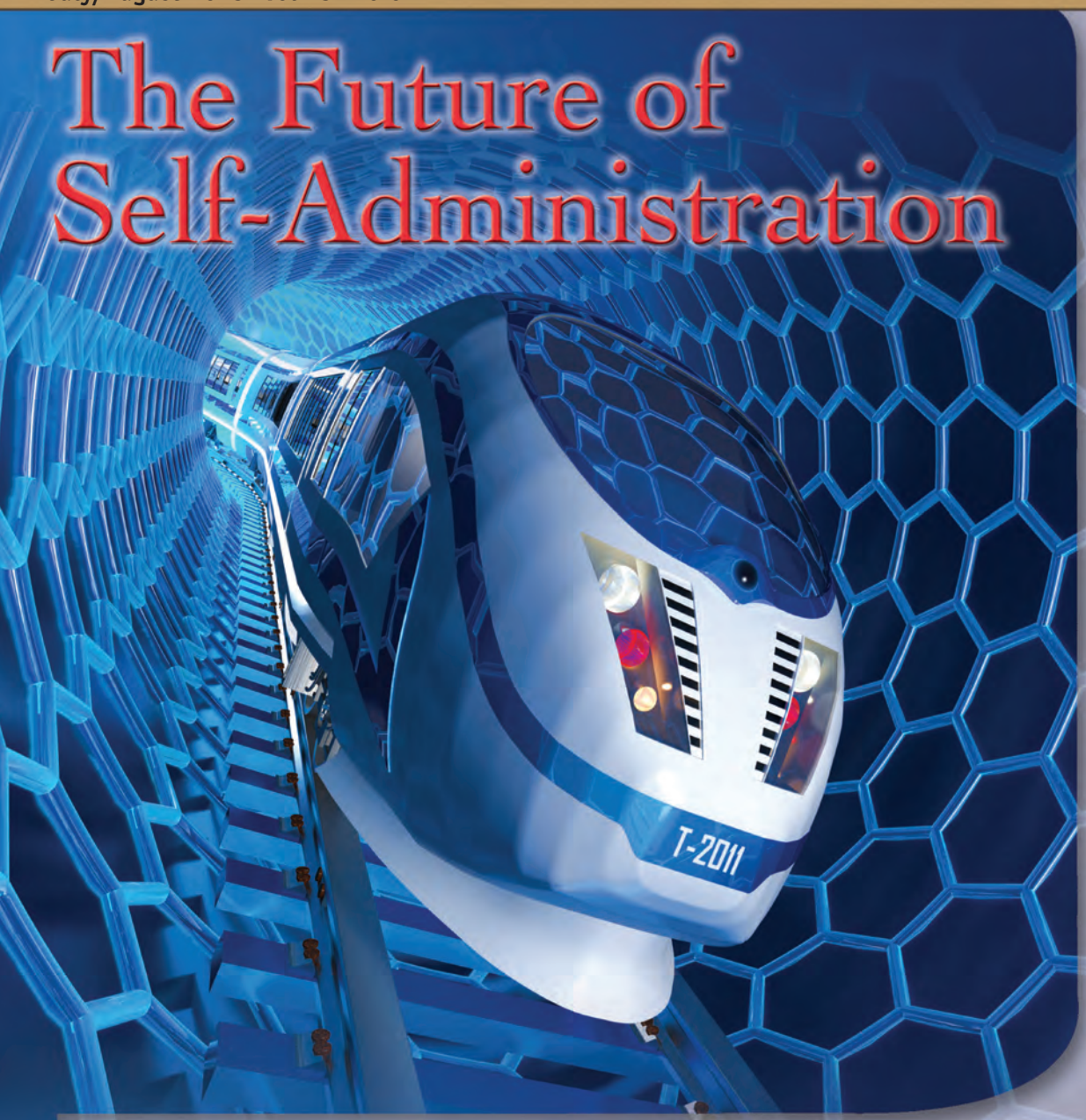
Drug Development & Delivery

July/August 2013 Vol 13 No 6 www.drug-dev.com

The Future of Self-Administration



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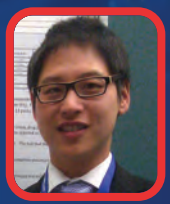

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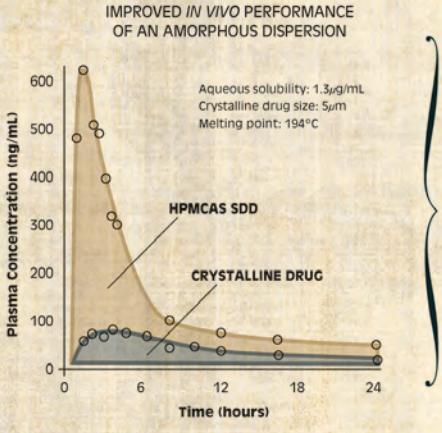

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Self-Administration's Future

"These factors are giving rise to a new generation of transdermal, topical, and subcutaneous drug products designed to satisfy caregiver and patient preferences while addressing managed care initiatives and the formulation limitations of new classes of therapeutic drugs. Because of their ability to safely and reliably satisfy treatment protocols and compliance goals, non-oral drug delivery products will have a significant impact on the future of drug self-administration."

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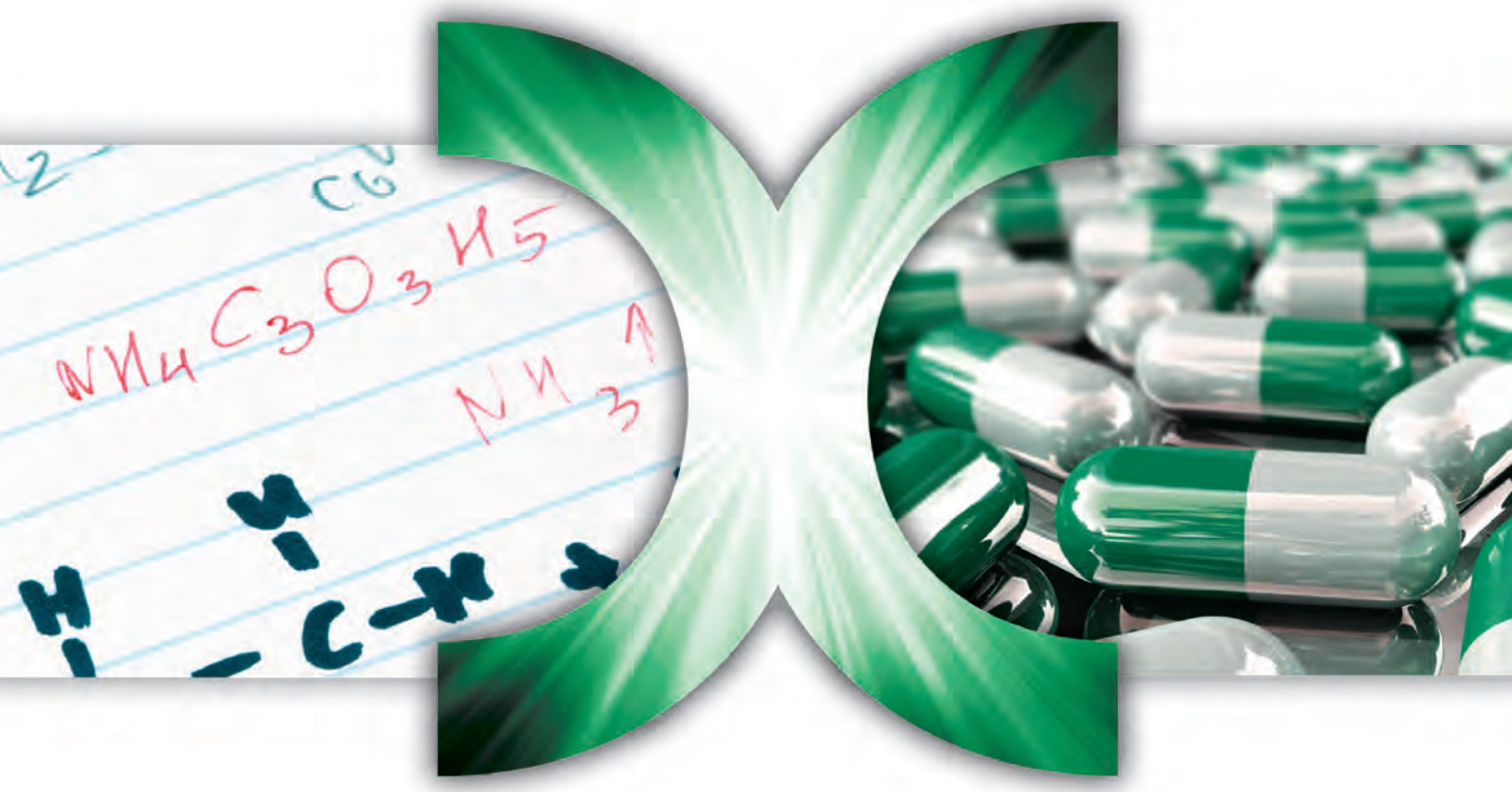
Departments



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KannaLife Sciences, Inc. & Biotech Enter Definitive Joint Venture Agreement

Kannalife Sciences, Inc. and Biotech Inc. have entered into a 50/50 joint venture agreement through the creation of South Park Ventures, LLC (SPV). As part of the Joint Venture agreement, KannaLife has acquired the rights, titles, and interests in Cannatol, a phyto-medical compound, derived principally from a highly standardized, consistent, and high yielding organic cannabidiol phyto stock, free from pesticide and mold contaminants in exchange for 1 million shares of KannaLife Sciences, Inc. common stock and a capital investment in SPV.

"We are blessed and truly fortunate to have partnered with Jason Cranford and Biotech Inc," said Dean Petkanas, CEO of KannaLife Sciences, Inc. in regard to the creation of South Park Ventures. "Jason Cranford is one of the top horticultural scientists in the United States and has proven himself time and again as one of the leading experts in the cultivation of naturopathic and botanical medicaments. Two years ago, he was awarded the prestigious Cannabis Cup, held in category for the first time and specifically to entries of cannabidiol (CBD) producing phenotypes. Jason Cranford's award winning specimen was an organically produced cannabis phenotype, hybridized over a 3-year period and tested with a certificate of analysis recording the highest yielding organic CBD (cannabidiol) yield known to date at over 34%. His botanical research and knowledge of plant variants will play a critical role in the establishment of reference standards for KannaLife's formulary, database, and standardization processes for botanical medicaments."

"Partnering with KannaLife Sciences opens up a window to establishing industry standards for phyto-medical products, which includes providing certification, quality control, and quality assurance standards for the growing of botanicals for use as medicine," added Jason Cranford, CEO of Biotech.

mPhase Technologies to Include R&D of Delivery Systems to its Smart NanoBattery Technology

mPhase Technologies, Inc. recently announced that it is broadening its focus on its path-breaking battery technology to include research and development of drug delivery systems. In February 2013, mPhase filed a US Letter Patent Application for a novel drug delivery system based on its Smart Surface technology.

The drug delivery patent is based on mPhase's Smart Surface technology enabling the automatic dispensing of a pre-set dosage of a drug agent or medication. mPhase believes the research could lead to a novel drug delivery system, possibly creating greater shareholder value.

Recently, mPhase received the 2013 North America Frost & Sullivan Technology Innovation Award for its pioneering nanobattery technology.

mPhase Technologies is a leading nanotechnology innovator in Smart Surfaces. Potential applications include energy storage systems, drug delivery systems, self-cleaning systems, liquid and chemical sensor systems, and filtration systems. mPhase has pioneered its first Smart Surface-enabled product, the mPhase Smart NanoBattery.

Rexam Healthcare Readies Clic-Loc 4 for Launch

Rexam Healthcare recently announced it will launch the latest version of its industry reference child resistant closure (CRC) - the Clic-Loc® 4 - later this year, in anticipation of the rapid, worldwide growth in demand for oral dose packaging protection.

Rexam's Clic-Loc is the first and only CRC available to combine more than 40 years of demonstrated safe and effective oral dose protection, adult-friendly operation and multiple manufacturer benefits. The Clic-Loc delivers superior ergonomics, is easily used on production lines, and creates an audible warning click to alert parents and caregivers.

The new Clic-Loc 4 will provide enhanced functionality and aesthetics, for industry-leading protection, production efficiency, and product differentiation. For example, it is designed with a wider application torque window and offers enhanced decoration.

Importantly, the Clic-Loc 4's senior-friendly, deeper, and coarser outer knurling pattern improves grip and offers easier operation for adults, based upon market research. V-rings allow for a liner-less option, and versatile 38-mm stock options include printed word, printed pictogram, or raised and highlighted word versions. Custom graphics, printed with up to three colors, are available for superior visual appeal. Overall weight and height are reduced. With a positive on-drive, no push-down is required.

Like the current Clic-Loc, the new edition is shrink-wrap friendly, and offers unsurpassed capper flexibility and variety. Importantly - with the aging of the worldwide population - the Clic-Loc is designed for secure and frustration-free usage by seniors and those with disabilities.

"The design of our Clic-Loc 4 underscores our commitment to putting patients first," said Russ Bryant, Global Marketing - Containers & Closures, Rexam Healthcare. "There is worldwide awareness of, and concern about, the tragic increase in young children who are accidentally exposed to medicine. Organizations such as Safe Kids Worldwide report chilling statistics and, as global industry leaders, we have preemptively developed the CRC we believe is the answer - for children, parents and our customers."

The Rexam Clic-Loc design was first introduced in 1972 and has earned over 4 decades of trust, respect, and confidence from the world's most innovative, respected, and demanding healthcare product manufacturers, due to its performance, features, and production line compatibility.

Bayer AG Strikes $520-Million Collaboration With Seattle Genetics, Inc.

Seattle Genetics, Inc. recently announced it has entered into a new antibody-drug conjugate (ADC) collaboration with Bayer HealthCare. Under the latest relationship, Bayer will pay upfront and option exercise fees of up to $20 million for worldwide rights to utilize Seattle Genetics' auristatin-based ADC technology with antibodies to several oncology targets. Seattle Genetics is also eligible to receive up to approximately $500 million in potential milestone payments, as well as royalties on worldwide net sales of any resulting products under the multi-target collaboration. Bayer is responsible for research, product development, manufacturing, and commercialization of all products under the collaboration.

"The significant clinical and preclinical progress across our ADC collaborations, and enthusiasm for our technology as demonstrated by this latest relationship with Bayer, continue to reinforce Seattle Genetics' leadership position in the field," said Natasha Hernday, Vice President, Corporate Development, at Seattle Genetics. "Across internal and collaborator programs, there are more than 15 ADCs in clinical development using our technology, and we have the potential to receive more than $3.5 billion in future milestones plus royalties from these strategic alliances."

"Bayer is committed to translating the science of cancers into effective therapies that can help people with cancer live longer and improve their quality of life," said Prof. Andreas Busch, Member of the Bayer HealthCare Executive Committee and Head of Global Drug Discovery. "Antibody-drug conjugates are promising approaches in oncology which can attack tumor cells in a much more targeted way for cancer patients, such that healthy cells are less severely affected. Antibody-drug conjugates are one of our focus areas in oncology research, and we are looking forward to strengthening our portfolio in this area of personalized medicine through the collaboration with Seattle Genetics."

Aragon Pharmaceuticals to be Acquired for $1 Billion

Aragon Pharmaceuticals Inc. recently announced a definitive agreement with Johnson & Johnson whereby Aragon will be acquired for $650 million in cash up front along with $350 million in contingent development milestone payments that could bring the total transaction value to $1 billion. The acquisition includes Aragon's androgen receptor antagonist program, including its most advanced compound, ARN-509, a second-generation androgen receptor signaling inhibitor that is currently being evaluated in a Phase II trial in patients with castration-resistant prostate cancer.

Prior to closing, Aragon will spin off an independent, newly formed corporation called Seragon Pharmaceuticals, which will be focused primarily on Aragon's Selective Estrogen Receptor Degrader (SERD) platform, including ARN-810, its lead SERD currently being evaluated in a Phase I trial for ER+ metastatic breast cancer. Seragon will be based in San Diego, CA, and will be financed by the current Aragon investors. It will retain members of the management team including, Richard Heyman, current Chief Executive Officer of Aragon, who will become Seragon's CEO. Johnson & Johnson will not have an ownership stake in Seragon nor retain any rights to its technology or product development pipeline.

"This agreement represents seamless transition between Biotech and Pharma and will provide an optimal outcome for the ARN-509 program and the prostate cancer patient community. The Aragon team is passionate about bringing game-changing therapies to cancer patients and is excited to have Johnson & Johnson carry forward this innovative prostate cancer treatment. Johnson & Johnson is clearly a recognized leader in the oncology field, and their development and commercial capabilities in the prostate cancer area are unparalleled," said Richard A. Heyman, PhD, Chief Executive Officer and one of the Co-Founders of Aragon Pharmaceuticals.

Aragon is focused on the development of second-generation anti-hormonal agents for hormone-driven cancers. The company's portfolio of small molecule therapeutics is in part based upon pioneering research by Charles Sawyers, identifying key molecular events that lead to drug resistance to traditional anti-hormonal therapies.

Avomeen Analytical Services Announces New Complex of Laboratories

Avomeen Analytical Services recently announced it has finished moving into its new location, which was inspired by the consistent growth the chemical testing laboratory has experienced during recent years. Avomeen's new location is over 25,000 sq ft and houses multiple state-of-the-art product testing and development laboratories.

Having multiple custom built laboratories linked in one central location allows Avomeen to help its clients save time and money by utilizing a single site to complete their entire project. Clients interested in new product development services appreciate that Avomeen's chemists can perform all of the steps needed in order to turn their original concept or idea into a finished product. Customers that require additional support in bringing their finished formulation to market can utilize Avomeen's chemists to source raw materials, locate a proper packaging supplier, patent their new formulation, and identify a proper formulation blender to manufacture the finished product on their behalf.

The new complex contains multiple laboratories that were specifically designed to be segregated from one another to ensure that cross-contamination between stages of analyses and multiple customers' projects do not occur. The new laboratories include an SEM/EDXA Lab, Chromatography Lab, R&D Lab, Formulation Lab, and a cGMP Pharma Lab. Avomeen's new pharmaceutical laboratory was specifically designed for method development and validation services under cGMP compliance. The testing laboratory continues to maintain its FDA-registration and its ability to handle controlled substances through its DEA license for schedule I through V controlled substances. The testing laboratories' new location is 4840 Venture Drive, Ann Arbor, Michigan, 48108.

