possible to uncover the effect of the carbohydrate (or carbohydrate-drug conjugate) on the cell.

Q: *Why haven't more pharmaceutical companies made more of an effort to discover and develop carbohydrate molecules?*

A: There are several reasons why drug developers have been reluctant to embrace carbohydrates as a starting point in pharmaceutical discovery. Classical organic chemistry courses, which are the training ground for medicinal chemists, practically ignore carbohydrates, and most chemists quickly forget what they learned about these compounds. Sugars are difficult to synthesize, characterize, and analyze compared with most other organic molecules. Their names are not easy to memorize, even by organic chemistry standards. The molecules undergo a relatively narrow range of chemical transformations, and they are difficult to purify by crystallization or column chromatography. For these reasons, sugars and particularly higher molecular weight carbohydrates have reputation (not entirely undeserved) for being hard to work with.
The chemical "difficulty" of carbohydrates has led to laziness among drug discovery scientists. Lacking a critical mass of druggable carbohydrate structures, chemists are reluctant to synthesize them, and biologists therefore have no reason to create assays for them.

Q: *How is Pro-Pharmaceuticals succeeding in this area?*

A: One of the keys to success in the ultra-competitive pharmaceutical marketplace is to find a lucrative specialty. We often hear that in this business, all the "low-hanging fruit" has already been harvested. What that means is that it is becoming more and more difficult to discover an entirely new class of pharmaceutical agent that operates through a

novel mechanism of action. In addition, a company like ours would have almost no chance of succeeding by discovering a new statin or angiotensin converting enzyme inhibitor. So while most companies run away from carbohydrates, we have embraced them for their novelty and rich pharmacology. We're proud that we count among our senior scientific staff some of the world's best-known carbohydrate-drug researchers.

Q: *Please describe your drug development program.*

A: Our lead cancer compound, Davanat, is a polysaccharide composed of mannose and galactose. Davanat is manufactured from carbohydrates that the US FDA has deemed GRAS (Generally Regarded as Safe). The shorter polymeric chains in Davanat render the carbohydrates water-soluble at up to about 60 mg/mL, which makes them suitable for injection. Davanat is used in combination with conventional cancer chemotherapy drugs to enhance the drug's effectiveness while reducing side effects. Davanat works by binding to lectins (carbohydrate receptors) located on the surfaces of cancer cells. Binding permits more of the cancer drug to enter the cell than normally would. Lectins are up-regulated on many cell surfaces, particularly in cancer and cells that mediate inflammatory diseases. Davanat targets specific lectin receptors, galectins, that are over-expressed on cancer cells and which bind strongly to the compound's galactose building block. Of the 16 galectins discovered, Davanat binds to three through one of the strongest biological interactions known.

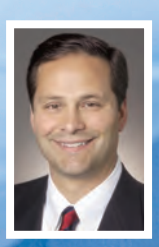
Carbon-14 labeling studies demonstrate that in the presence of Davanat, the chemotherapy agent 5-fluorouricil (5FU) accumulates to a higher degree and remains inside cancer cells longer than it normally would. Thus, co-administration of Davanat and 5FU may allow for higher doses of chemotherapy administration with no increase in toxicity, or more efficient utilization of conventional doses of chemotherapy agents. Davanat has enjoyed considerable success in the clinic. The compound is currently being tested, in combination with 5FU, in a Phase I study in solid tumors, and Phase II studies in metastatic colorectal cancer, biliary cancer, and colorectal cancer. We also have programs for administering Davanat under compassionate use in combination with chemotherapy and a biologic, and for treating breast cancer. In the ongoing Phase II colorectal cancer trial, 43% of patients experienced tumor shrinkage of more than 30%, and 4 patients had stable disease for up to 7 months. We are proud of the fact that 3 out of 20 patients who completed this study survived for more than a year, and 2 have lived more than 2 years. Each of these patients had previously failed numerous treatments, and none were expected to live more than a few months. We were able to improve median survival time for all patients by 6.7 months. Two other carbohydrate drugs in development at our company, GR200 and GR300, which also bind to galectin receptors, have been shown to reverse liver fibrosis in rats when used as a stand-alone therapy. Pro-Pharmaceuticals is working with Dr. Scott Friedman, a leading liver disease expert at the Mount Sinai School of Medicine in New York, on clinical development of GR200 and GR300. Pro-Pharmaceuticals also has carbohydrate-based programs for treating microbial, cardiovascular, and inflammatory diseases, as well as adjunctive therapy with chemotherapy agents other than 5FU.