Avomeen performs testing services on a wide range of consumer and industrial products. At this new location, materials tested include pharmaceuticals, neutraceuticals, cosmetics, polymers, rubbers, additives, adhesives, chemicals, cleaning products, coatings, packaging, medical devices, as well as food and beverages. The new facility allows for larger workspaces for chemists, additional meetings rooms, and areas for more expansive training. Already frequently serving clients nationwide, the expansion allows Avomeen to continue to grow and conduct its custom product testing and development services for a larger number of clients.

Avomeen's clients range from entrepreneurial start-ups to major fortune 100 companies. Its chemists primarily serve technology companies, manufacturers, distributors, lawyers, and other laboratories that require complex testing services.

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Management Insight

Lessons From the Auto Industry

By: Derek Hennecke, CEO & President, Xcelience

Part 6 of a 6-part series offering an overview of this year's six best business books with insights into what they can teach the Pharma industry.

Chevrolet is an all-American car. Ferrari is thrilling. Kit Kat goes with coffee on your break. Campbell's soup conjures up images of warm kitchens and loving mothers in aprons. These are examples of branding - the images that come to mind when you think of a particular product.

Branding may begin very early in the product lifecycle, such as with the identification of a missing segment - let's say a pain product that can't be abused. But in our industry, marketers rarely have the luxury of so much time. More often, the drug is developed first, then the marketing department identifies the target consumer, and finally an image is designed to appeal to that customer.

Branding is a vitally important part of the sales process, but there is such a thing as too much branding, says Bob Lutz in his straight-talking book, *Car Guys vs. Bean Counters*. One of America's most respected business leaders, Mr. Lutz is a veteran of GM, BMW, Ford, and Chrysler, but he's best known for the last decade of his career when he was pulled out of retirement to turn GM around. GM had become so wrapped up in developing brand images, says Mr. Lutz, that the company had lost sight of the need to develop excellent, high-quality, and desirable cars.

GM's Saturn brand may well go into the MBA textbooks as the poster child for over-branding. The target buyer for Saturn was defined as the "post-modern transportation user" who saw his or her car only as means of getting from A to B. The brand focused exclusively on customer friendliness in the sales experience - so much so that the character of the car itself was deemed irrelevant. As such, the car developed for this buyer was, well - characterless. Just a means of transportation. It was soon buyer-less as well, and the last Saturn rolled off the assembly line in 2009.

In a similar branding blunder, GM marketers decided that the five-spoke wheels of the Chevrolet were a defining characteristic; so only Chevys could have five spokes, thereby enhancing the brand's market differentiation. Unfortunately, this strategy failed to take into account all of the other carmakers, many of which continued to actively produce five-spoke models.

Opel, in an attempt to please a price-conscious target market, accepted cost-cut upon cost-cut, until the factory was actually ordered to stop polishing and smoothing the metal prior to painting, a process known as "metal finishing" which was, at the time, necessary to ensure a lump and blemish-free paint job. The resulting patchy paint job did not transition smoothly into American garages.

With Mr. Lutz at the helm, GM began to relearn the art of making iconic cars. Product excellence returned to the forefront of considerations with the development of the Chevrolet Volt, the Equinox, the Cadillac CTS, and the Buick LaCrosse, among others.

Branding is not forgotten in the new GM, merely repositioned. The new LaCrosse, for example, is a vastly improved product that is also completely rebranded. For years, LaCrosse was a fixture of the over 68 year olds' Florida garage; admittedly an endangered market. The new LaCrosse has been completely rebranded for a youthful buyer, offering Bluetooth and other high tech features and featuring Shaquille O'Neal as a celebrity endorsement.

In *Car Guys vs. Bean Counters*, Mr. Lutz offers a hotly opinionated, straight up, cigar-smoking take on American industry, and the fight to return to product excellence. Sometimes arrogant and not one to mince words, he may offend at times, but his experience provides food for thought that can be applied to any industry.

PHARMA BRANDING

Pharma will never be able to brand the way the car industry does. We simply don't have as much time as the car guys have. Lee Iacocca could begin with a concept: "We need a good fast sports car that most people can afford." He could put his designers to work creating a car for that segment. His marketers could choose a racy and exciting name - like Ford Mustang. Then they could spend literally decades developing and refining the image.

It takes 36 to 48 months to bring an average car from paper to product - a remarkably long time in the retail segment where R&D for most products is usually said and done in fewer than 6 months, with brand development tacking on another year. The marketing efforts that support the brand then come into place and can stand behind the brand for decades. Brand destruction rarely happens in the retail world, and the concept of lifecycle management is virtually unknown.

In pharma, R&D takes 10 to 15 years. Drug patents last 20 years, but because they are applied for before clinical trials, the effective life of a drug once it hits the market is 7 to 12 years. After that, the brand fizzles and self-destructs.

True, there are some drugs that have hung around. Premarin launched in 1942 and didn't peak until 2001. That's nearly 60 years. Augmentin launched in 1981 and also peaked in 2001, a run-up of 20 years. Most drugs however are launched like fireworks, appearing on the marketplace in a sudden bright flash before fading to black.

Pharma branding rarely begins before product development. More often than not, our products are created first, and markets are identified after. It would be folly to pour resources into brand development in Phase I or II, where the rate of failure far exceeds the rate of success.

Phase III, however, is a different story. In this phase, the fledgling drug is going to meet its first targeted patients and doctors, and it needs to do so with at least a tentative persona associated with it. AstraZeneca claims the ideal time to develop a brand is between Phase II and Phase III.

"The marketing team is heavily involved in [Phase III] clinical trials," Jon Parton, Director of Direct Marketing at AstraZeneca told *BrandChannel* last May. "With a brand's product profile already established, if a particular claim is important, the team needs a study to prove it. We're not selling coffee - we can't say

things we can't support."

Unfortunately, far too often, branding in many companies doesn't begin until well into Phase III. This can be because of internal delays or factors beyond the company's control - another company launches a competing product, a change in government policy, or another R&D breakthrough causes the product to be fast-tracked unexpectedly.

Then there is the rather sticky question of defining whom we are branding for. Who are we really selling to? Is it the patient? The prescriber? Or the payer (insurance company or the government)? Even within these three segments are numerous sub-segments. All patients with type 2 diabetes, for example, are not the same. They may be at different stages in the disease, have different contraindications, and different compliance rates. Physicians too can be categorized, primarily into those who are more or less willing to try new products. Those more willing will be targeted for new drug releases; those less willing gain the marketing attention of companies trying to defend established products.

Payers are a relatively recent addition to the segmentation game, and they too can be sub-divided into those who prescribe with the sole purpose of minimizing cost, and those who emphasize a holistic approach to curing a patient's condition.

These three segments and their sub-segments define the pharma customer, and serve a purpose in trying to simplify a very complicated picture, but the model is increasingly unsatisfactory. More and more patients and patient advocacy groups are making more prescribing decisions than their doctors. Early adapting doctors are often constrained from prescribing when payers prohibit it.

Perhaps as compensation for a brief product lifecycle and fragmented target market, our industry throws a lot of money at the problem. According to the London-based medical Journal BMJ, the pharma industry spends $19 on marketing for every $1 spent on R&D. It wouldn't be hard to argue that this represents significant over-branding. Mr. Lutz would tell us to put a little more of this money back into R&D, and get back to focusing on product excellence.

PHARMA MANUFACTURING

Transplant an engineer from a 1950s car plant into a modern factory and he'd barely recognize the place, write Gonce, Andrew, and Schrader in *Plantopia? A Mandate for Innovation in Pharma Manufacturing*, published by McKinsey and Company. Welding robots buzz and hum, fast changeover paint booths blast color, and the just-in-time parts delivery system supplies outsourced parts precisely as they are needed.

Transplant a chemist from the same generation and my guess is he'd be a little disappointed. Sure, we have computers and HPLCs, but is the manufacturing process changed enough to make him wonder if he'd wandered into the right place? Probably not. The blockbuster model of excess capacity is still the norm, despite the recent death, or at least near death, of the blockbuster model. The drug development pipeline is serving up drugs that need smaller batches, shorter runs, and higher quality, but the manufacturing process remains unchanged. There have been moves toward leaner production, tweaking here and there, but not redesigning from the ground up, as other industries have done.

"Pharmaceutical manufacturing operations are inefficient and costly," wrote the FDA in 2004, as quoted by Gonce, Andrew, and Schrader. "Compared to other industrial sectors, the rate of introduction of modern process design principles, new measurement and control technologies, and knowledge management systems is low. Opportunities for improving efficiency and quality assurance...are not generally well recognized." A scathing rebuke from arguably the paramount bureaucracy of our industry. Ouch.

Nothing much has changed since that quote was transcribed a decade ago. By now, we should see widespread use of continuous batch manufacturing and biologics production in disposable reactors. Online process analytical technology (PAT) and control limits - long since entrenched in the automotive industry - should be mainstream in pharma too. Why is Quality by Design (QbD) almost unknown in our industry? We haven't even adopted the basic U-shaped packaging line or work cell, which is no longer even considered new in consumer goods manufacturing. Outsourcing, while growing, is still considered cutting-edge, whereas it should be basic practice.

Gonce, Andrew, and Schrader identify three possible models for production that could be used as blueprints for what they call "Plantopia" - the ideal pharmaceutical plant. They are Intel, Disney, and Nucor.

THE INTEL MODEL

Intel produces 10 billion transistors a second, which ought to earn it a black belt in manufacturing, if there were such a thing. In fact, the iconic semiconductor manufacturer considers its manufacturing processes to be a key strategic asset, equal in importance to its famous cutting-edge product designs.

Intel uses a methodology called design for manufacturability (DFM), which involves manufacturing in the design process to ensure that the final design can enter seamlessly into production. It's a process that emphasizes speed but also agility, so that manufacturing can shift gears to accommodate design improvements as they arise.

How would this translate into the pharma world? Imagine a standard tablet core produced at very high speeds with state-of-the-art control systems, with precise and flexible coating processes capable of speeding an array of products to market, suggest Gonce, Andrew, and Schrader. Imagine no gap between development and manufacturing, and perfect product launches that begin best-in-class costs.

This Intel-inspired pharma plant would be fully integrated, beyond Quality

by Design (QbD), highly automated, with Six Sigma performance levels on all key parameters. All designs that failed to align with the common platform would be outsourced. All products would be cost-effective, even after patent expiry. Products would come to market in half the time.

THE DISNEY MODEL

The Disney model offers inspiration for developing complementary products and services offered to support the core product. Think of all the wonderful movies Disney produces (accessories sold separately). The accessories are not a tag on. Movies are in fact chosen and developed based on their ability to sell additional products, games, theme park attractions, etc.

Imagine a pharma plant that tracked and trended patient behavior using, among other things, a microchip imbedded in a pill or vial to track intake time. Such data could be used to improve efficacy and compliance, creating something like an ongoing clinical trial constantly generating new and insightful patient data. The outcome could save healthcare systems billions of dollars in waste, according to Gonce, Andrew, and Schrader.

Would you like an app that could tell you all of your new medications drug interactions? What if pills came with customer support hotlines? This is the Disney model, which stresses ancillary services offered to support the core product.

Medco is on the forefront of this approach, using healthcare information it's been gathering for years from subscribers and opening nine therapeutic resource centers with over a thousand pharmacists trained in one of a dozen or more chronic diseases. These specialists use Medco's extensive database to help patients manage their illnesses, particularly diabetes and cardiovascular problems, which account for 90% of all drug spending and 75% of all healthcare costs. This type of forward thinking saves Medco money, but also saves employers, taxpayers, and patients money as well, not to mention keeping people healthy.

THE NUCOR MODEL

Mammoth, smoke-belching, 24-hour steel mills are rapidly being confined to the pages of history. Nucor reinvented it. Small and lithe, the new mini-mill is a tenth the size of the old mills, using less than half the amount of electricity. By recycling steel, Nucor cut costs and was free to locate a mini mill anywhere vehicles are scrapped, which is pretty much everywhere. The plants are strategically placed close to customers and able to turn on and off according to demand.

The Nucor vision of a pharma plant would be located right next to the hospital. It would be small and quick, able to produce to demand within hours or minutes by simply adding API to an existing standardized core production system, say Gonce, Andrew, and Schrader. Quality would be automated, and packaging would be standardized to reduce cost. Each plant would be run by an operator who would administer a central marketing management system, and monitor data to root out problems and repair systems remotely.

THE LUTZ VISION: LESS BRANDING; MORE R&D, BETTER MANUFACTURING

The Lutz vision of pharma would start by redirecting resources away from branding and putting it back into R&D. Then it would revamp the manufacturing process to make it do what it was meant to do - produce medications efficiently, cost effectively, and close to consumers, while developing ancillary products to support the core product in its role of helping the patients manage their illnesses. With all the money that would be saved, pharma could put it into - you guessed it - more R&D for more excellent products (accessories sold separately). ◆

BIOGRAPHY

Derek G. Hennecke is President and CEO of Xcelience, a CDMO in formulation development and clinical packaging located in Tampa, FL. Mr Hennecke launched Xcelience as a management buyout in 2007, and the company has more than doubled in size. Prior to starting Xcelience, Mr. Hennecke worked for DSM as a turn-around manager in the global drug development community, managing an anti-infectives plant in Egypt, technical and commercial operations in a JV in Mexico, and a biologics facility in Montreal. He developed the formulation and business strategy of several drug compound introductions such as clavulanic acid, erythromycin derivatives and Tiamulin. A Canadian, he covets the Florida sun, but can't be kept away from the rink for long. He is an avid fan of the Tampa Bay Lightning.

Marketing Matters

3E Trilogy: Entertain, Educate & Engage…..Become an Infotainer

A multiple part series on effective messaging and communications in the life science industry.

By: David F. Scelba, Partner, LifeSciencePR

In my previous column (May 2012, page 24-25), I provided a general overview of my four trilogies and four simple steps to implementing a social media strategy. In this column, I'll explain in greater detail my 3E Trilogy …Entertain, Educate & Engage.

Now, it doesn't really matter if you're in the Life Science industry or frankly any other marketplace. The fact is that effective communications means commanding and keeping your audience's attention, and the most effective way to keep their attention is to entertain them.

One of the best teachers I had in high school was my history teacher Mr. De Nooyer. He was someone who clearly understood the importance of entertaining to educate, and he engaged every student, even those with challenging attention spans. As an example, he would dress up in colonial garb when he was discussing the Revolutionary War. He even wore a German uniform and spoke with a German accent to dramatize the unspeakable evils of the concentration camps of World War II. At the time, we all thought he was nuts, but the truth is, he was a master communicator. His classroom antics and theater helped the lessons "come alive" in an incredibly entertaining and memorable way. It's been more than 40 years since I sat in his class, but I can still remember his lessons like it was yesterday. Mr. De Nooyer was a teacher's teacher and an incredible salesman.

With today's technologies and multiple social media outlets, Mr. De Nooyer's entertaining lessons could have been delivered and distributed to an infinite number of virtual classrooms and inquisitive students throughout the world.

But while YouTube, Facebook, Twitter, LinkedIn, Pinterest, and all the other social media outlets deliver content to the right targeted audiences, they won't gain an audience if the content isn't entertaining.

The key to implementing a successful social media strategy is the development of interesting content and, of course, the creative execution. You've all heard the saying, "Content is King," and it's absolutely true, but only if it's presented in an entertaining manner.

By now everyone knows video is the most efficient and effective communications tactic used throughout all websites, blogs, social media networks, and mobile apps. Just as Mr. De Nooyer was never embarrassed about wearing uniforms or acting in front of the live class, you shouldn't be self conscious or feel silly reading from a teleprompter in front of a video camera.

So let your creative juices flow and become an "Infotainer" with the ultimate goal of entertaining your audience. If you develop good content and creatively present it, you'll educate your audience and engage them in ongoing communications. Engagement acts as one measurement matrix of your content and creativity, and is an indicator of whether you're doing a good job communicating.

Entertain, Educate & Engage … my simple 3E Trilogy to better, more effectively, and efficiently leverage social media communications to achieve your company's strategic marketing and communications initiatives! ◆

BIOGRAPHY

David F. Scelba is the Founder and Chairman of SGW Integrated Marketing & Communications and is a Partner at LifeSciencePR. He is responsible for the development of the company's new interactive products and services and plays a key role as senior strategist for developing clients' integrated marketing communications programs. He is also involved in researching and investigating acquisition opportunities and for initiating negotiations on behalf of the company. As a consultant to the broadcast, computer, and telephone industries Mr. Scelba experienced the technology convergence first hand. This unique background provides him the ability to develop innovative products and services that generate the most cost-effective and efficient marketing strategies available today. His diversified B2B, consumer, and retail experience encompasses industries such as: automotive; biochemical; broadcast; education (K-12-colleges/universities); healthcare; hospitals; life science; microwave; pharmaceutical (research/drug delivery); political; professional video/audio; medical; telecommunications; and more. He is a keynote motivational speaker whose audiences include marketing professionals, college professors, MBA graduate students, and undergraduates seeking careers in the marketing- and communications-related industries. He also mentors business and government leaders on the use of technologically innovative tools for better communication with their targeted audiences. Mr. Scelba earned his BA and MA in education, a CFP Certification, with series 6 qualifications, Health/Life and Real Estate Licenses, which contribute to his common sense marketing philosophy.

The Second Quadrant

Out of the Shadows: Excipients Take the Spotlight; Part 2

By: Marshall Crew, PhD, President & CEO, Agere Pharmaceuticals, Inc.

A multiple-part series discussing today's most challenging issues in solubility.

In June's edition of *The Second Quadrant*, we heard from leading excipient providers about challenges faced directly related to formulating with excipients for greater bioavailability. They also made suggestions for exploiting opportunities by better leveraging the power of adjuvants and collaborating with other players in the ecosystem. The conversation concluded with observations about the barriers that must be crossed to fully realize solubilization potential.

In Part II, we've asked representatives from Ashland, BASF, Croda, EMD Millipore, and Shin-Etsu to continue the dialogue and share their thoughts on past breakthroughs that have enabled progress to date, and what we can expect as we approach the next decade. They've also revealed surprising or little known aspects of the role excipients play in moving our industry forward to overcome the bioavailability barriers we face.

"…drug manufacturers have adopted more active roles with the excipients' manufacturers to streamline time and cost by building a true partnership."
(Dr. Shaukat Ali, Technical Sales Manager, BASF Corporation - Shaukat.ali@basf.com)

PAST BREAKTHROUGHS

Q: What have been the most significant developments in bioavailability understanding, equipment, or platforms in the past 5 years that directly involve excipients or how they're used?

Dr. Shaukat Ali: The non-conventional formulation technologies have now been widely recognized in the industry to increase solubility and bioavailability of drugs. The solid dispersions technologies requiring polymers for dissolving poorly soluble drugs for tableting and liquid dispersions technologies requiring lipid-based emulsifying drugs systems (surfactants and solubilizers) for soft/hard gel capsules, have been leading platforms adopted by many industries as the viable options. With a recent surge in Class II and Class IV drugs, and trends in availability of new and innovative polymers, such as Soluplus® by BASF, the drug manufactures are weighing in investing more in the solid

"…enabling technologies may become the new norm and cease to be considered as specialized formulation technologies."
(Dr. Vivian Bi, Technical Director, Solubilization & Contract Research Services, Ashland Specialty Ingredients - Vbi@ashland.com)

dispersions/solutions technologies to expedite formulation and drug development processes.

Dr. Vivian Bi: Throughout the past 5 years, the pharmaceutical industry has embraced amorphous solid dispersion technology as a viable, FDA-acceptable enabling technology to increase the bioavailability of poorly soluble drugs. This is not a new technology, the concept has been around for over 50 years, but adoption and acceptance has taken some time due to concerns over the long-term stability of the solid-dispersion intermediate. Excipients have played a critical role in contributing to the stability and are one of the key components for success.

In recent years, hot-melt extrusion (HME) has become a mainstream method for processing amorphous solid dispersions. The in-line analysis capacity of HME has provided

"We see the industry heading toward higher scrutiny in regards to excipient quality.... increasing supply chain transparency for excipients."
(Jeffrey L. Shumway, Associate Director Sales Development, Bioavailability Enhancement Process Solutions, EMD Millipore - Jeffrey.shumway@emdmillipore.com)

additional momentum in its development. Thermal behavior of excipients, which in the past was often not evaluated, has become one of the key factors that dictate the HME process as well as the performance of solid dispersion.

Further, a series of recent investigations by Dahan et al on the interplay between apparent increases in aqueous solubility and decreases in intestinal membrane permeability, revealed the trade-off between these two parameters when using solubility-enabling technologies.[1,2] The trade-off was identified in cyclodextrin-, surfactant-, and cosolvent-based systems. Meanwhile, research on nifedipine solid-dispersion formulation indicates concomitant increase in the drug's flux through the intestinal membrane in addition to its significant solubilization enhancement effect, and the two-fold advantage of solid dispersion has explained why it is so effective in bioavailability enhancement. These research results suggested a thorough understanding on the in vivo behavior of APIs in the presence of excipients can help predict the impact of excipients on API permeability, in addition to their solubilization effects.

Sakaé Obara: With respect to Shin-Etsu, a new drug product was approved and marketed in 2011, which is the first case in the US and Europe of solid dispersion using one of our polymers, HPMCAS. This was also the first time Shin-Etsu became involved with a QbD approach, in which we prepared a series of samples with various properties for a DoE evaluation by the excipient user. Another drug product using the same polymer was launched in this period, but in this case, using a different application method (co-precipitation), because neither spray-dry nor melt-extrusion could be used due to the characteristics of API. For such APIs, other new technology, such as KinetiSol® (developed by DisperSol Technologies, TX) is now also available.

Jeffrey Shumway: The past 5 years have provided a significant shift in the need for bioavailability understanding; equipment and platforms that directly involve excipients and have driven better understanding of novel applicability of existing excipients. As an example, compounds such as meglumine, an amino sugar derived from sorbitol, with historic application as a contrast reagent for medical imaging, can be used as a solubility-enhancing excipient or in applications for improving stability of biomolecules as a counter-ion.

WHERE WILL WE GO FROM HERE?

Q: Where do you see the industry heading throughout the next 5 years, and the role excipients and excipient providers will play?

Dr. Shaukat Ali: The pharma industry has kept all options on their

drug development disposal, with clear understanding to shorten the development time and reduce cost, and bring the innovative drugs faster to the market. Therefore, the drug manufacturers have adopted more active roles with the excipients manufacturers to streamline time and cost by building a true partnership.

Dr. Vivian Bi: Poorly soluble APIs will continue to present significant challenges in drug development. Enabling technologies, such as solid dispersion, lipid-based drug delivery systems, nano-crystalline particles and so on, will continue to play key roles in the development of poorly soluble APIs. With more in-depth understanding of mechanisms, formulation design, characterization, and manufacturing processes, the cost, timeline, and risks inherent in developing these APIs will be reduced significantly. In the near future, such enabling technologies may become the new norm and cease to be considered as specialized formulation technologies. By gaining better understanding of existing excipients and developing unique grades of existing excipients as well as new excipients, excipient providers can make important contributions to the increased use of these enabling technologies.

Serge Kechichian: The drug pipeline will continue to lean heavily and more significantly toward drugs within the low solubility BCS Class II and IV categories. Because of this, a greater dependence will fall upon excipient manufacturers to provide more novel solubility and bioavailability solutions. For those drugs with higher solubility, formulators will be looking to increase half-life and lowering the drug dosage. Thus, the need for increased drug stability and efficacy will increase in demand. For these types of formulations, higher purity excipients that contribute to enhanced drug stability, efficacy, and ultimately bioavailability and performance will be looked at more.

Sakaé Obara: An even closer relationship between excipient providers and users will be essential. Each project should develop into a closer technical collaboration, rather than a simple relationship of vendor and customer. Every API is unique, and this means that going forward, we will need to consider tailor-made excipients; this remains a big challenge and dictates closer vendor-customer interactions. Another opportunity for helping our customers realize the potential of Shin-Etsu excipients lies in helping them understand more about our excipients. Although in one monograph, it is typical that an excipient has multiple grades that have different characteristics and should be properly chosen.

Jeffrey Shumway: We see the industry heading toward higher scrutiny with regard to excipient quality. There will be a particular focus on the excipient supply chain, which will be partially driven by governmental regulations. As part of the Drug Supply Chain (Title VII) of

"…a greater dependence will fall upon excipient manufacturers to provide more novel solubility and bioavailability solution."
(Serge Kechichian, Key Account Manager, Health Care, Croda - serge.kechichian@croda.com)

the FDA's Safety and Innovation Act (FDASIA), excipient manufacturers will be required to register their excipient manufacturing sites with the FDA, whereby a unique facility identifier will be required. The drug manufacturer will then be required to list all sites in which excipients are used in their generic drug manufacturing process. These requirements are just one step toward increasing supply chain transparency for excipients.

Efforts by the International Pharmaceutical Excipients Council (in which EMD Millipore is an active committee member), have encouraged the use and development of new and novel excipients. They have developed a novel excipient evaluation procedure as an independent process to help reduce the cost and uncertainty related to use of novel excipients in pharmaceutical formulations. Ultimately, this encourages the use of novel excipients in drug development programs and encourages drug formulation innovation. We believe that excipient manufacturers, distributors, and excipient users will

"An even closer relationship between excipient providers and users will be essential."
(Sakaé Obara, Technical Director, Shin-Etsu Chemical Co., Ltd. - obaras@shinetsu.jp)

continue to work more and more closely together to achieve higher quality for these materials with the ultimate goal of increased patient safety.

NEW OR SURPRISING INSIGHTS

Q: Is there any information about solubilization excipients, their applications, or the benefits they can deliver you believe DDD readers would find surprising?

Dr. Shaukat Ali: *Drug Development & Delivery* readers are all aware of the challenges the industry is facing today. With challenges mounting in the solubilization of NCEs, there are only few options available in the solid dispersions (eg, spray-drying, hot-melt extrusion, Kinetisol®, and electron-spraying among others) or the liquid dispersions (eg, self-emulsifying drug delivery systems or SEDDS/SMEDDS. BASF is addressing the need for new materials and developing innovative excipients. It is expected that with more choices in the excipients selection and understanding their safety and regulatory profiles, the industry will continue to assess both solid and liquid dispersions technologies to expedite drug development to reduce time and cost to meet unmet needs and patient compliance.

Dr. Vivian Bi: Hypromellose acetate succinate (HPMC AS) has been proven to be an effective solid-dispersion carrier, as evidenced by the FDA approval of three new pharmaceutical products formulated as solid dispersions with HPMC AS. Until last year, the three commercial grades of HPMC AS (L, M, and H) were only available from a single source. Ashland announced in December 2012 that it will be adding all three grades to its portfolio of excipients for solubilization and other pharmaceutical applications in 2013. In addition, Ashland is

working closely with its customers to design new grades of HPMC AS with improved functionality for solubilization. These novel and exciting excipients will provide additional solutions for conquering the challenges of poorly soluble APIs.

Serge Kechichian: High purity excipients can greatly impact solubilization and stability due to the lower peroxide levels present. Having ultra low peroxide levels have provided tremendous cost savings for large pharmaceutical companies; as high as $2 million. The increased solubilization that is permitted by the utilization of Super Refined excipients go hand in hand with an increase in permeability and bioavailability.

Sakaé Obara: New grades for processes of solubility enhancement are continuously being developed. While new excipients and new process technologies are current hot topics in the pharma-tech world, it may not be well-known that two commercial products (both immediate release and delayed release) claiming solid-solution were first marketed back in 1979 in Japan, using conventional excipients.

Jeffrey Shumway: Recent developments and understanding regarding inorganic solubilization-enhancing excipients, which have already received Generally Recognized As Safe (GRAS) designation by the FDA, may provide novel solutions for APIs with challenging solubility properties and may serve as potential solutions to reduce formulation complexity.

NEXT STEPS

In subsequent issues, we will learn the thoughts and perspectives of solubilization technology providers, researchers, equipment providers, and the pharmaceutical and biotechnology companies. To ensure *The Second Quadrant* serves as a forum for interactivity and collaboration, I invite you to send your reactions, thoughts, and suggestions so we can continue our dialogue. I look forward to hearing from you, and together moving toward greater solubilization.◆

REFERENCES

1. Dahan A, Beig A, Ioffe-DahanV, et al. The two-fold advantage of the amorphous form as an oral drug delivery practice for lipophilic compounds: increased apparent solubility and drug flux through the intestinal membrane, AAPS J. (in press).
2. Dahan A, Miller J. Drug precipitation-permeation interplay: supersaturationin an absorptive environment. Eur J Pharmaceut Biopharmaceut. 2012;82:424-428.

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Amorphous Dispersion Formulation Development: Phase-Appropriate Integrated Approaches to Optimizing Performance, Manufacturability, Stability & Dosage Form

By: John Baumann, Dan Dobry, and Rod Ray, PhD

ABSTRACT

Given the ever-increasing number of compounds that present oral absorption challenges, efficient and "phase-appropriate" formulation development is crucial for robust optimization of key formulation attributes and successful progression of these compounds. Amorphous dispersions enable progression of low-solubility compounds and open multiple opportunities for optimization and understanding during formulation and process development. Deep understanding of the critical-to-performance attributes of amorphous dispersions as they relate to performance, manufacturability, stability, and downstream manufacture into solid dosage forms makes efficient and robust formulation development possible.

This paper discusses the development and use of amorphous spray-dried dispersions (SDDs) and the testing methodologies used to optimize the formulation and spray-drying process for performance, manufacturability, stability, and incorporation into final dosage forms. Innovative models and tools are used to predict and select the optimum formulation and process early in the development process. Use of guidance maps, process development flowcharts, in vitro tests, and models all enable efficient and successful formulation development.

INTRODUCTION

Amorphous SDDs provide multiple opportunities for co-optimization of performance, manufacturability, and stability during formulation development. Process and formulation development are inherently tied to the end goal of developing a robust formulation that can meet the desired bioperformance targets, maintain adequate physical stability, and enable a path to future scale-up (Figure 1). Use of "phase-appropriate" formulation and development models, both experimental and in silico, can be coupled to identify the overlap of process and formulation space.

A previous article contributed by Bend Research was focused on amorphous SDDs, a widely applicable platform technology that has precedence from discovery through commercialization, to improve solubility.[1] Use of guidance maps and determination

FIGURE 1

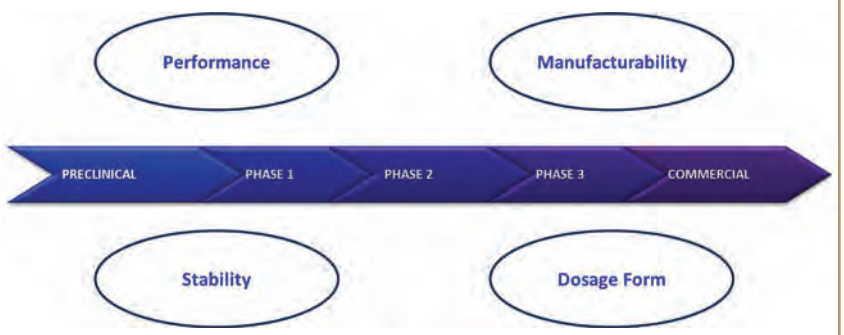

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TABLE 1

In Vitro Test[a]	Compound/Formulation Property									
	Disintegration Rate	Gastric Dissolution	Dissolution Rate	Free Drug Content	Bile Micelle Partition Coefficient	Drug/Polymer Colloids	Ionization	Absorption–Lipid Bilayer	Precipitation Crystallization	Precipitate Composition
Microcentrifuge dissolution–MFDS	X		X		X	X			X	
Microcentrifuge dissolution–gastric transfer	X	X				X	X			
Syringe dissolution		X	X							
Light scattering				X	X	X				
Membrane permeation			X	X	X				X	
NMR				X	X					
Ultracentrifuge				X	X	X			X	
Solubility versus [NaTC/POPC]					X					
Solids redissolution										X
Solids analysis										X
Computation					X		X	X		
Solubility versus pH							X			

[a] MFDS = model fasted duodenal solution, NMR = nuclear magnetic resonance, [NaTC/POPC] = the concentration of sodium taurocholate/1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.

Summary of in vitro tests and key compound/formulation property information.

of critical-to-performance attributes can enable rapid selection of lead SDD formulations for progression of compounds. Rational selection of in vitro techniques to make informed decisions about selection of formulations and the process space can be conducted in a phase-appropriate manner.

PERFORMANCE

Use of SDDs to address the solubilization problems associated with DCS Class IIa/b compounds requires development of a deep understanding of the critical-to-performance attributes for specific drug molecules.[2] Evaluation of key molecular properties and the use of guidance maps based on the physicochemical properties of the molecule streamline formulation screening to enable lead formulation selection. In addition, use of innovative and mechanistic in vitro tests to generate inputs for in silico models provides efficient feedback for definition of critical-to-performance attributes.

Definition of the key problem statement for each unique compound, based on the properties of the compound and target dose, is important to achieve the desired performance attributes. Typically, the primary goal with SDDs is to increase the bioavailability of insoluble compounds by raising the concentration of free drug. Additional delivery challenges and problem statements that are commonly encountered include the following:

1. Dissolution Rate – Dissolution rates are limited for compounds with high lipophilicity. Polymer selection and the addition of surfactants can be critical, as can optimization of SDD particle size.

2. Sustainment – Crystallization of soluble drug, which leads to decreased free drug and active species, must be avoided. The active loading in the SDD formulation may be limited.

3. Activity of Nanospecies – Free-drug levels and ability of colloidal and micelle structures to source free drug must be evaluated.

FIGURE 2

Overview of spray-drying process development scale-up train.

Nanoparticle formation may be critical to the performance of the SDD.

4. Precipitation During Gastric-to-Intestinal Transfer – Precipitation may occur due to high supersaturation for drugs with high solubility in gastric media during transfer to intestinal media. SDDs are formulated to minimize solubility in low-pH gastric media with enteric polymers to sustain the active species of drug in higher-pH intestinal media.

Based on the absorption challenges for the specific molecule, in vitro assays that indicate bioperformance are used orthogonally to understand the key species present and to ensure a robust formulation. Table 1 lists the specific in vitro tests and key formulation properties used to assess the various processes and physicochemical properties that are important during final dissolution of the formulation into critical active species that will enable absorption.

Each test specifically studies the kinetics of formation of one or more of the following: (1) active species that are present in solution, including free drug; (2) drug in bile-salt micelles; and (3) activity of the remaining solid or precipitate formed during the test. Outputs from these tests are also used as inputs into predictive biomodels that guide formulation selection and optimization.

Previous publications have discussed use of the DCS system and formulation maps to guide formulation of SDDs.[3] These approaches streamline formulation selection by using historical experience to evaluate a small number of formulations that are likely to solve the key challenges for a given drug compound and to select the most appropriate in vitro tests. Mechanistic understanding of the key processes is critical to predicting how the formulation will perform in vivo and solving delivery challenges.

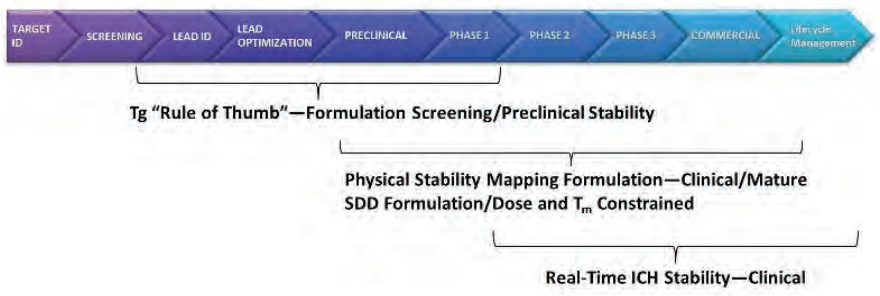
MANUFACTURABILITY

The deep understanding and optimization of the SDD formulation is then combined with careful process development based on engineering fundamentals. This approach results in a robust, high-performance drug-product intermediate that can be manufactured using a scalable process.