Q: *What are some of the challenges a development-stage pharmaceutical company faces?*

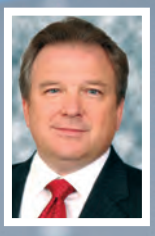
A: The FDA has wisely raised the bar for approving cancer drugs. Years ago, tumor shrinkage was considered a valid study endpoint. Today, new drugs must also demonstrate a survival benefit which, after all, is what cancer therapy is all about. Preliminary results with Davanat suggest that we should demonstrate lifespan improvements sufficient for approval. But getting there will not be easy. Financing has been a huge challenge, particularly these days with the credit crunch and bank failures. Fund managers who used to invest in companies like ours are currently in freeze position and extremely risk-averse. With Phase lll trials consisting of hundreds of patients and costing millions of dollars, will need to join forces with a mid-sized or even a large pharmaceutical partner to get the job done. ■

SPECIALTY PHARMA
Strategies For Business Development

Eric F. Hayashi
President & CEO, LabConnect LLC



William Sharbaugh
Chief Operating Officer, PPD



David Spaight
President, MDS Pharma Services

Central Lab Strategies

How Your Central Lab Can Keep Clinical Trials Flexible & Cost Effective

By: Cindy H. Dubin, Contributor

The total R&D investment of bringing a new product to market has been estimated to be close to $543 million. All new products need go through clinical trials, and every stage of a clinical trial involves logistics. The effective transport of clinical trials to investigator sites and patient samples back to central laboratories are critical if a product is to be launched on time and within budget. Delays are expensive and even a few days could potentially cost millions. The pressure of bringing drugs to market quickly and cost effectively has lead to many clinical trials now being carried out in Asia, Eastern Europe, and Latin American. Each country has its own guidelines, which can be highly regulated, so it is crucial to understand the complexities of shipping materials to a variety of destinations. *Specialty Pharma* posed these issues to executives at some of the leading central labs, including Eric F. Hayashi, President & CEO, LabConnect LLC; William Sharbaugh, Chief Operating Officer, PPD; and David Spaight, President, MDS Pharma Services.

Q: ***There have been concerns in pharma that classically structured clinical trials are not flexible enough to make use of the data generated during the trial. How do you respond to this?***

Mr. Sharbaugh: For several decades, drug development has been based on a series of experiments and clinical trials, which occur in series (Phases I-III), eventually leading to a regulatory decision. Over time, this approach has resulted in increased cycle time and cost. There is definitely a need to evolve toward greater use of more flexible trial designs based on resource optimization and real-time information processing, while continuing to protect scientific integrity. Adaptive trials methodology provides a broad range of design flexibility options relative to fixed designs from a near-fixed two-stage design with one formal interim analysis to highly flexible response-adaptive designs. For example, it would be beneficial to use a highly flexible, adaptive design for a trial like a dose-response study for a treatment to accelerate the cure of the common cold. The treatment follow-up is relatively short, allowing time for earlier treatment responses to be used to adapt future randomizations. Some drug developers believe adaptive concepts can speed the transition between phases, for example, Phase I-II or Phase II-III if the trials are properly designed. However, adaptive principles alone are not the answer to improving drug development, and further regulatory guidance and harmonization are required by regulators and industry to define the practice of adaptive trial design. There is not a need for a radical shift toward all-adaptive designs. Adaptive clinical trials can take extra time and resources to design. Therefore, the potential for faster decision-making must provide a pay-off that justifies the extra investment.