The SDD technology and spray-drying process are widely applicable from early stage discovery to formulation development to commercialization. Figure 2 provides an overview of the standard spray-drying process train and typical batch quantities, comparing the different scales of equipment used at each development phase.

Optimization of the spray-drying manufacturing process is straightforward using a fundamental engineering approach.

FIGURE 3



Use of phase-appropriate physical stability tools.

The goal is to demonstrate a robust process space that can be easily scaled. A rational flowchart methodology based on this approach can be applied to optimize the spray-drying process, focusing on two core processes: atomization and drying.[4]

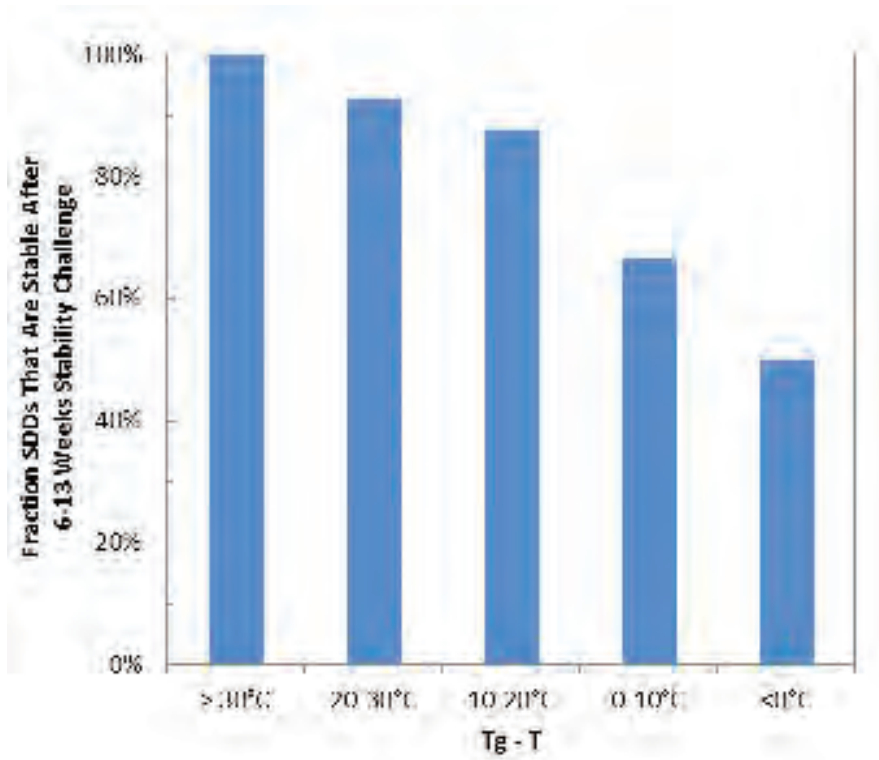
Impacts of the process on critical formulation attributes must be considered during development to ensure the formulation is amenable to future scale-up. The two key processes — atomization and drying — both require a fundamental understanding of the following potential impacts on the SDD formulation:

1. Atomization – More energy is required as the spray-dryer scale increases to maintain the same droplet size and, thus, particle size. It is important to understand the atomization limitations to ensure an equivalent particle size can be produced at larger scales, particularly for high-lipophilicity compounds for which dissolution rate is a critical-to-performance attribute.

2. Recycling of Drying Gas – Closed-loop operation of the spray dryer, which uses a condenser to control the amount of residual solvent in the incoming drying gas, leads to slower drying rates for the SDDs. Slower drying rates impact the final residual-solvent content and compressibility of the SDD particles, which can impact physical stability and manufacturability of the final dosage form. Glass-transition temperature (Tg), a key physical-stability indicator, can be measured as a function of residual-solvent content to predict a process operating space that poses a low risk for physical instability.

3. Densification of Atomized Spray Plume – Higher mass fluxes of droplets through a similar contact area also contribute to slower drying rates. Understanding this change across spray-dryer scales makes it possible to predict operating-space constraints related to physical stability and SDD compressibility for manufacture of the final dosage form.

FIGURE 4

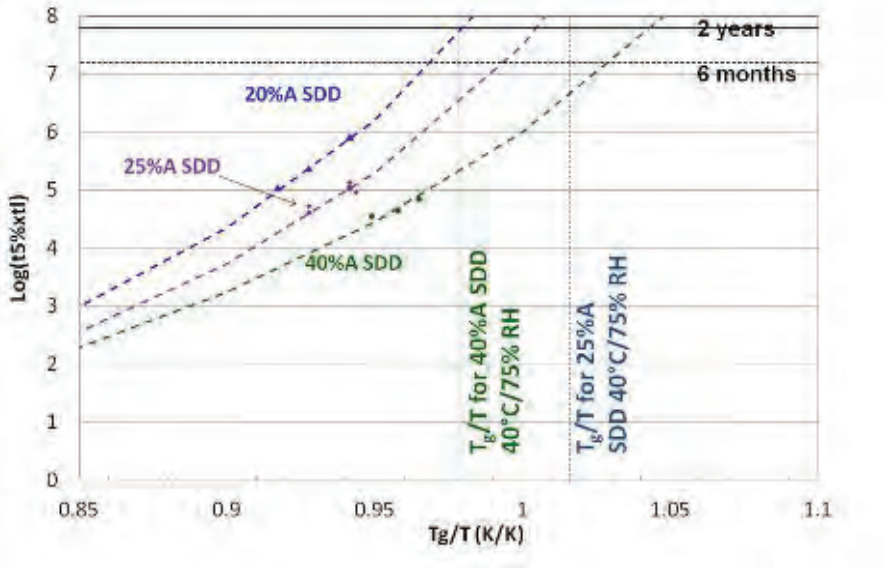


Physical-stability results after a 6- to 13-week stability challenge using Tg and storage temperature (T)

STABILITY

The physical stability of SDDs is maintained during the spray-drying process through the rapid drying kinetics of high-surface-area droplets. Rapid quenching of the droplets to a low-mobility state through use of high-Tg polymers is critical to achieving homogeneous amorphous dispersions. Because SDDs are formulated such that physical stability is dependent on molecular mobility rather than thermodynamic

FIGURE 5



Physical-stability map of HPMCAS-L SDDS of a model compound with various drug loadings (%A), showing time (seconds) to 5% chrystallization (t5% xtal) as a function of Tg/T ratio.

miscibility of the formulation components, phase-appropriate tools can be selected during formulation optimization to ensure that a robust formulation and process are selected, as shown in Figure 3. It is important to consider the failure mechanisms that may be encountered during the manufacture and storage of SDDs to ensure that the appropriate formulation and in-process controls are used. Formulations with a propensity for crystallization or amorphous phase separation can be identified using characterization techniques, including modulated differential scanning calorimetry (mDSC), powder x-ray diffraction (PXRD), isothermal calorimetry, scanning electron micrography (SEM), and dissolution performance tests.

Initially, Tg can be measured as a function of relative humidity (RH) to estimate appropriate storage conditions when crystallization is considered a risk (Figure 4). Additionally, this simple test can be applied to the solvent-wet SDD during the spray-drying process to constrain the operating space to a robust region and to select secondary-drying conditions for removal of residual solvent.

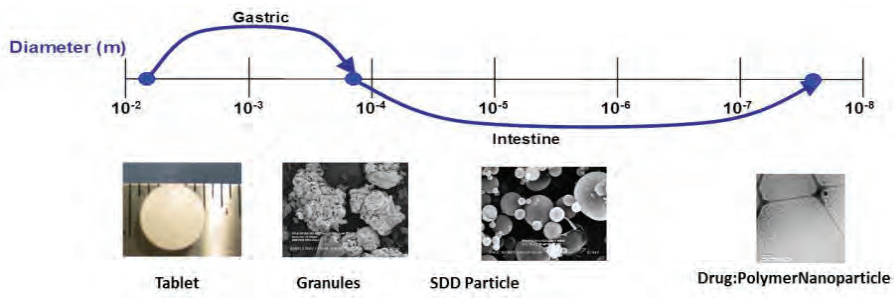
For quantitative prediction of shelf-life stability, semiempirical approaches can be used with extrapolation to determine crystallization risk for storage hold times and conditions (Figure 5). Isothermal calorimery, ie, thermal activity monitoring (TAM), is useful for rapidly extrapolating physical stability by predicting crystallization kinetics because results have been consistent with accelerated and real-time stability data.5 This approach enables selection of a physically stable SDD formulation and appropriate in-process hold times, as well as final packaging configurations based on the Tg of the SDD.

FINAL DOSAGE FORM

SDDs can be incorporated into a variety of dosage forms while maintaining their performance and stability attributes. SDD particle properties can be optimized for dosage-form manufacturing to provide additional flexibility in compression profiles and performance.

Phase-appropriate selection of dosage forms provides flexibility for early phase toxicology and clinical studies, while providing a starting point for development of dosage forms that are suitable for scale-up and commercialization. Sachet or suspension formulations are often employed to support toxicology through Phase I studies. These dosage forms can be rapidly formulated and prepared extemporaneously. Formulated solid

FIGURE 6



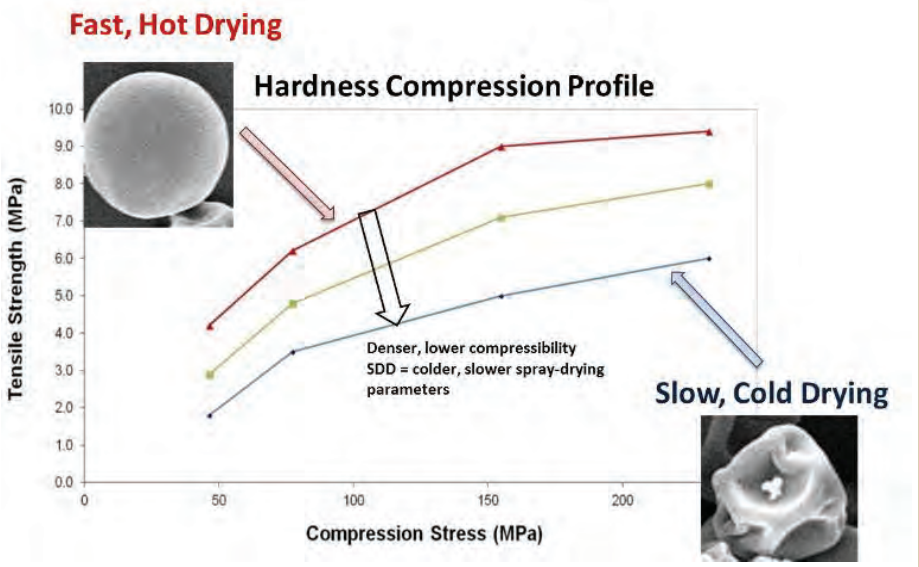
Dissolution mechanism for an IR SDD tablet.

dosage forms, including tablets and capsules, are primarily used for immediate-release (IR) formulations — the most common application of SDDs. Additionally, controlled-release (CR) formulations, including osmotic (eg, swellable-core technology) and hydrophilic matrix tablets, can be designed to modulate the delivery rate of molecules with SDD technology.

Downstream formulation of SDDs into IR formulations suitable for in vivo dosing are designed to deliver native SDD particles within the upper small intestine to maximize the absorption window. In tablet formulations, for which SDDs are incorporated into granules to enhance manufacturability, rapid disintegration (eg, less than 5 minutes) is desired to promote breakdown of the tablet into granules and subsequent rapid dissolution into native SDD particles and finally high-activity species or free drug (Figure 6). Formulations are optimized to maintain equivalent dissolution profiles and thus bioperformance of the tablet, granules, and native SDD to ensure performance is maintained over the wide range of biorelevant conditions that the dosage form will encounter during in vivo dosing. Additionally, rapid disintegration of the dosage form is achieved in either gastric or intestinal fluid to promote performance robustness.

As shown in Figure 7, key properties of the SDD formulation can be optimized around the downstream dosage-form manufacturing process. Compressibility and particle size of the SDD are defined to allow for adequate compressibility and performance of the final dosage form. Dry granulation is commonly employed to enhance the flow characteristics of the tablet formulation and allows for incorporation into both tablets and capsules.

FIGURE 7



Effect of spray-drying conditions on hardness compression profile for process optimization.

SUMMARY

SDDs enable the evaluation and progression of low-solubility compounds throughout the development and lifecycle of a molecule. A "phase-appropriate" approach for formulation development relies on understanding the key attributes and problem statements for the given compound and approaches based on deep science and engineering fundamentals. Use of guidance maps, complementary in vitro tests, and biomodels promotes efficient optimization and inherent robustness of the formulation. Identification of critical-to-performance attributes for the specific compound makes it possible to employ effective testing strategies that ensure SDD formulation performance and stability attributes will be maintained. The spray-drying process can also be designed to accommodate formulation needs and produce engineered particles amenable to a wide range of solid dosage forms and sachet approaches for in vivo delivery. By considering the interplay of these different considerations during formulation selection and process development, low-solubility compounds can successfully be advanced and positioned for subsequent scale-up activities. Early integration of performance, manufacturability, stability, and dosage-form selection can be used to identify and mitigate potential risks during scale-up, leading to efficient compound advancement. ◆

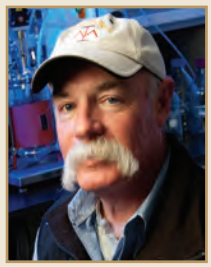
REFERENCES

1. Bloom CJ, Lyon DK. Formulation selection: amorphous dispersions & other tools for drug discovery formulation support. Drug Dev Delivery. 2013;13(3):32-37.
2. Butler J, Dressman J. The developability classification system: application of biopharmaceutics concepts to formulation development. J Pharm Sci. 2010;99:4940-4954.
3. Friesen DT, Shanker RM, Crew MD, Smithey DT, Curatolo WJ, Nightingale JAS. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. Mol Pharm. 2008;5(6):1003-1019.
4. Dobry D, Settell DM, Baumann JM, Ray RJ, Graham LJ, Beyerinck RA. A model-based methodology for spray-drying process development. J Pharm Innovat. 2009;4(3):133-142.
5. Bloom CJ, Marsac P, Jordan FD, Sather CA, Vodak DT, Lowinger M, Liu HXi, Lupton L. Prediction of crystallization kinetics for a spray-dried dispersion using isothermal calorimetry. Poster 3293 presented at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition, Chicago, Illinois, October 14-18, 2012.

BIOGRAPHIES

John Baumann is the Director of Spray-Dried Particle Engineering at Bend Research, where he has worked since 2004. Mr. Baumann manages a spray-drying process-development group focused on the preparation of pharmaceutical intermediates and the scale-up and transfer of spray-drying processes from research laboratories to production in a current Good Manufacturing Practice (cGMP) environment. He holds a bachelor's degree in Bioengineering from Oregon State University.

Dan Dobry, a Vice President at Bend Research, leads a group focused on formulation and process engineering for novel drug-delivery technologies. In addition to business development and client relationship management, Mr. Dobry's responsibilities include managing the process-engineering group, which is focused on formulation and process engineering for novel drug-delivery technologies. He has worked for Bend Research since 1998 and holds a bachelor's degree in Chemical Engineering from Oregon State University.



Dr. Rod Ray is the CEO and Chairman of the Board of Directors for Bend Research Inc., a world-class independent scientific development and manufacturing company. A Bend Research employee since 1983, Dr. Ray has led the company from a small contract R&D firm to a company with six facilities in Bend, Oregon, and nearly 300 employees. He holds a bachelor's degree from Oregon State University and master's and doctoral degrees from the University of Colorado, all in Chemical Engineering.

EGFR Mutations, Apoptosis & Gefitinib Response: A Model for Integrating Genomic Biomarkers Into Successful Precision Medicine

By: Sirosh Bokhari, PhD

INTRODUCTION

Biopharma companies worldwide are facing multiple challenges with the evolving marketplace and business practices. Throughout the past decade, the bar for regulatory approval, reimbursement, and market adoption has constantly risen, driving a shift in the drug development paradigm from "one size fits all" to Precision Medicine. More recently, Biopharma companies have felt pressure on their drug pricing, and this trend is expected to continue. Strategically directing research and clinical efforts, making the right pipeline decisions and lowering drug costs will be critical for Biopharma companies to adjust to the new realities.

FROM BIOMARKERS TO PRECISION MEDICINE: CHALLENGES AT EACH STEP OF THE WAY

Biomarkers play a critical role in enabling Precision Medicine. In particular, genomic biomarkers have become an integral part of the new drug development paradigm, especially in oncology. Yet, progress toward true Precision Medicine is slow. Genomic biomarker assay development and validation pose multiple technical difficulties. It is not easy to generate sufficiently robust data, at every stage of development, to select the compounds with the best chance of success, especially for small and mid-size Biopharma companies with limited resources. And, once drug candidates are administered, using genomic biomarkers to get an objective measurement of drug efficacy and adjust the dose when necessary remains challenging.