Mr. Hayashi: We have seen a significant shift in the past 5 years alone: testing requirements are becoming more complex; the country mix is changing; and the trials themselves are being designed differently, such as adaptive trials. Because our systems are designed around these complexities, LabConnect has found a niche in the central lab marketplace with clients that need a customized solution in terms of specialty testing and sample storage, complex lab kit design, and logistical complications versus the larger central labs that find it more difficult to accommodate. Their systems were just not designed for this level of specialized testing and customization. Perhaps more important for price-sensitive clients is that we're able to make these changes cost-effectively due to our business model. For example, our information systems are designed around the expectation that our clients may wish to change the tests they want to run mid-stream. Changing a test necessitates changes to requisitions, kit designs, testing validation, quality checks, and so forth. On a different level, adding, say a new geographic area, may require working with a "regional expert" lab. We have designed our proprietary clinical trial management systems to be able to "sit on top of" multiple LIMS (Laboratory Information Management Systems) for simple deployment at the lab integrating with their LIMS and resulting in harmonized operations and combinability of the data.

Q: ***Late-stage failures account for 60% of drug terminations. How are you using clinical forecasting to ensure the success of your clients' drug development programs?***

Mr. Spaight: There are many reasons why drugs are terminated in the late stages of development. These can include regulatory, economic, efficacy, safety, and even market drivers. While many of these factors are both common and unavoidable, MDS Pharma Services Global Central Lab leverages its reach and experience to help our clients avoid the pitfalls that can be avoided, and assist them in navigating the complexities of developing safe and effective drugs to help the people who need them.

Our Central Lab forecasting involves mining our program database to assist our clients in better planning enrollment periods, and developing solid global strategies that maximize resources and reduce patient risks. By leveraging our distributed kit building and distribution network, we are able to plan and execute program start-up processes based on years of local and regional experience. Additionally, MDS Pharma Services engages our logistics partners to help manage program and investment risks. Use of forecasting is at the heart of our program planning cycle and with our experience and global reach, we are able to deliver the Quality On-Time™ results to ensure the success of our clients programs.

Mr. Hayashi: We provide several trending tools to our clients that allow them to monitor trends in test results on an individual subject basis as well as an aggregate basis. We also support focused data reviews on a test-by-test or group-of-test data review. For example, we're able to identify why subjects fail during screening and differences in screen failures among sites. Armed with this information, our clients are able to refocus their screening efforts, or perhaps even change their trial design, resulting a reduction in screen failures.

Mr. Sharbaugh: Clinical drug development is a complex, competitive business operating in an evolving regulatory

environment. Drug terminations late in the clinical development lifecycle are costly, and even small improvements in success rates would have a positive impact on the industry. The answer, like the problem, is multifaceted and depends on the attributes of the molecule, the scientific quality of the development program, and the ability to execute. As one of the largest, most experienced research organizations in the world, PPD has a large pool of talent and a rich historic database that can be mined to design efficient development programs aimed at improving the probability of technical and regulatory success while reducing cycle time and cost.

The earlier we become involved in the process, the more impact we can have. Ideally, we would like to be involved with a molecule in the early phases of development and follow it through its entire lifecycle to provide continuity during the development process. Our global medical, statistical, and regulatory teams can harness our large trial database to help refine the trial design with a client to ensure a molecule has the best chance possible to obtain approval. In addition, we have a robust trial feasibility process that can provide insight into trial design. The best trial plans will fail if they cannot enroll patients. Through feasibility, we help clients select the inclusion and exclusion criteria, model enrollment, incorporate feedback from investigators, consultants, epidemiologists, and analyze prescription and insurance data. The triangulation of this data gives us information to improve country selection, site identification, and enrollment forecasts, as well as identify back-up strategies and alternative plans, tailored to the client's needs.

During the trial, our CRAs and project managers focus on quality and execution. Our medical, pharmacovigilance, data management, and statistical teams look for safety trends and signals that could impact the overall results of the trial. Their evaluation could lead to an early stop of the trial for positive or negative reasons, both of which lead to reduced drug development costs. Because of the complex nature of drug development, strategic partnerships between pharmaceutical companies and CROs provide a unique opportunity to harness the scientific and operational knowledge of both organizations. A study conducted by the Tufts Center for the Study of Drug development (TCSDD) concluded that use of CROs leads to faster completion of large clinical trials. In addition, PPD's experience designing and executing development programs through our compound partnering division has resulted in accelerated cycle times.

Q: ***Outsourcing clinical trials to India and China has increased because of the potential cost savings. How have you had to compete with the draw of the clinical trial providers in those countries?***

Mr. Hayashi: I agree that cost savings have been a driver, but probably not as strong a driver as speed: that is access to qualified study participants and establishing a marketing foothold. Our situation is somewhat unique in that most of the proliferation in clinical trial providers has been with regional CROs. Because we are exclusively a central lab–and not a CRO–we are able to work with rather than compete against, these new providers. We also have a unique advantage in our specialty areas, which is emerging markets such as India, Central and Eastern Europe, and Latin America. Our advantage here is that our labs in these countries are well-established regional experts with extensive in-house analytical capabilities. In India, for example, our lab network partner has more than 3,600 available assays and processes more than 8,000,000 samples annually. This, of course, translates to cost savings because the tests are routinely available. It also means that we provide not only US-based global project management experts, but also country-based, regional project manager experts who ensure our trials run smoothly. We believe successfully conducting trials in emerging markets requires local regulatory expertise, intimate site support, and logistical expertise in getting kits to the sites and back to our lab on time, in good condition, and cost effectively. For example, in India, because we have an in-house national courier network, being proximal to sites translates to significant savings both in shipping costs, which can be quite significant, but also fewer cancellations as some samples have short stabilities. The sites enjoy this approach as well as they can work with regional project teams that not only speak the language but "know" the culture.

Mr. Spaight: The expansion of clinical trials in India and China was initially driven by cost savings. However, as those markets mature, other factors such as participant and patient populations, drug-naïve participants, and approval by regional agencies are also important factors. MDS Pharma Services works with our clients to the greatest extent possible to determine the most suitable approach, including geography, for their drug development activities. We are able to offer our central lab support in virtually any region of the world, thanks to our extensive network of harmonized, directly owned CAP Certified Laboratories. Our reach and experience spans the globe with strategically placed facilities in Asia, Europe, and the Americas all bound by global SOPs and an advanced Global Lab Information Management and Reporting System. In fact, we welcome the opportunity to support the many pharmaceutical and biotech companies now making China part of their global clinical trial programs. MDS Pharma Services has been in China for more than 10 years and has managed more than 30,000 patients in clinical trials. As an industry pioneer, we introduced standardized clinical research services to China and were the first western contract research organization to own our own facility there. We were also the first clinical laboratory in China to receive accreditation from the College of American Pathologists.

Mr. Sharbaugh: With clinical research in Asia Pacific growing more than 50% in just 2 years (2005-2006), according to CenterWatch, the region has become a fast-growing, emerging market that is becoming increasingly important to global drug development. It is also a region that is particularly important to PPD's strategic growth. There are a number of reasons why China and India have become important regions for conducting clinical trials. First, there is a growing amount of innovative discovery and development activity taking place in China and India, and both countries have an increased

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desire to commercialize compounds. In addition, India and China offer large populations of potential patients to enroll in clinical trials, and speed is always a factor in trial execution. There is also increased awareness and desired access to Western drugs, and India and China are now participating in large global Phase II and III program as regulations eliminating phase lag have been passed. As North America and Europe become more saturated with trials, investigators, and sites, India and China are viable alternatives for patients and sites. Traditionally, late-stage development has played a dominant role in the Asian market with the focus being on clinical research in registration studies. As the capabilities of China and India increase, and as pharmaceutical and biotech companies continue to expand in this region, we are seeing a significant increase in the number of Phase III, II, and even Phase I studies. The region is also extending into therapeutic areas beyond traditional infectious disease studies, which were more common 10 years ago. Now, there are larger numbers of oncology and cardiovascular studies being conducted in both countries. The number of metabolic-related studies in areas like diabetes is also growing as Western diseases are becoming more prevalent in Asia Pacific. India's regulatory environment is being redesigned to compete with Europe. In addition, clients looking to market a drug in India or China have an easier time getting regulatory approval after they have completed a trial there. While China has a relatively long regulatory approval process, it is improving and working to bring regulatory filings more in line with the rest of world. However, while China may take longer to gain approval to start the study, they have faster patient recruitment times than the US or Western Europe. It is also important that we don't overlook Eastern Europe and Latin America as vibrant emerging markets for clinical research. These are also areas of focus for PPD, and we are one of the largest CROs in each of these regions.