SYSTEMS BIOLOGY CAN UNLOCK BIOMARKER POTENTIAL

For biomarkers to truly make Precision Medicine a reality, biomarker data must enable drug makers to make the right strategic pipeline decisions at every phase. In order to develop tests based on genetic data, it is imperative to understand gene function not only on the genetic level (DNA), but also on transcriptional (RNA) and post-transcriptional (protein, Post Translational Modification) levels. Gene expression at RNA and protein levels are often correlated, however, this correlation can be far from linear, depending not only on the gene candidate, but also on external stimuli. Although initial mRNA levels can be predictive of the presence, absence, or abundance of proteins, many factors such as translation, modification, transport, regulation, complex formation, or degradation can change the dynamics of that correlation. Complementary profiling of protein and mRNA levels with respect to given perturbations, followed by analysis of the discrepancies between protein and mRNA levels for each gene, have shown that plotting these

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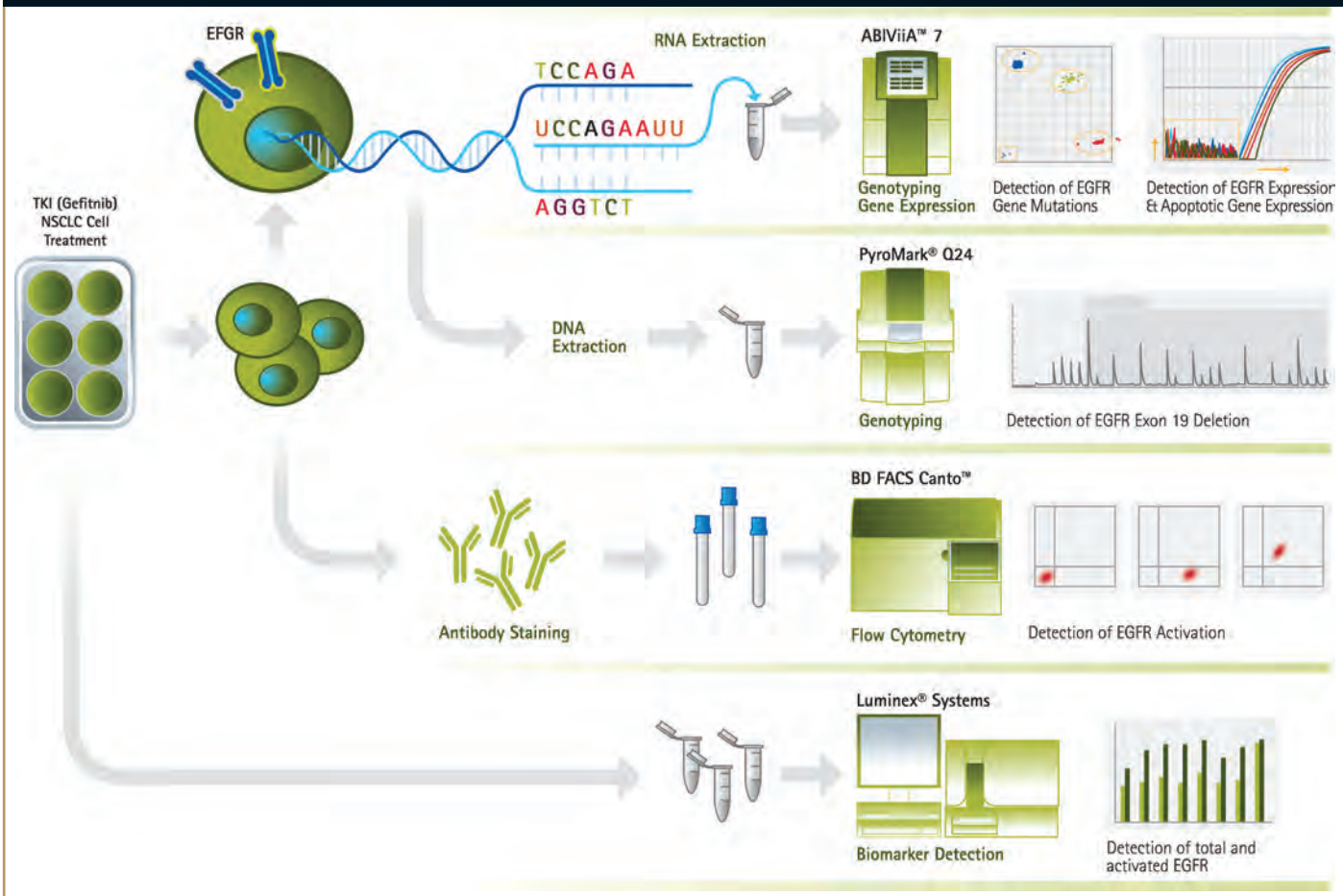
FIGURE 1



Experimental strategy for cross-platform biomarker analysis of TKI response in NSCLC lines with respect to EGFR mutation status.

discrepancies results in data points that are clustered with respect to gene function network.[1,2]

It is clear that large-scale correlations of protein and genomic biomarker data can lead to a more robust systems pharmacology and Precision Medicine strategy. The first step toward that goal is integrating broad RNA biomarker screening into drug development strategies. Compared to analyzing protein function directly, which can be time-consuming and labor-intensive, numerous mRNAs can be screened in less than a day, and the data can be used to predict protein function. For a Biopharma company, such genomic biomarker screens, in combination with targeted protein function analysis, are instrumental for understanding drug effects, devising specific treatments, and identifying therapeutic targets.

CROSS-PLATFORM VALIDATION: INTEGRATING MULTIPLE TYPES OF BIOMARKER DATA FOR BETTER DECISIONS

At EMD Millipore, a cross-validation proof-of-concept study was performed by measuring changes in mRNA and protein biomarkers using multiple detection methods, following application of the tyrosine kinase inhibitor (TKI), gefitinib, to non-small cell lung carcinoma (NSCLC) cell lines harboring various mutations in the epidermal growth factor receptor (EGFR) gene. Mutations in the EGFR gene have been associated with overexpression and hyperactivation of the receptor, which may lead to a number of cancers, including NSCLCs.[3] Targeted inhibition of EGFR using small molecule drugs or antibodies, in combination with identification of genetic mutations in the EGFR pathway, is an effective approach to precision cancer therapy. We have however, only begun to uncover the vast potential that this field has to offer.

NSCLC cell lines harboring various EGFR mutations were used to determine EGFR expression and activation as well as apoptotic gene expression following gefitinib treatment. Cross-platform validation was carried out to correlate the levels of protein biomarkers as measured by flow cytometric analysis and MILLIPLEX® MAP bead-based immunoassays using the Luminex® technology.

NSCLC cell lines were evaluated for their EGFR mutational status using the QIAGEN Pyromark® Q24 Pyrosequencer. The Pyromark Q24 sequencer allows real-time detection of single nucleotide polymorphisms (SNPs), gene deletions, methylation, and microbial identifiers using the pyrosequencing technology. It is ideal for the detection of short sequences and can run 24 samples in 15 minutes. Mutation analysis confirmed that the NSCLC cell line A549 was wild-type for EGFR, the H1650 cell line had an exon 19 deletion, and the H1975 line had L858R and T790M substitution mutations. Exon 19 deletions and the L858R mutation constitute the most common mutations associated with EGFR TKI sensitivity and are also associated with a greater than 70% response rates in patients treated with the TKIs gefitinib or erlotinib. T790M substitution and exon 20 insertions, on the other hand, are responsible for acquired resistance to TKIs.[4] EGFR mutant cells H1975 expressed two-fold higher EGFR mRNA as compared to wild-type.

In order to correlate the mutational status to TKIs sensitivity, NSCLC cells were treated with gefitinib and assessed for the mRNA and protein expression of apoptotic markers by qPCR, flow cytometry, and MILLIPLEX® MAP bead-based immunoassays. The qPCR analysis was conducted using a Taqman® low density array of apoptotic markers and analyzed on the Applied Biosystems® (ABI) ViiA7 real-time PCR system. Integrated with the ABI® Twister II® Robot, it is a high-throughput and automated platform for running and analyzing thousands of qPCR reactions. It is compatible with both the SYBR® Green and Taqman chemistries. Gefitinib induced higher expression of several apoptotic markers in EGFR-mutant cells as compared to wild type.

Flow cytometric analysis indicated higher total and phosphorylated EGFR in mutant cells and analysis using MILLIPLEX® MAP assays on the Luminex 200™ instrument validated the results. Apoptotic markers were also correlated on several mRNA and protein levels: Bcl-2, a prosurvival marker, was constitutively expressed at higher levels in mutant cells, however, there was no significant change in total or phosphorylated Bcl-2 following treatment with gefitinib. Collectively, the results not only provided a comprehensive overview of EGFR expression and TKI susceptibility in mutant cell lines, but they were also indicative of the regulation patterns driving conversion of mRNA to protein for the different markers. High throughput mRNA analysis enabled the screening and selection of multiple apoptotic markers for protein level analysis using flow cytometry or the Luminex platform.

ELUCIDATING MECHANISMS OF DRUG RESISTANCE: THE NEXT STEP

This EGFR study provided an excellent model for how Precision Medicine has become a reality in NSCLC therapy. A genomic biomarker-driven approach not only determined the predictive value of EGFR mutations for administration of first-generation TKIs, but also provided evidence of the development of resistance due to secondary mutations and therefore the need for second-generation TKIs.

Resistance to TKIs eventually develops in 30% of the treated patients and is attributable to several factors, including secondary EGFR mutations or alterations in PI3K/Akt, IGF1R, pTEN or NFκB signaling, or increased IGF1R signaling. Other mechanisms of resistance include Met amplification, PI3KCA mutation, Axl amplification, or epithelial-to-mesenchymal transition (EMT). The T790M resistance mutation, often referred to as the "gatekeeper mutation," is found in 50% of the patients that develop resistance to EGFR TKIs. T790M may be conferring resistance by altered binding of TKI in the EGFR ATP pocket.[5]

Mechanisms to overcome resistance to EGFR TKIs include either second-generation EGFR inhibitors, such as PF00299804 (Pfizer) to induce response in patients with an EGFR exon 20 insertion, or WZ4002, to specifically target T790M EGFR and inducing growth inhibition both *in vitro* and *in vivo*.[6,7] Additional therapeutic strategies include using PI3K, Akt, or IKK inhibitors or an IGF1R antibody in combination with EGFR TKIs.

Extending our initial cross-platform validation study, we investigated underlying mechanisms of resistance to erlotinib and gefitinib in NSCLC cell lines with activating or resistance-conferring mutations. Moreover, we evaluated effectiveness of PI3-AKT or IGF1R inhibitors as therapeutic approaches to antagonize resistance. NSCLC cells harboring exon 19 deletions or T790M mutation were treated with erlotinib or gefitinib and evaluated for EGFR, PI3-AKT, or IGF1R activation. Cells were treated with an IGF1R inhibitor from EMD Millipore or a PI3-AKT inhibitor and evaluated for EFGR and downstream pathway activation and susceptibility to TKIs. These studies were executed on multiple platforms to investigate expression at transcriptional and translational levels. H1975 cells with the T790M resistance mutation demonstrated more resistance to Gefitinib when compared to the H1650 cells; mRNA profile of H1975 cells showed high expression of the PIK3CA, PIK3R2 and prosurvival BCl2 whereas the proapoptotic BCl2L11, Caspase 6, Caspase 8 and Fas were expressed at very low levels. Moreover, H1975 cells expressed higher p-EGFR, p-BCl2 but low p-Akt, however, EGFR activation was inhibited following treatment with WZ4002. The cross platform analysis demonstrated correlation in expression at mRNA and protein levels, however, some markers did not correlate indicating post-translational regulation.

EMD MILLIPORE GENOMIC BIOMARKER SERVICES: UNLOCKING THE POTENTIAL OF BIOMARKERS

EMD Millipore's goal is to help Biopharma companies unlock the potential of biomarkers in drug development and monitoring. Building on its experience and leadership in protein-based biomarker services, EMD Millipore has added genomic capabilities to its arsenal, providing custom-tailored cross-platform analyses of sample or systems on the transcriptional and translational levels, as illustrated in the EGFR studies described.

In its St. Charles, MO laboratory, EMD Millipore works with Biopharma companies on exploratory studies, such as exploring genomic sequence variations, which potentially impact compound efficacy or toxicity, and evaluating differences in RNA expression to monitor drug response or toxicity. Moving into the clinic, EMD Millipore completes assay optimization and validation in compliance with GLP or CLIA requirements. At each stage of development, EMD Millipore offers Biopharma clients the opportunity to validate their data across multiple platforms, such as flow cytometry and Luminex technology, thereby enabling clients to make robust pipeline decisions.

TO DEVELOP COMPANION DIAGNOSTICS, INTEGRATE BIOMARKERS FROM THE START

As Biopharma companies successfully advance their compounds in the early phases of clinical development, their goal is to narrow down the number of meaningful biomarkers that might ultimately become companion diagnostics. Co-developing drugs and diagnostics is a landmark of achieving Precision Medicine. The US Food and Drug Administration (FDA) has recently published guidelines to that effect, recognizing the potential of such combination to address some of the challenges facing the industry.

Yet the hurdles to developing companion diagnostics are even higher than those facing biomarker development, particularly for small- and mid-size companies. Indeed, most of those companies aim at generating proof-of-concept data for their compounds with limited resources and constrained timelines. By not recognizing the importance of integrating biomarkers early in the drug development process and not considering

companion diagnostics as an ultimate goal, these companies are simply not ready to select a companion diagnostic partner and negotiate agreements with long-term implications.

EMD Millipore understands and addresses the need for a smooth transition from biomarkers to companion diagnostics in a timely and cost-effective manner. EMD Millipore facilitates this transition by validating assays on clinically well-established platforms, in its GLP and CLIA compliant laboratory. As a nimble CRO dedicated to quality, EMD Millipore is able to meet Biopharma companies' tight clinical timeline, generate robust, reproducible data, and help companies reach their inflection point. EMD Millipore contributes to creating value for those companies by validating the assay that enhances the profile of their compounds. EMD Millipore strengthens their negotiating position as they seek partners to undertake the final stage of clinical development.

Genomic biomarkers will continue to significantly impact drug development and patient treatment. Biopharma companies strive to deliver on those biomarkers' promises but face significant challenges to do so. EMD Millipore uniquely combines genomic- and proteomic-based platforms, assay development and validation expertise, quality systems, and flexibility to create value for Biopharma companies' pipeline. In addition to the already well-established platforms, EMD Millipore keeps up with the latest technologies and developments to be able to offer the best solutions for Biopharma companies with quality and time in mind. With the development of revolutionary genomic platforms, it will not be long before physicians will be able to conduct a genetic test in the time it takes to write a prescription. Next-generation sequencers, robotic qPCR systems, and disposable microfluidic cartridges are already becoming the new normal, redefining conventional concepts of molecular biology. EMD Millipore constantly evaluates new technologies to strengthen its portfolio of biomarker services and evolves with the needs of Biopharma companies. EMD Millipore's goal is to create value for its customers by unlocking the potential of their biomarkers and compounds. ◆

REFERENCES

1. Washburn MP, Koller A, Oshiro G, Ulaszek RR, Plouffe D, Deciu C, Winzeler E, Yates JR, 3rd. Protein pathway and complex clustering of correlated mRNA and protein expression analyses in Saccharomyces cerevisiae. Proc Natl Acad Sci US A. 2003;100(6):3107-3112.
2. Griffin TJ, Gygi SP, Ideker T, Rist B, Eng J, Hood L, Aebersold R. Complementary profiling of gene expression at the transcriptome and proteome levels in Saccharomyces cerevisiae. Mol Cell Proteomics. 2002;1(4):323-333.
3. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304(5676):1497-1500.
4. Mayo C, Bertran-Alamillo J, Molina-Vila MÁ, Giménez-Capitán A, Costa C, Rosell R. Pharmacogenetics of EGFR in lung cancer: perspectives and clinical applications. Pharmacogenomics. 2012;13(7):789-802.
5. Ercan D, Zejnullahu K, Yonesaka K, Xiao Y, Capelletti M, Rogers A, Lifshits E, Brown A, Lee C, Christensen JG, Kwiatkowski DJ, Engelman JA, Jänne PA. Amplification of EGFR T790M causes resistance to an irreversible EGFR inhibitor. Oncogene. 2010;29(16):2346-2356.
6. Engelman JA, Zejnullahu K, Gale CM, Lifshits E, Gonzales AJ, Shimamura T, Zhao F, Vincent PW, Naumov GN, Bradner JE, Althaus IW, Gandhi L, Shapiro GI, Nelson JM, Heymach JV, Meyerson M, Wong KK, Jänne PA. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. Cancer Res. 2007;67(24):11924-11932.
7. Zhou W, Ercan D, Chen L, Yun CH, Li D, Capelletti M, Cortot AB, Chirieac L, Iacob RE, Padera R, Engen JR, Wong KK, Eck MJ, Gray NS, Jänne PA. Novel mutant-selective EGFR kinase inhibitors against EGFR T790M. Nature. 2009;462(7276):1070-1074.

BIOGRAPHY

Dr. Sirosh Bokhari's 10 years of research experience covers molecular and cell biology, molecular genetics, molecular oncology, microbiology, and pathology. Trained at Stanford University and the University of the Punjab, Dr. Bokhari most recently served as staff scientist at Washington University in St. Louis, Missouri, before joining EMD Millipore, where she is responsible for managing the genomics biomarker laboratory operations and conducting nucleic acid testing in a GLP environment. Dr. Bokhari can be reached at (636) 720-1037 or sirosh.bokhari@emdmillipore.com.

SPECIAL FEATURE

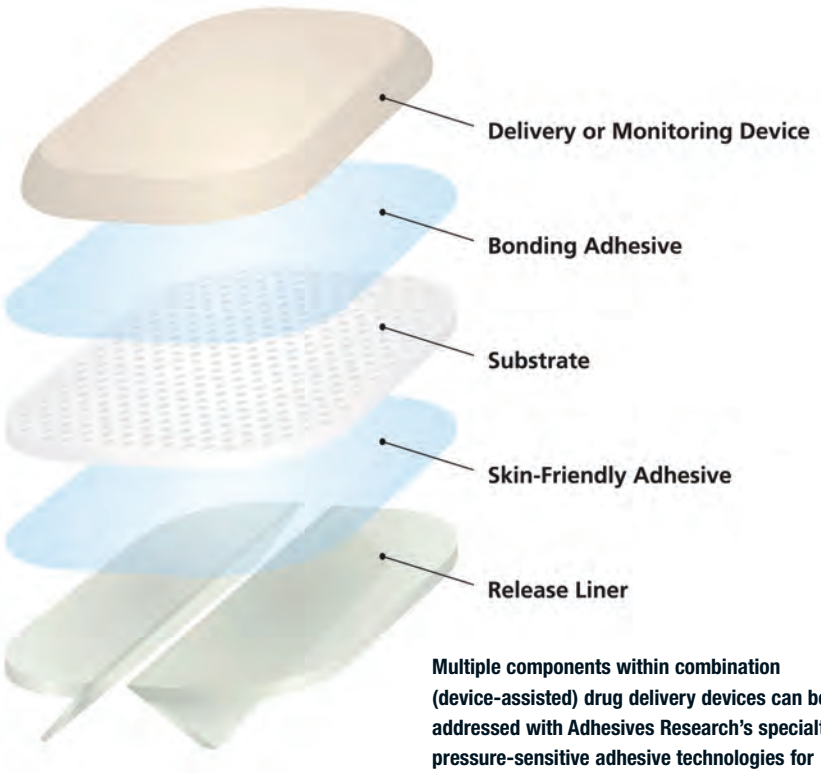
Transdermal, Topical, and Subcutaneous Drug Delivery: Extending Pipelines and Improving Self-Administration

By: Cindy H. Dubin, Contributor

Skinvisible introduced four lines of patented products for out-licensing in the over-the-counter/cosmeceutical market this past year.