Q: ***Along the same line, there are benefits to performing trials in the EU, yet there are several obstacles to final drug approval. What should pharma understand about conducting trials abroad, and how is trial authorization in the EU different from the US?***

Mr. Spaight: MDS Pharma Services is a global contract research organization providing a full range of drug development capabilities to clients from around the world, with many in both the US and Europe. We are therefore well aware of both the advantages and challenges of conducting trials in these areas. The fundamentals of conducting trials are similar in both the US and Europe. Requirements include a clear description of the drug product, a history of the drug in both animals and humans (if the latter is available), and the clinical protocol, which describes the work to be conducted. The conduct of the clinical trials is very similar in the US and EU and is described in guidelines from the International Conference on Harmonization. Nevertheless, each regulatory jurisdiction has its own specific timelines and detailed requirements, for which MDS Pharma Services has extensive experience across the board, including all the EU member states.

From an execution standpoint, decisions about where to conduct trials and with which outsourcing partner should also take into account the size of the trial, the required participant/patient numbers and population, and the ability of the outsourcing partner to meet the support needs with services such as Central Lab and Cardiac Safety Testing. By conducting trials abroad, sponsors are able to access larger and different patient populations, as well as lay the foundations for successful global product launches upon commercialization of the drug under development.

Mr. Sharbaugh: There are many differences across a broad spectrum of topics, such as regulatory guidance on study conduct, safety reporting, drug approval, GMP, GCP, and GLP to name a few. A good example is the Clinical Trials Directive, which was approved in 2001, although it was not fully implemented in most countries until 2006 and even then only in the European Union economic area. The directive attempted to streamline clinical trials processes as multiple requirements made Europe a complicated area for drug development. While the directive has improved these processes, there continues to be problems with its implementation in some countries, and there are further improvements to be made. In addition, the clinical trials directive is only applicable to countries that are members of the European community. We still must account for different processes for Eastern European countries, such as Russia and the Ukraine, which are emerging regions for drug development. Although the Clinical Trials Directive was an important step toward creating uniform legislation in Europe, biopharmaceutical companies continue to face different requirements when conducting clinical trials with European countries as there is not a unified approach to drug development processes. An in-depth understanding of the laws of all countries where trials are being conducted is required, and this is how working with a large global CRO like PPD pays off for sponsors. As an example, when planning trials in Denmark, France, Portugal, and Sweden, it is only necessary to apply to one ethics committee. Yet, Germany, Spain, and the Czech Republic have local ethics committees in addition to a central ethics committee. These local committees each give opinions on trial design and conduct, which can slow the start of a clinical trial.

Mr. Hayashi: Because we're not a CRO, but rather exclusively central lab experts, we don't provide regulatory consultation services with regard to approvals per se, so I'll defer to the CRO veterans with that expertise. However, in answer to the second part of your question, I believe one area our clients often underestimate is the logistical costs associated with working with a central lab. There's a big difference in the costs of transporting a sample across multiple borders versus using a regional laboratory proximal to the site. We often find ourselves early in the trial design process when our clients are still selecting countries. This is particularly the case in Central and Eastern Europe, because we have so much experience there. During the trial design phase, we provide our input from a lab's perspective with regard to optimal countries and lab locations from a transportation cost perspective and sample integrity perspective. ◆

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Drug Delivery Survey

Drug Delivery Prospects for the Next Decade: An Informal Survey of Big Pharma

By: Josef Bossart, PhD

Introduction

Given the challenges of the current economy, it is very easy to question our business beliefs. With most economic indicators heading downward and drug delivery company stock prices following along, one shouldn't assume this is a trend that points to a declining interest in Drug Delivery. To address this point, Bionumbers in collaboration with Drug Delivery Technology magazine, conducted an informal survey with Big Pharma personnel to get their sense of how Drug Delivery fit into their plans for the next decade. Their response was positive and provides support for continued investments in technology discovery and validation.