The growing number of elderly people is a large consumer of home care drug delivery devices. The global aging population is set to increase from 784 million in 2011 to 2 billion by 2050 and 2.8 billion by 2100. An increase in the number of geriatric patients and a rise in demand for convenient drug delivery options pose major opportunities for the development of innovative and easy-to-use drug delivery systems.

Add to that the fact that, according to EvaluatePharma, a pharmaceutical researcher, patent expirations between 2012 and 2018 will result in an estimated $290 billion loss in sales of branded products. These patent losses coupled with faltering



Multiple components within combination (device-assisted) drug delivery devices can be addressed with Adhesives Research's specialty pressure-sensitive adhesive technologies for enhanced product performance.

pipelines are causing pharmaceutical companies to reposition currently marketed drugs through reformulation using novel drug delivery technologies.

These factors are giving rise to a new generation of transdermal, topical, and subcutaneous drug products designed to satisfy caregiver and patient preferences while addressing managed care initiatives and the formulation limitations of new classes of therapeutic drugs. Because of their ability to safely and reliably satisfy treatment protocols and compliance goals, non-oral drug delivery products will have a significant impact on the future of drug self-administration.

Thus, according to recent news reports, analysts are predicting that the transdermal delivery market could be worth as much as $31.5 billion by 2015 from a value of $21.5 billion just three years ago. "The growing interest in transdermal, topical, and subcutaneous drug delivery is a reflection of the industry's quest for alternative routes of administration, much needed for the delivery of new chemical entities (biologics in particular) as well as for enabling and enhancing the drug pipelines for known compounds that stand to benefit from reformulation," says Jasmine Musakhanian, Marketing & Scientific Director, Pharmaceutical Division, Gattefossé USA.

ADHESIVES RESEARCH—SECURING DRUG DELIVERY TO THE SKIN

Adhesives Research (AR) is a custom developer and manufacturer of specialized pressure-sensitive adhesives (PSAs) and coatings that address the material challenges of body-worn drug delivery devices. These devices typically require an adhesive to mount a needle or patch component securely to the skin for wear times from under an hour up to 7+ days, depending on the drug therapy. The adhesive must be able to carry the weight of the device, yet remain comfortable without damaging patient skin during wear or upon removal, explains Susan Newsom, Pharmaceutical Business Manager.

"We are noticing an increased interest for enabling adhesive technologies in combination products (device-assisted drug delivery) such as patch-pump applications," says Ms. Newsom. Developers of body-worn devices are seeking adhesives that securely bond to a wide range of patient skin types and patient activity levels while remaining comfortable during wear and upon removal. Developers are also building their devices from flexible, specialty elastomeric materials to improve patient comfort during wear. These low-surface energy elastomers present their own bonding challenges.

AR is addressing the growing need for specialty skin-friendly adhesives while overcoming the thickness issues of gel formats and limitations of current commercially available acrylic adhesives through the development of a low-trauma adhesive (LTA) platform technology for gentle removal. This high-moisture vapor transmission rate (MVTR), customizable PSA technology maintains reliable, intimate skin contact for up to three days and can be removed and reapplied without the adhesive bonding to itself. The LTA formulation has high, immediate tack to skin upon application, yet removes cleanly without leaving any residue, and is biocompatible, non-cytotoxic, non-irritating or sensitizing. "The LTA technology exhibits good-to-excellent ratings for resistance to gamma sterilization, unlike silicones, which are often unable to withstand these sterilization

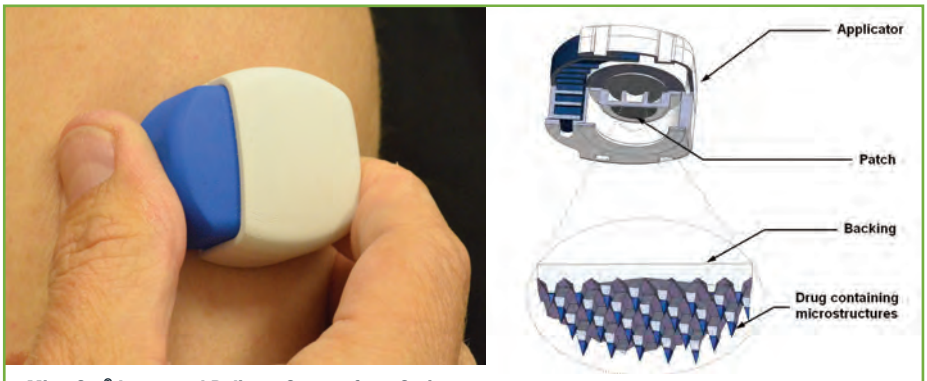
techniques," says Newsom.

Adhesives Research is addressing the growing need for long-term wear (LTW), skin-friendly adhesives for body-worn drug delivery devices through a new adhesive technology. Its tailorable LTW adhesive platform meets the critical design parameters required for adhesives in applications requiring a more aggressive adhesive to secure a load-bearing device in place for up to seven days. This new technology offers high moisture vapor transmission rates (MVTR) for breathability, good wear properties, minimal edge-lift, and tolerable removal with no adhesive residue remaining on skin.

AR also offers a conformable, medical-grade PSA tape technology for bonding low surface energy (LSE) materials such as TPE (thermoplastic elastomers) without a secondary curing step for increased manufacturing ease and efficiency. The adhesives are non-cytotoxic and can be provided in transfer, single-sided or as a double-sided tape configuration with a skin-friendly adhesive on the opposite side. AR's family of adhesives for LSE bonding include acrylic, hybrid, and silicone chemistries formulated for immediate and permanent bonds with minimal pressure.

CORIUM—EXTENDING TRANSDERMAL DELIVERY TO BIOLOGICS

Transdermal delivery of large molecules is a major emerging opportunity. Worldwide sales of biologics are expected to grow to $87 billion by 2014, and an estimated 50% of all future approvals are expected to be biologics. The market is embracing biologics and next-generation molecules that mimic the actions of biologics, and the demand is increasing for advanced delivery systems for these molecules.



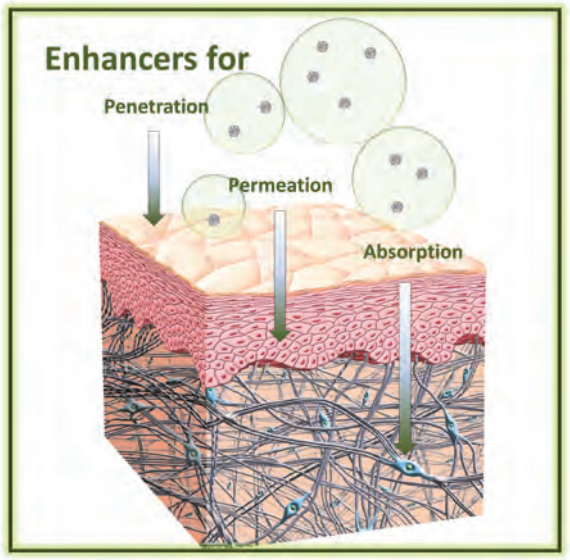
MicroCor® Integrated Delivery System from Corium.

Transdermal delivery of large molecules as an alternative to intramuscular, subcutaneous, or intravenous routes of administration can add significant patient benefits and improve the economics of treatments in the future–both in the developed and developing worlds. The active transdermal delivery of macromolecules using microneedle patch technologies is one of the major trends in addressing this market.

Transdermal delivery of biologics is a new field, and Corium's clinical-stage MicroCor® transdermal technology platform is designed for safe, effective, and convenient transdermal delivery of most types of biologics (peptides, proteins, nucleic acids) and vaccines. Corium has completed a Phase 1 clinical study and a number of preclinical evaluation programs with partners using this technology with peptides, proteins, vaccines, and small molecules. These programs are advancing to the next stages of development based on positive results. "In addition, using our Corplex™ technology and other passive transdermal technologies, Corium has developed and is commercializing with its partners several new transdermal and oral film products that have delivered on the promise of consumer acceptance and market success," says Peter Staple, CEO.

Corium has both passive and active delivery transdermal programs. The passive programs revolve around the Corplex platform for the delivery of small molecules, especially those molecules that are otherwise difficult to formulate. Corplex is a suite of technologies incorporating combinations of materials that utilize the properties of both traditional pressure sensitive adhesives (PSAs) as well as bioadhesives. Corium has the capability to apply this technology to develop products that can be made in liquid (sprays, film formers), semisolid (gel, creams and ointment-like) and solid (powder, particles, dry and wet films, and patches) forms. The platform is also applicable for transdermal delivery of small molecules where side effects, compliance, pill burden, or poor bioavailability are a concern. Some ideal candidates include hormone therapies, pain medications, and central nervous system diseases (e.g. Parkinson's disease, Alzheimer's disease, Schizophrenia, etc.).

Corium's MicroCor transdermal delivery system delivers drugs from an integrated transdermal system in a one-step process and is applicable to the delivery of peptides, therapeutic proteins, potent mAb's and



Gattefossé delivery enhancers help target different layers of the epidermis.

vaccines. "Delivery through the skin is an excellent means for rapid uptake of these molecules, and is also an ideal route of administration for eliciting a more efficient and robust immune response to an antigen compared to intramuscular injection," says Mr. Staple. The system integrates drug molecules directly into arrays of solid-state biodegradable microneedles, which penetrate the outer layers of the skin to release the drug for local or systemic absorption. The microstructures can be fabricated from a variety of materials and in different lengths (200μm or longer), offering significant flexibility in the depth (stratum corneum to dermis) and duration of delivery (rapid to sustained administration).

MicroCor systems are thermally stable, which provides unrestricted portability, and are biodegradable, which eliminates needle-stick injuries, needle reuses, and medical waste disposal. This results in a more efficient, cost-effective approach to patient care, says Mr. Staple.

GATTEFOSSÉ—EXCIPIENTS FOR SOLUBILITY, PERMEATION, AND PENETRATION

Needle-free passage of drugs to and across the skin layers is a significant challenge. Formulation requires appropriate vehicles enabling solubilization and suspension of the active in the dose; facilitating passage of the active across the outermost layer and barrier function of the skin, the stratum corneum; permeation of the active in subsequent layers of the epidermis; and if the case may be, partitioning and diffusion of the active into the dermis thus reaching the systemic circulation.

As a provider of excipients and formulation technologies, Gattefossé USA faces a growing demand for its topical excipients, notably solubilizers and penetration/permeation enhancers. Functionality, safety, and regulatory acceptance are among the top criteria in demand. Gattefossé's product offer crosses various drug delivery systems and includes solubilizers (Labrasol), penetration enhancers (Transcutol®), permeation enhancers (Labrafil®), and building blocks for nano-emulsions and solid lipid nano-carriers (SLN).

Much like drugs, excipients take considerable time and years of research and development before they are introduced to the market. The development path at Gattefossé, from conception to industrial-scale production batches, is long and involves clinical studies to establish safety and stability studies for up to five years after manufacture, explains Jasmine Musakhanian, Marketing & Scientific Director, Pharmaceutical Division, Gattefossé USA. Alongside the physico-chemical properties and the formulation, efficacy of the excipient must be characterized.

"We recognize that with new molecules, novel devices, and/or new administration routes, the tendency is to work with well-established, reliable, safe, and thoroughly characterized excipients," she says. "Having introduced a number of novel excipients to the market (in recent years) we now are focusing on product support. Ensuring that excipient dossiers are up to date with scientific data is our primary aim. To that effect, we recently launched a comparative study of topical penetration and permeation enhancers, the results of which will be published later this year."

The landscape is ripe for solubility, penetration, and permeation enhancers. "The prospects of improved patient compliance, tolerance, and efficacy combined with the promise for a healthier product pipeline and line extensions for known compounds are strong," says Ms. Musakhanian. "Therefore, the quest for new and improved modes of drug delivery is expected to continue in the coming years."

SKINVISIBLE—DIFFERENTIATING THE DERMATOLOGICAL SPACE

The demand for proprietary pharmaceutical products continues to grow, however there is additional pressure in the

topical space because there are limited new drug compounds in dermatology. Thus, the demand for delivery systems like Skinvisible's patented technology Invisicare® to differentiate products is at the forefront of new product development. Invisicare can be tailored to any ingredient and consists of both hydrophilic and hydrophobic polymers that form a complex that is added during manufacturing.

Skinvisible, a contract research and development company, targets pharmaceutical, consumer-goods, and cosmetic companies seeking patent protection. "We achieve this by licensing out our finished formulations on an exclusive basis or providing life cycle management for companies with products coming off patent by reformulating with Invisicare," says Terry Howlett, President and CEO of Skinvisible.

Invisicare provides an enhanced delivery of ingredients, influencing how products act and their effect on the skin. It binds products to the skin and resists wash-off or rub-off, it controls the release of active ingredients and, if desired, can increase the release of actives; sometimes 2 to 4 times the release of a branded product, states Mr. Howlett, which can decrease skin irritation. "Additionally Invisicare has a stabilizing effect on actives as illustrated by our two recent patents granted for stabilizing avobenzone in sunscreens and retinoic acid in acne formulations."

Skinvisible has seen increased demand for proprietary products in the over-the-counter and cosmeceutical marketplace as "me-too" products cannot meet market share expectations, explains Mr. Howlett. The company has introduced four lines of patented products available for exclusive out-licensing in the over-the-counter/cosmeceutical market this past year, including acne therapy, foot and leg therapy, anti-aging, sun care and sunless tanning (which includes broad spectrum sunscreens that received a U.S. patent for stabilization of avobenzone for eight hours). "These product lines address the growing demand for proprietary products with distinctive consumer benefits that translate into messaging that resonates with consumers," says Mr. Howlett.

Topical and transdermal drug delivery systems can potentially provide improved therapeutic outcomes with greater safety compared to actives delivered orally and intravenously. "Skinvisible's research and development will continue to focus on developing new versions of Invisicare in order to meet the growing demand for unique drug delivery systems. This, along with our endeavor to shorten development and commercialization time for our clients, is Skinvisible's focus for the coming years."

TAPEMARK—TRANSMUCOSAL/TRANSDERMAL DELIVERY FOR DISCRETE SINGLE-DOSING

Driving market growth in transdermal and transmucosal drug delivery is consumers' desire for discrete, single-dosing solutions that fit active lifestyles. When the drug delivery solution fits the consumer's active lifestyle and offers the flexibility the consumer seeks, compliance increases and efficacy improves, says Patricia Kitchen, Vice President, Research & Development, Tapemark, a full-service contract development and manufacturing organization.

A transdermal patch, for example, is convenient, user-friendly, and can be applied discretely. Because transdermal delivery works so well for the consumer while offering advantages such as bypassing first-pass metabolism and localized efficient drug delivery, the market will continue to grow. Additional market expansion is expected from generic competition for branded products reaching patent expiration.

One area that is growing is that of active transdermal technology, such as iontophoresis, which delivers drugs via low-level electrical current through the skin's pores. This can provide faster and more controlled drug delivery than passive transdermals, as well as the delivery of larger molecule drugs, says Ms. Kitchen.

One example is IontoPatch® technology from Travanti Medical, a business unit of Tapemark, currently used in the physical therapy market. IontoPatch is an extended time-released electronic transdermal drug delivery system. A self-contained flex battery produces an electric current to carry drug molecules non-invasively across the skin and to underlying tissue.

Tapemark is also active in the oral thin film market, which offers transmucosal delivery that fits the model of convenient, discrete, single-dosing solutions for active lifestyles. Oral thin films administer the contents via absorption in the mouth buccally or sublingually. This allows the contents to bypass the first-pass metabolism, making the product more bioavailable and providing more rapid onset of action.

For transmucosal formats, Tapemark

Tapemark's patented Snapplicator® dispenses a precisely measured single dose of a topical drug, offering portability and convenience demanded by active consumers.

supports formulation, blending, and coating the oral thin film, in addition to converting and packaging in Tapemark's SoluStrip™ format. Each dose of film is individually packaged in its own pouch, offering convenience and portability while enhancing compliance and safety, explains Ms. Kitchen.

In the topical delivery market, Tapemark has had success with its patented Snap!® and Snapplicator™ single-dose packaging formats. Again fitting the model of discrete single-dosing solutions, Snap! dispenses a precisely-measured dose of a variety of topicals, including gels, lotions, and ointments. Snapplicator adds an applicator for "no-touch" dispensing and application, a feature that lets the consumer apply the correct dose. This also avoids patient contact with the drug or the condition being treated, when desired, and can deliver a combination of two different semi-solids dispensed simultaneously.

In the topical space, Tapemark offers single-use pads and topical patches created by coating or dispensing the active pharmaceutical ingredient onto a nonwoven material.

Ms. Kitchen says: "Oral thin films, gels, and particularly transdermals are developing delivery technologies. As interest in them grows, so will the number of ways in which they are used. In the next few years, consumer demand for convenient, discrete products that fit active lifestyles will drive investment into new delivery formats. Medicines and supplements traditionally administered through means of solid oral dosage will begin converting to other delivery forms, including transdermal, oral thin films, topical, and gels."

Tapemark recently expanded capabilities and physical facilities to meet market needs for transdermal and transmucosal drug delivery, and is adding formulation, blending, and coating to its existing converting and packaging capabilities, with blending and coating expected to be online this fall.

3M—TRANSDERMAL DRUG DELIVERY FOR CAREGIVER-INTENSIVE CONDITIONS

According to a 2010 IMS Health and Mintel Report, an estimated 74% of 65- to 69-year-olds in the United States are affected by at least one chronic condition, placing a burden on health care providers, patients, and caregivers, and emphasizing the importance for pharmaceutical companies to consider patient and caregiver-focused drug delivery technology. This is especially important because care that was once administered by an institution is now shifting to being administered in the patient's home.

Simultaneously, as the aging population continues to grow, many pharmaceutical companies are facing a significant patent cliff. Many of today's leading products are coming off patent in the next three to four years, prompting companies to seek new ways to protect their

brands as long as possible. Reformulation to transdermal delivery offers a path for a pharmaceutical company to extend its branded product lifecycles.