Survey Parameters

Bionumbers used Survey Monkey (www.surveymonkey.com) to conduct an online survey of 1,144 Big Pharma personnel qualified using Drug Delivery Technology magazine's subscriber database. Of this total, 115 addresses were unavailable because they had either opted out or the email invitations were bounced. The survey was rather long, consisting of 21 questions. A total of 40 responses were received, for a 4% overall response rate. Complete survey questions and tabulated results are available at www.bionumbers.com.

Survey Results

RESPONDENT PROFILES: All of the respondents were employed at one of the top 20 Big Pharma companies. Their responsibilities included Product Development (38%), Research (25%), Regulatory Affairs (10%), R&D Management (10%), Discovery (5%), and Business Development (5%). Of the participants, 69% said their company had a group involved in drug delivery technology (technology discovery/development), and 90% said their company had a drug delivery formulation group (technology application).

TECHNOLOGY SOURCING: The participants were asked to rank the importance of their current sources of drug delivery technology. In terms of importance, internal resources (Internal) was judged as most important followed by, in order, in-licensed technology (In-licensed), public domain technology (Public) and academic technology (Academic). For the decade 2010 to 2020, 78% of participants believed that In-licensed technology would be more important, as compared to 6% that believed it would be less important. In the case of Internal technology, the results were evenly split with 44% of respondents believing it would be a more important resource, and 44% believing it would be less important. More complete details are presented in Table 1.

TECHNOLOGY APPLICATION: A similar question was asked concerning resources for product formulation development. By far, the most important resource for technology application in 2008 consisted of Internal Teams followed by Drug Delivery companies, and Fee-for-Service organizations. For the period of 2010 to 2020, it was expected that

	More Important	Less Important	Little/No Change
Internal	44%	44%	12%
In-licensed (Royalty Bearing)	78%	6%	16%
Public (Non-Royalty Bearing)	38%	21%	41%
Academic (Royalty Bearing)	40%	22%	38%

Table 1. Technology Sourcing 2010 to 2020 (Relative to 2008).

the contributions of both Drug Delivery and Fee-for-Service companies would increase, 82% and 67%, respectively, versus a 63% increase for Internal Teams.

Technology Product Focus: According to respondents, Cancer, Inflammatory Disease, and CNS products were the therapeutic areas most likely to receive greater Drug Delivery attention in the 2010 to 2020 period. Urology and dermatology products were expected to receive the least attention of the 13 surveyed therapeutic areas.

Application by Class of Active: Unsurprisingly, the majority of respondents indicated that small molecules were most suitable for drug delivery technologies, followed by "Midi" molecules (600-5,000 daltons). Surprisingly, a reasonably large number of respondents indicated that drug delivery had high or moderate suitability for macromolecules, including antibodies. These macromolecules were also considered to offer the greatest opportunity for Drug Delivery in the next decade.

Drug Delivery Performance – Small Molecules: A large number of respondents (82%) believed the performance of Drug Delivery for oral delivery as applied to small molecules was excellent or good. A similarly high percentage of respondents (75%) were satisfied with current drug delivery technologies used for injectable products. The lowest ratings were reported for drug delivery technology performance as applied to pulmonary, transdermal, and nasal applications.

Drug Delivery Performance – Macromolecules: Respondents in general were not satisfied with the performance of current drug delivery technologies as applied to macromolecules. Only injectable technologies squeezed out a greater than 50% excellent/good rating. Not surprisingly, oral and transdermal drug delivery technologies were identified as having unacceptable performance as applied to macromolecules.

	Most Important	Important	Less/Not Important
Validated Technology	53%	41%	6%
Extended Patent Protection	47%	41%	6%
Uses GRAS Materials	41%	53%	6%
Low Manufacturing Cost	35%	47%	18%
Internal Application*	35%	29%	35%
Low License Costs	18%	71%	12%

Table 2. Drug Delivery Technology Selection Criteria

Drug Delivery Formulation Needs: For the period 2010 to 2020, the respondents judged the need for new drug delivery formulation technologies in order of importance were: Macromolecules (especially oral and transdermal), followed by Small Molecules (especially improved bioavailability).