The benefits of using a transdermal patch to target the needs of the aging population can ultimately translate to a dosage form that is more patient and caregiver friendly. For instance, in caregiver-intensive settings, the transdermal patch offers important advantages, particularly for patients taking multiple medications. The ability for the patient to self-administer the patch, and the appeal patients may find in a decreased number of pills to swallow each day are factors that can contribute to increased compliance. Additionally, caregivers may also find value in the ability to visually confirm a secure placement of the patch, which is much easier than confirming that a pill has been swallowed.

With regard to the patent cliff, transdermal delivery can offer a number of competitive advantages for pharmaceutical companies. "For example, a pharmaceutical company that focuses on lifecycle management earlier and includes transdermal delivery as a parallel path during development could obtain a better position to extend the life of the drug, and strategically introduce a variety of formulations to drive patient preference," says Jordan Fineberg, Global Transdermal Business Manager at 3M Drug Delivery Systems.

3M Drug Delivery Systems has pioneered advancements in passive transdermal delivery including the first 7-day stand-alone drug-in-adhesive transdermal patch, and offers transdermal solutions at any

Patient-focused drug delivery from 3M Drug Delivery Systems.

product development or manufacturing stage, Mr. Fineberg points out.

"Transdermal drug delivery has the potential to offer improved safety and efficacy by avoiding first-pass metabolism and maintaining more constant drug levels, versus the peak and trough effect seen with oral delivery," explains Mr. Fineberg.

Passive transdermal systems allow a drug to diffuse through the skin at the targeted therapeutic dose range where it can act locally or penetrate the capillaries for systemic effect. Passive systems are most useful in delivering small-molecule drugs because of the barrier properties of the skin.

Additionally, transdermal devices can deliver multi-day dosing at a specific pharmacokinetic profile, which is a distinguishing factor for the drug delivery method. Another key aspect of transdermal delivery is its ability to deliver more than one drug in a single patch, which adds additional convenience for patients.

"Looking into the future, the aging population will continue to grow. We see a trend of caregiver-intensive and chronic care indications placing pressure on pharmaceutical companies to provide delivery devices that offer convenience to the patient and potential for increased compliance. This demand will drive the industry to explore and develop patient-centric delivery forms, and may fuel the next wave of transdermal products," says Mr. Fineberg.

"Overall, transdermal delivery will continue to offer a number of competitive advantages for many pharmaceutical companies that consider it to be an attractive option for lifecycle management of key drugs."

4P THERAPEUTICS—TURNING THE INJECTABLE INTO THE TRANSDERMAL

Pharmaceutical companies are looking to reposition currently marketed products and grow pipelines, presenting a significant opportunity for drug delivery companies. 4P

Therapeutics is taking advantage of this market trend by providing partners with transdermal drug delivery technologies. 4P Therapeutics has expertise in developing novel transdermal drug delivery products using multiple transdermal technologies and leveraging a fully integrated development infrastructure. Its primary focus is on developing transdermal products for currently injected or infused compounds. These include compounds on the market or in development. The company also develops conventional transdermal systems and has found that pharma companies are combining drug delivery technologies with their NCEs in development.

In the last year, 4P Therapeutics has entered into multiple partnerships with companies ranging from a global healthcare conglomerate to small biotech companies and an academic institution. An example would include its partnership with Medicure International, Inc., a specialty pharmaceutical company in Canada, whereby Medicure is focused on developing a transdermal patch for Aggrastat® (tirofiban HCl), Medicure's lead product currently marketed as an IV formulation for the treatment of acute coronary syndromes, explains Steve Damon, President and CEO, 4P Therapeutics.

4P Therapeutics initially partnered with Medicure to demonstrate the pre-clinical feasibility of delivering tirofiban transdermally as an alternative to its current IV delivery. After successfully completing the initial feasibility studies, 4P Therapeutics and Medicure entered into a product development and commercialization partnership. This approach allowed Medicure to assess the pre-clinical feasibility of delivering tirofiban transdermally and offered the flexibility to generate valuable data before entering into a broader partnership with 4P Therapeutics and committing additional resources to the project.

"This development program presents an important life cycle management strategy for Aggrastat," says Mr. Damon. "Drugs in the Glycoprotien IIb/IIIa inhibitor class (GPI), including tirofiban, are currently only available for IV delivery. Transdermal delivery of a GPI promises to offer several benefits over IV delivery, including ease of administration using a transdermal patch that can potentially be self-administered, possible reduction in hospital length-of-stay to lower healthcare costs, and the potential for new indications that could lead to additional market penetration."

To date, 4P Therapeutics and Medicure have demonstrated *in vivo* proof-of-principle for transdermal tirofiban. The development program is now focusing on refining the transdermal tirofiban formulation in preparation for initial human studies.

4P Therapeutics' approach to partnering for the development of new transdermal products revolves around a model to assess feasibility. The model establishes pre-clinical feasibility followed by proof-of-concept in human clinical trials. "Once the feasibility has been established and considerable risk has been mitigated, 4P therapeutics and our partner can then choose to enter into a broader agreement for developing products," says Mr. Damon.

The company's feasibility model consists of efficient *in vitro* and *in vivo* screening to determine the feasibility of delivering a compound in pre-clinical and Phase 1 clinical studies. As an initial step, 4P Therapeutics' team can determine the feasibility of delivering a compound through the evaluation of the compound's physical characteristics and delivery requirements. The 4P Therapeutics' team selects the technology that presents the best probability for development success before moving into *in vitro* testing. Then, feasibility testing in pre-clinical models is performed.

The company's integrated capabilities include in-house, pre-clinical development, including bioanalysis, CMC development, IND preparation, and strategy for combination products. Its Atlanta-based facility is equipped with a vivarium for pre-clinical testing, an in-house Phase 1 unit for clinical development, manufacturing facilities for process development and early-stage clinical manufacturing.

ZOSANO—MAKING THE CASE FOR MICRONEEDLES

In the area of transdermal microneedle drug delivery, Zosano is observing significant clinical data points that validate that intradermal drug delivery using a microneedle patch can match efficacy and safety of subcutaneous injectables with increased compliance, convenience, room-temperature stability, and usability, states Peter Daddona, PhD, Chief Scientific Officer, Zosano.

The Zosano transdermal microneedle technology delivers drugs into the skin for rapid dissolution and absorption by skin capillaries. This passive delivery method

provides rapid onset without the pain or challenges of injectable products, Mr. Daddona explains. "The microneedles are long enough to produce desired pharmacokinetic profile and meaningful efficacy, but they are short enough so that they don't interfere with the nerve endings and therefore cause virtually no pain," he says. Because the microneedles protrude only into the skin epidermal and dermal skin layers and not the subcutaneous fat (like hypodermic needles) there is less patient-to-patient absorption variability.

Zosano's technology has demonstrated consistent delivery and similar consistency vs. an injectable product. The dry, drug-coated microneedle patch and packaging provides room-temperature stability data on the company's lead product, PTH (> three years), and Zosano expects to have this advantage in future products as well.

Zosano's Phase 2 results for daily administration of PTH illustrated this, showing comparable improvement in spine BMD vs. Forteo® and better improvement in hip BMD vs. Forteo. Zosano achieved faster Tmax than the injection and lower incidence of hypercalcemia. Moreover, as part of the Phase 2 study, Zosano completed a patient acceptability study and received extremely strong responses in all areas, but particularly with regards to ease of administration, self-application, skin tolerability, and general usability, explains Mr. Daddona. Zosano plans to initiate a PTH Phase 3 study in 2014.

As validation of this perspective, Zosano has seen increased interest from investors and pharma partners. Zosano signed a licensing deal with Asahi Kasei in 2011 with $33 million in upfront and milestones for PTH in Japan, China, Korea, and Taiwan.

To capitalize on the trend that a transdermal microneedle patch can match the efficacy and safety profiles of an injectable, Zosano has completed several preclinical studies with glucagon and human growth hormone. "Our current strategy is to develop glucagon internally and partner our hGH program," says Mr. Daddona. The product concept for glucagon will be to create a room-temperature, stable, ready-to-use patch comparable in efficacy to the fast onset as seen in the current rescue kit for severe hypoglycemia. "However, our major advantages will be our ease-of-use and simple "press and apply" application, which will allow for faster time-to-injection for a patient or caregiver in an emergency situation."

Zosano has carefully selected target markets where its products will serve the highest unmet medical need. The severe osteoporosis market presents such an opportunity with a currently marketed product (Forteo) that is a daily injection for two years of treatment, requires refrigeration, and also necessitates a fast-onset of action to reduce fracture incidence. Zosano not only produces a faster onset compared to Forteo, but also does not require refrigeration and possesses the clear patient usability advantages of a patch application compared to a hypodermic needle injection, states Mr. Daddona.

The second target market where Zosano expects to introduce its technology is in severe hypoglycemia caused by insulin overdose. The current product for severe hypoglycemia is a glucagon rescue kit,

Zosano's lead ZP-PTH transdermal microneedle patch and reusable applicator system has demonstrated consistent delivery vs. an injectable product.

which is provided as a sub-optimal and kluge needle-injection system that is a very challenging to use, requires a multi-step reconstitution, possesses an unstable formulation, and a limited shelf-life, explains Mr. Daddona. "The core competencies and advantages of Zosano's microneedle technology directly fill the voids in this market," he says. ◆

MASS SPECTROMETRY

Mass Spectrometry Access for All - A New Solution to the Age Old Challenge of a Multi-Vendor Open Access Laboratory

By: Hayley Crowe

In today's laboratories, mass spectrometry has become one of the primary tools to provide analytical results to a wide range of scientific disciplines and problems. It is no longer a tool solely used for analytical chemistry, but is now being applied to pharmacological data, protein analysis, environmental and food monitoring, forensics analysis, and peptide quantitation, just to name a few. Biologists, chemists, analysts, and students would all like access to results provided by these powerful instruments. However using these instruments requires extensive training on software, instrument use, and maintenance, as well as data analysis.

The complexity of mass spectrometry has often denied access to results for many laboratories, as they need results generated quickly and don't have the time to invest in continuing training processes. Depending on the type of samples and results required, it can take anywhere from 1 month to 1 year to be fully operational. Many times, a single administrator in the lab will take on the responsibility of training new scientists to use mass specs in their lab. This requires their time as well, to get the new users up and running. Each instrument in the laboratory is often controlled by completely different software, making the training process very long and overwhelming by the

FIGURE 1

AxION eDoor software interface provides a single, web-based software hub for sample submission, instrument control, and results analysis.

time the user has been brought up to speed on each instrument, or requiring that a user be limited to utilizing only one of the instruments in the laboratory.

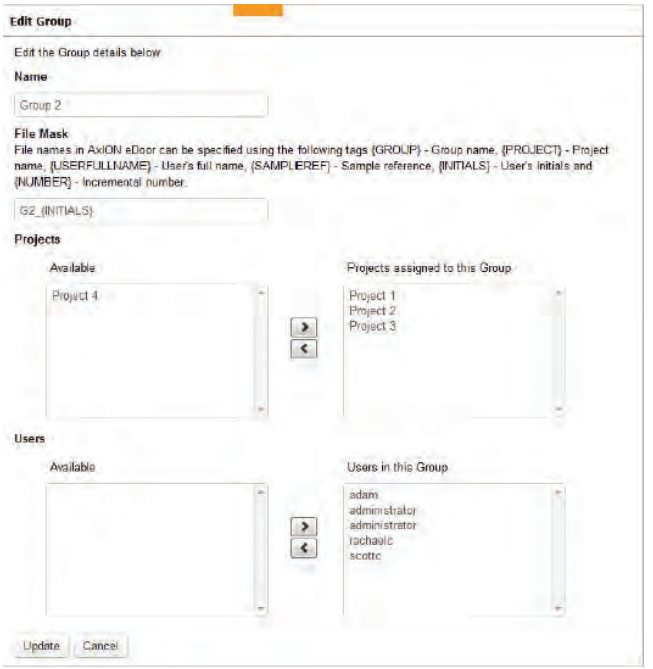
In addition to the time and effort required to train a new scientist, developing a chromatographic method, sample preparation for mass spectral analysis, and mass spec maintenance also require extensive training for optimal analytical performance. Data analysis presents another set of problems for new analysts who have no prior mass spectrometry understanding. Data processing packages, interpretation of mass spectra, and providing meaningful, accurate results takes some experience. Providing users the access to quality, mass spec results while maintaining a productive, efficient laboratory has historically been quite a challenge.

We present a solution that takes into account all the complexities associated with analytical mass spectrometry analysis outlined in the previous paragraphs. The development of a web-based, multi-vendor, open-access software platform addresses these challenges. AxION® eDoor™ presents a new way to allow access for all to mass spectrometry. It enables management of multiple locations, types of analysis, and scientists through a simple-to-use, web-enabled interface portal.

It gives the lab administrator control over the mass spectrometry laboratory without all the challenges of training new analysts who simply want mass spec results. Training is streamlined through use of a single interface that works with and controls multiple mass specs with many different types of software packages (Figure 1). Sample submission and training takes < 5 minutes with a very modern, user-friendly, web-based interface that can be accessed anywhere an internet connection is available. By using a single interface, user error is decreased considerably, and automated sample analysis is achieved. In addition, instrument and results monitoring can be done remotely. Administrators can easily manage their open-access laboratories, which has in the past proven to be challenging, time consuming, and inefficient. The intuitive interface allows the administrator to set up the system with users and groups, assign them to specific projects, and then monitor and manage the instruments and samples analyzed (Figure 2). Administrator customizable templates for sample submission are pre-defined and can include an array of options, such as lab notebook number, chemical formula, sample barcode, and compound concentration. These fields can be set up to be optional or required for sample submission. This streamlines the passage of information needed for sample analysis as well as for input into the automatically generated reports. Methods and experiments, including automatic data processing and reporting are set up and assigned to specific users, groups, and projects. The data processing and reporting can be set up to be as simple as a chromatogram with the top five peaks and associated spectra reported or complete quantitative curves and sample concentration reported. Typically, sharing data across project teams has been achieved via email or group meeting; however, this can now be accomplished by allowing access to results via a group or project or by setting up results to be automatically emailed directly to those groups (Figure 3).

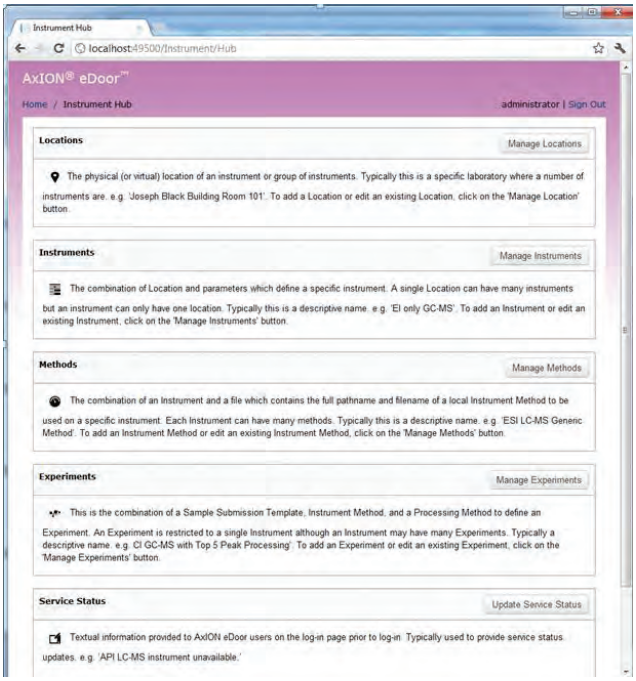
Tracking of usage can also be done by running a user, group, or project reports. The administrator does not have to keep a record of samples submitted, as the software can provide tracking details regarding a sample, from the user, bar-coded sample ID numbers, and group the

FIGURE 2



The instrument hub enables the administrator to easily manage users, methods, projects, and usage reports.

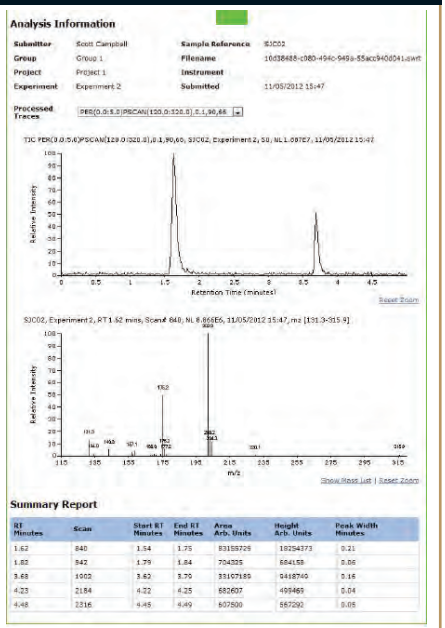
FIGURE 3



Groups can easily be set up with multiple users and projects.

sample associated. In addition, the interface is able to track instrument maintenance and notify the administrator of the next preventative maintenance as well as to provide notification of current problems. The server for the entire system is located internally to the laboratory, eliminating concerns about company firewalls, as the system is not accessible externally. The entire system provides the lab administrator an enormous increase in productivity, sample throughput, and efficiency regardless of the instrument vendor or instrument control software.

FIGURE 4



Laboratory touch screen for submitting samples in the laboratory. Results can be viewed by any device that has internet access.

This new way of open-access laboratory, multi-vendor instrument control provides greater accessibility for users as well. Users only have to learn a single interface to obtain mass spec results from multiple mass spectrometers and types of analyses. It requires users to perform four simple steps to get from sample to results: enter sample information via web, go to the lab and enter sample ID at the laboratory touch screen, place the sample in the instrument and position indicated, and wait for results to be delivered via email. Instruments are automatically assigned to submitted samples, providing faster results and decreased backlog of samples. Results are emailed back in an interactive HTML, PDF, or directly in the software via web, providing truly remote access to mass spectrometers and the results generated (Figure 4).