Drug Delivery Technology Selection Parameters: Respondents ranked the relative importance of a variety of parameters when selecting drug delivery technology for a project. The most important parameters for technology selection were in order of importance; validated technology, GRAS-only excipients, and extended patent protection. Two parameters ranked lower in importance were the ability to implement the technology internally (presumably necessitating use of an external resource at additional cost) and low technology licensing costs. The full results are presented in Table 2.

Drug Delivery Applications (2010-2020): A greater number of respondents (65%) indicated that drug delivery products would represent a larger portion of all pharmaceutical products in the next decade. There seemed to be general pessimism with respect to an increase in the number of inhaled products being used for the treatment of systemic disease. Complete results are presented in Table 3.

Drug Delivery Resources: When asked about resource trends for the next decade, 76% of respondents believed there would be the same or more internal drug delivery activities resourced within Big Pharma. An even larger number (94%) expected there would be the same or more drug delivery activities conducted with external partners; either formulation service providers or drug delivery companies.

Observations

The number of survey respondents are less than one might wish. Qualitatively, the respondents are well positioned to provide good insight into the thinking within Big Pharma about the future of drug delivery technology, products, and needs.

It shouldn't come as a surprise that there is a general upbeat tone with respect to the future of Drug Delivery. According to the survey participants, Drug Delivery not only has meaningful challenges it needs to address, it also is perceived as making a greater contribution, and gaining importance, in the next decade.

Drug delivery companies will be a critical source of proprietary technology in the next decade according to the survey. Big Pharma seems convinced it will need to source technology externally rather than solely rely on developing it in-house. This is consistent with trends in other industries in which smaller companies are generally looked upon as the source of innovation for new technologies and product breakthroughs.

There is little surprise that Cancer is expected to receive the greatest attention in terms of drug delivery pipeline products for Big Pharma. This fits with existing trends for the full Big Pharma portfolio. Cancer has

	More	About the Same	Less
DD as a Percent of All New Products	65%	35%	0%
Lifecycle DD Products	65%	29%	6%
New Applications for Approved Products	47%	41%	12%
Poor Solubility Products	47%	47%	6%
Inhaled Products for Systemic Disease	30%	53%	18%
Non-oral Macromolecules	59%	41%	0%

Table 3. Drug Delivery Applications (2010-2020)

become a major focus for many Big Pharma companies, and Drug Delivery may simply be a means to fill out the therapeutic area for these companies. The drop in urology and dermatology drugs is a little surprising. Do the respondents believe there are inherently fewer urology products or is it that the majority of these product opportunities, many targeted to erectile dysfunction and incontinence, are considered to be adequately addressed? Is the lack of interest in dermatology products a reflection of fewer drug delivery opportunities or a sense that this is not a focus area for Big Pharma? These are questions that deserve further study by any drug delivery companies involved in these fields. Dermatology, and drug delivery-enhanced dermatology products, certainly promise to be a major opportunity for Specialty Pharma companies.

While small molecule products are considered to be well handled by drug delivery, at least by oral and injectable routes, there seems to be considerable interest in improving performance for pulmonary, transdermal, and nasal applications. At present, these applications are of course at least an order of magnitude more difficult for small molecule drug delivery than oral and injectable delivery. The situation with macromolecules, ranging from the high hundreds of daltons through to the 200+ kDa weight of monoclonal antibodies, is quite different with only injectable delivery now considered to be adequate. The delivery of macromolecules by almost any other route than injection continues to be a major area of need and opportunity for drug delivery technology development.

Perhaps the most interesting finding of the survey was the relative lack of sensitivity concerning the cost of in-licensed technology. Yes, license costs were considered important, but less so than were technology validation and extended patent protection. This is consistent with a Big Pharma willingness to pay for value. Higher prices can be supported when they provide premium product benefits. Of course, that logic falls apart when business people and lawyers who are interested only in price are negotiating the deal. Firmly establishing the value of a technology before the negotiations begin and insisting on the participation of a Big Pharma R&D representative in negotiations can reinforce the true value of the technology to the licensee.

It was encouraging to see that Big Pharma expects to outsource more drug delivery activities to both drug delivery companies who have their own proprietary technologies, and contract service companies that provide both proprietary and non-proprietary technologies. Big Pharma it seems will continue to increase its use of the best qualified outside providers to meet their ever-more demanding corporate objectives.

Reflections

While the global economy seems in the midst of a major recession, this may be just the time for drug delivery companies to be prepared to catch the rebound by investing in technology discovery and validation that will "deliver" the products of the next decade. Big Pharma is seemingly depending on it. ◆

Dr. Josef Bossart

Managing Director
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is Managing Director of Bionumbers (www.bionumbers.com), formerly Bionumbers, a boutique research group based in Austin, Texas, focused on analyzing the numbers and parameters that drive biopharma success and profitability. Dr. Bossart has held senior sales, marketing, operational, and business development positions within the biopharmaceutical industry with a number of companies, including Enzon Pharmaceuticals and Rhône-Poulenc Rorer. He earned his PhD in Medicinal Chemistry from The Ohio State University. He regularly authors articles and reports focused on Drug Delivery and Specialty Pharma.

February 2009

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But Mom & Dad…..You Promised

By: John A. Bermingham

Anyone who has children has heard this lament: "But mom and dad, you promised." If you have five children as my wife and I do, you have heard this many times. All parents have the best intentions when they make a promise to do something with their children only to have to cancel due to an unforeseen circumstance. This is particularly true when it is a business issue that is causing the conflict. Sometimes the business wins; sometimes the child wins. It is a matter of balance.

This is not necessarily true when you have people in your company making promises they know they cannot keep. What's worse are CEOs who promise their Boards, their bankers, or both to achieve certain financial goals only to miss them repeatedly.

I recently became President & CEO of a distressed company that is basically a good company but was run into the ground by the previous management team. The private equity firm that owns this company asked me to assess the company for them and to identify what was wrong. Basically, it was the fact that the management kept promising to deliver results month after month and never delivered. They had a reason for every failure experienced by the company, explaining to their Board and bankers it was the recession, fuel costs, the housing market (they are in the home goods industry), and yes, Wall Street was also to blame.

The fact is they missed their monthly revenue forecast 14 months in a row, even though they repeatedly assured the Board and bankers they would meet the forecast. When they failed on their promise month after month, they then blamed the culprits in the aforementioned paragraph. Fourteen months in a row!!!

When I conducted my assessment, I queried each senior manager individually (including the CEO) as to why they consistently missed their forecast (promise). See aforementioned excuse paragraph again. When I asked them what their recovery plan was to resolve the continual revenue shortfall, each manager said there was nothing they could do.

I have to tell you that when I hear this from an individual or management team, it really raises the hair on my neck. Well, what hair is left anyway. How can you repeatedly promise to deliver the goods month after month and repeatedly fail to deliver on your promise month after month and expect to keep your job? Just like repeatedly making promises to your child and failing to keep them, when you do this in business, you have to expect problems to arise quickly just as you would with your child. You lose credibility in either case. So what to do?

In business, just like at home, only make promises you know you can keep. Sounds easy, right? Not so. Many people do not want to commit to a lower financial target than they originally budgeted for because they believe they will get in trouble with the boss. So they make promises they know they have little chance to accomplish….bad idea.

You need to say this is the new forecast, and that while it is lower than the budgeted plan, it is achievable and you have a recovery plan you are going to implement to try to make up the shortfall. You can't promise you can make up the shortfall from the budget, but you are going to try with this recovery plan. I can accept that.

Remember that when you promise your boss you can deliver on a financial target, he or she will promise his or her boss/Board/bankers that the financial target will be hit. When you miss, you have caused your boss not only embarrassment and loss of credibility, but potential company problems as well. And along with keeping your promises, make certain you do not blame outside factors for your failure. When you fail, as we all do occasionally, it is your failure, period. So what are you going to do about it? Blame outside factors? I am thinking of having a sign placed outside of my office that reads: "Don't tell me about the storm. Did you deliver the cargo? No? Then what are you doing about it?" ◆

BIOGRAPHY

John A. Bermingham is 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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