First-time users and experienced analysts can now access mass spectrometry analyses without needing extensive training or experience in mass spectrometry. This results in freeing up the time of the laboratory administrator to work on other tasks and increase laboratory productivity, throughput, and efficiency while analysts continue to work on ground-breaking research. ◆

BIOGRAPHY

Hayley Crowe is the Commercialization Leader for Mass Spectrometry at PerkinElmer, Inc. Ms. Crowe earned her BS in Microbiology from University of Michigan and MS in Molecular and Cellular Biology from Eastern Michigan University. She then continued her research at Pfizer and Novartis in metabolic profiling and lipidomics using mass spectrometry prior to working at PerkinElmer.

DRUG DEVELOPMENT Executive

West
By your side
for a healthier world™

West Pharmaceutical Services: Celebrating 90 Years of Healthcare Innovation

West Pharmaceutical Services, Inc. (West) is a global manufacturing company focused on the development of advanced systems for packaging and delivering injectable therapeutics and other healthcare products. West works side by side with the world's leading pharmaceutical, biotechnology, generic, and medical device companies to ensure that its customers' life-saving therapies are available for administration. Every day, more than 100 million West components are consumed in the global healthcare markets, from vaccines to protect children to diabetic care to advanced biologics to treat cancer. For 90 years, West has been an innovative technological leader collaborating with its customers to bring critical drugs to the global markets. Donald E. Morel, Jr., PhD, Chairman and CEO, West, recently spoke with Drug Development & Delivery about how the company works closely with pharmaceutical and biotechnology companies to deliver life-changing therapies safely and effectively to patients.

Donald E. Morel, Jr., PhD

Chairman & CEO,

West Pharmaceutical Services, Inc.

"West is well positioned to address the global drivers of the injectable drug market based on what we perceive to be the major trends - an aging population in western markets requiring greater treatment of chronic diseases, increased access to healthcare in emerging markets, rising generic volume, new biologic products coming through the approval process, and the need for safe, accurate, easy-to-use self-administration systems."

Q: Can you please provide our readers with some history and background on West?

A: West was founded in Philadelphia by Herman O. West and J.R. Wike in 1923. In the early 1930s, West was approached by Josiah Lilly to develop a package that could be punctured many times and yet maintain sterility within the container and not introduce any particulate contaminants. The concept of an elastomer septum held in place by an aluminum overseal was born and used by Lilly to package the first mass-produced insulin for human use along with life-saving antibiotics.

As the pharmaceutical industry grew and

more products were brought to market, West built a reputation as an industry leader and over time, established partnerships in Japan, Europe, and Mexico. West became a global company focused on innovative packaging and delivery technology for parenteral drugs, vaccines, and diagnostics, as well as products for dental and veterinary care. Today, the company is headquartered in a new research and development office complex located in Exton, Pa., with manufacturing, sales offices, and technical centers located throughout the US, Europe, South America, India, China, and the Asia Pacific rim.

Q: How has West evolved from its founding in 1923 to its current role?

A: When West was founded, the company focused on rubber products for dental and consumer applications. In the early 1930s, H.O. West was asked to develop a novel packaging system for injectable medicines and launched the core products that helped the company build its reputation. Through the next five decades, West grew through partnerships, acquisitions, and international expansion to become a global leader in systems for packaging injectable drugs as well as large-scale manufacturing of components for disposable medical devices. West also began to manufacture closure systems for a range of consumer products as well.

Since the early 2000s, West has grown rapidly from sales of $376 million in 2001 to more than $1.25 billion at the end of 2012. The company's product portfolio covers a range of elastomer products for drug packaging, aluminum overseals, and complex devices for drug administration and reconstitution. We are a global leader with our Daikyo partners in the development of advanced materials and packaging components for complex biologic molecules as well. Today, our skill set ranges from materials science and coatings to engineering design of complex devices, process technology, automated assembly, and project management using a thorough understanding of QbD and cGMP.

Q: How does West work with healthcare partners to bring pharmaceutical products to market?

A: Throughout the course of its 90-year history, West has been fortunate to work with and support the product development efforts of the world's leading healthcare and consumer companies. From early stage conceptual design to large-scale manufacturing, West's scientists and engineers seek to understand the customers' challenges and product needs, and offer innovative, cost-effective solutions to meet those needs globally. To be successful over such a long period requires patience, a willingness to listen, and a culture focused on the customer and the ultimate end user, the patient.

Q: What are some of the most memorable milestones from your career at West?

A: First and foremost was the company's response to the Kinston, NC, explosion and fire in early 2003. Despite the loss of six colleagues and loss of the plant, our operations teams sprang into

action to redeploy production in response to the needs of our customers. By the end of the year, we had not missed a single order. It was the worst time in the history of West, yet the experience brought out the best in our people and built bonds that have lasted to this day.

The acquisition of The Tech Group and Medimop in 2005 was key in the company's expansion into devices. Reaching $1 billion in sales in 2007 was a major milestone for the company.

West without Borders launched in 2004 and serves as the focal point of the company's charitable programs around the globe. Since its founding, West without Borders and other associated charitable programs have raised more than $6 million to support STEM education, cancer research, veterans initiatives, and educational and outreach programs for special needs children. It is a program that has impacted thousands of children around the globe, and one that brings an enormous sense of pride to all West employees.

Q: What are some of the biggest challenges the pharma industry faces today?

A: The pharmaceutical industry collectively is facing a number of challenges ranging from rising development costs, to low research and development productivity, to the slow pace of recovery among the world's largest economies. In addition, a large number of major drugs will lose their patent protection through 2017, and generic competition is increasing rapidly.

From a packaging standpoint, the industry and regulatory bodies are demanding cleaner and more innovative packaging systems. The increasing prevalence of drugs of biologic origin is necessitating new approaches to delivery as well, and customers are increasingly looking to devices to differentiate their products in therapeutic categories for chronic conditions such as rheumatoid arthritis.

Finally, counterfeiting is a problem that must be addressed, especially for very high-value drugs such as biologics and oncologics.

Q: Are there any future projects you're excited about?

A: I am excited about the overall future prospects for our business given our recent investments in plant infrastructure, information systems, and product research and development. West is well positioned to address the global drivers of the injectable drug market based on what we perceive to be the major trends – an aging population in western markets requiring greater treatment of chronic diseases, increased access to healthcare in emerging markets, rising generic volume, new biologic products coming through the approval process, and the need for safe, accurate, easy-to-use self-administration systems.

In our device business, there are several projects underway that have significant potential. More than 15 years ago, our Daikyo partners developed a unique polymer resin, Crystal Zenith®, for use as an alternative to glass in primary packaging. The material has been used extensively in Japan for contrast media and a range of biologic drugs. We have been developing a 1 mL insert needle syringe based on the Crystal Zenith polymer that eliminates

the glue used to set the needle, tungsten particulate, and silicone oil-in-glass syringes while offering superior break resistance. The Crystal Zenith polymer also has great flexibility in that it can be molded into complex shapes for custom containers and can be used throughout the life cycle of a drug from bulk storage to vials to prefilled syringes to custom cartridges. In the biologic and oncology drug markets, it is becoming increasingly evident that advanced plastic systems will find a market.

We have been working on a number of autoinjector concepts in addition to a novel platform based on a patch injector that can be used to administer volumes larger than 1 mL over an extended period of time.

On the packaging side, we recently introduced NovaPure® components developed in accordance with the principles of Quality by Design or QbD. The QbD philosophy results in a product of superior quality attributes by incorporating an analysis of raw materials, process capabilities, design, and manufacturing methods collectively, building quality into the product.

In terms of our manufacturing footprint, we have completed our first elastomer facility in China, which is now operational, and will begin production from our first facility in India in early 2014. Due to volume growth in key product lines, we are also undergoing a major conversion at our Kinston, N.C., facility.

Q: Global healthcare needs and regulations evolve on a day-to-day basis. How has pharma globalization impacted West?

A: In terms of globalization, the primary impact on West is the ever-increasing complexity of the business in terms of supply chain, varying regulatory requirements, and understanding local market nuances. For example, in certain geographic regions, Luer syringes are used almost exclusively whereas in other markets, fixed needle systems are preferred. In China, the market is converting from glass IV systems to flexible bags and blown bottles. There are numerous other examples that add SKUs to the business and the associated costs of managing them. We manufacture over 36 billion pieces annually composed of more than 4,500 SKUs that get consumed in the healthcare markets. Quality expectations increase year by year, not only in terms of cleanliness, but also delivery timing and accuracy. Our people must understand that full, complete adherence to cGMP is non-negotiable and mandatory; our quality system must be uniform and well understood. For a US-based company, we must also ensure full compliance globally with provisions in the Foreign Corrupt Practices Act.

We are measured by our conduct every day. The senior leadership team constantly communicates the expectations outlined in our corporate Code of Conduct. West plays an incredibly important role in the pharmaceutical supply chain globally. Our mission remains unchanged from H.O. West's vision – to work side by side with our customers to bring the best possible products to market for the benefit of patients everywhere.◆

Daikyo Crystal Zenith® is a registered trademark of Daikyo Seiko, Ltd.

Daikyo Crystal Zenith® technology is licensed from Daikyo Seiko, Ltd.

NovaPure® is a registered trademark of West Pharmaceutical Services, Inc., in the United States and other jurisdictions.

Technology & Services Showcase

Innovative Platforms

Adhesives Research, Inc. has over 20 years of experience developing and manufacturing custom pressure-sensitive adhesive tapes, specialty coatings, films, and laminates for the for the world's leading pharmaceutical companies. We offer the pharmaceutical industry a wide range of coating technologies and adhesive capabilities for transdermal, oral, and topical drug delivery. Based upon proven PIB, acrylic, silicone, and dissolvable film technology platforms, Adhesives Research's skin-friendly adhesives are available with conductive, porous, occlusive, hydrophilic, hydrophobic, gentle, or long-term adhesion functional properties to meet the unique needs of our clients' applications. For more information, contact Adhesives Research at (800) 445-6240 or visit **www.adhesivesresearch.com**.

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Specialty Ingredients

ASHLAND

Ashland Specialty Ingredients offers industry-leading products, technologies, and resources for solving formulation and product performance challenges in key markets, including personal care, pharmaceutical, food and beverage, coatings, and energy. Using natural, synthetic, and semi-synthetic polymers derived from plant and seed extract, cellulose ethers and vinyl pyrrolidones, Ashland offers comprehensive and innovative solutions for today's demanding consumer and industrial applications. Ashland is a highly respected supplier of excipients and tablet film-coating systems to enable the formulation and delivery of active ingredients. Using our wide range of products, developers create reliable formulations for tablet binding, controlled-release formulations, tablet film coating, drug solubilization, and tablet disintegration applications. For more information, contact Ashland Specialty Ingredients at (877) 546-2782 or visit **www.ashland.com/ddd/pharmaceutica**l.

Licensing & Capabilities

Aveva has a number of products for license from its development pipeline along with a full complement of R&D capabilities to produce transdermal drug delivery systems that fortify pipelines and maximize product life cycles. Aveva Drug Delivery Systems is one of the world's largest manufacturers of, and a pioneer in, transdermal drug delivery systems with a rich history of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs. Products for licensing include Sufentanil, Fentanyl, Clonidine, and Nicotine. For more information, contact Robert Bloder, VP of Business Development, at (954) 624-1374 or visit **www.avevadds.com**.

Technology & Services *Showcase*

Analytical Testing & Deformulation

AVOMEEN ANALYTICAL SERVICES

Avomeen Analytical Services provides advanced analytical testing and product development services to the pharmaceutical and material science industries. Our chemists are experts at solving complex problems for our clients through our specialization in deformulation and failure analysis services. Avomeen also provides a wide variety of additional analytical testing services, including method development & validation, stability & release testing, extractable & leachable analysis, chemical characterization, quality control testing, and litigation support services. Avomeen's laboratory is FDA-Registered, DEA-Licensed, and cGMP-Compliant. Let our friendly staff assist you through our quick & easy custom quoting process or arrange a free consultation with one of our PhD chemists. For more information, contact Avomeen Analytical Services at (800) 930-5450, email at scientist@avomeen.com, or visit **www.avomeen.com**.

Development & Manufacturing

BEND RESEARCH®
ACHIEVE VALUE THROUGH SCIENCE

Bend Research is a leading independent scientific development and manufacturing company with more than 35 years of experience in the development of pharmaceutical delivery systems. To achieve its mission of improving health through the advancement of its clients' best new medicines, the company uses a multidisciplinary problem-solving approach grounded in science and engineering fundamentals to address the most difficult challenges. As a leader in novel drug delivery technologies and formulations, Bend Research provides expertise in solubilization technologies, such as spray-dried dispersions and hot-melt extrusion formulations, as well as biotherapeutic, controlled-release, inhalation, and nanoparticle technologies. Capabilities include formulation science, process development and engineering, dosage-form development, cGMP manufacturing, and analytical services for the advancement of drug candidates from early discovery to commercialization. Bend Research also pioneers, advances, and commercializes new technologies. For more information, contact Phoenix Barringer of Bend Research at (800) 706-8655 or Phoenix.Barringer@BendResearch.com or visit **www.BendResearch.com**.

Biologics Development

Catalent's proprietary Gene Product Expression Technology (GPEx®) sets the standards in mammalian cell line engineering. GPEx allows rapid selection of the best clinical candidate from a group of potential molecules, providing a stable Master Cell Bank to rapidly generate proteins for clinical trials. GPEx technology can ensure genetically stable cell lines are produced 100% of the time. The advanced mammalian cell line technology in GPEx accelerates timelines, increases reliability and yield, and provides superior cell stability compared to any other method, with flexibility and unmatched versatility. Catalent provides a faster path from gene to clinic and offers high-performance cell line biologics development and biomanufacturing. Catalent boasts a new, state-of-the-art, biologics manufacturing facility in Madison, WI, allowing for batch sizes from 10-1,000 L. To learn more about Catalent's global Biologics capabilities, call (877) 587-1835 or visit **http://www.catalent.com/index.php/development/biologics/overview**.

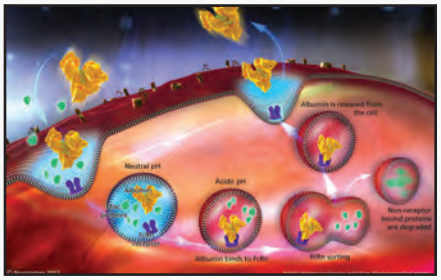
Super Refined® Excipients

CRODA
Health Care

Croda manufactures a complete range of high purity excipients and delivery aids, offering superior quality for the global pharmaceutical market. These excipients are ideal for multiple dosage forms, including topical, parenteral, oral, and ophthalmic formulations as well as advanced delivery systems. Croda's Super Refined® excipients go through a proprietary process to remove the polar and oxidative impurities that can cause performance and stability issues. These excipients are ideal for use when working with sensitive drug actives, helping to maximize the stability and overall performance of the drug product. Excipients in the Super Refined range include PEGs, polysorbates, oils, and triglycerides, propylene glycol, castor oil, and a range of topical penetration enhancers, such as oleic acid and dimethyl isosorbide. For more information, contact Croda at (732) 417-0800 or visit **www.croda.com/healthcare**.

Technology & Services Showcase

Tunable Half-Life Extension Technology



Novozymes' tunable half-life extension (HLE) technology can flexibly extend half-life to reduce the dosing frequency of drugs from days to weeks. Based on albumin, Novozymes offers HLE by genetic fusion, Albufuse® Flex, or chemical conjugation, Recombumin® Flex, enabling the tunability of HLE to meet the needs of a specific disease or application. Leading the way in improving patient quality of life, Novozymes' technology is already being widely used in the fields of diabetes, haemophilia, and neutropenia. Through the optimization of drug half-life, dosing frequency and healthcare costs can be reduced while increasing patient compliance. Long patents until at least 2030 also provide manufacturers with a unique competitive edge in current challenging markets. For more information on Novozymes' HLE technology, please visit **www.halflifeextension.com**.

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PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (920) 850-3056 or visit **www.pharmacircle.com**.

Specialty Services Provider

Piramal Pharma Solutions is the Contract Development and Manufacturing (CDMO) arm of Piramal Healthcare (Piramal Enterprises Ltd.) and is one of the only CDMOs providing support throughout the entire pharmaceutical drug product life-cycle. It also provides specialty services of Antibody Drug Conjugation & Clinical Trial Supplies for pharmaceutical companies. Piramal Pharma Solutions supplies competitive products and services through a globally integrated network of sites across North America, Europe, and Asia accredited by US FDA and EU regulatory authorities. This allows a comprehensive range of services across the drug lifecycle - from Drug Discovery Solutions, Manufacturing, and Packaging of Phase I-III Clinical Trial Supplies through to Commercial Volumes for API and Formulated drug product to be offered. Piramal respects the Intellectual Property Rights and does not infringe any process or product knowingly and/or unknowingly. For more information, contact Dr. Detlef Behrens at detlef.behrens@piramal.com, Brian Shaughnessy at brian.shaughnessy@piramal.com, or email **strategicmarketing.cell@piramal.com**.

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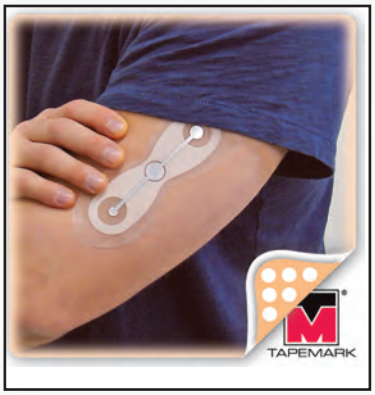
Rexam Healthcare, a global leader in healthcare rigid plastic packaging and medical devices, will launch the latest version of its industry reference child-resistant closure (CRC) - the Clic-Loc® 4. Clic-Loc is the first and only CRC available to combine more than 40 years of demonstrated safe and effective oral dose protection, adult-friendly operation, and multiple manufacturer benefits. The Clic-Loc delivers superior ergonomics, is easily used on production lines, and creates an audible warning click to alert parents and caregivers. Like the current Clic-Loc, the new edition is shrink-wrap friendly, and offers unsurpassed capper flexibility and variety. Importantly, with an aging worldwide population, the Clic-Loc is designed for secure and frustration-free use by seniors and those with disabilities. The new Clic-Loc 4 will provide enhanced functionality and aesthetics, for industry-leading protection, production efficiency, and product differentiation. For more information, visit Rexam Healthcare at **www.rexam.com**.

Technology & Services Showcase

Development & Manufacturing



Tapemark is a full-service pharmaceutical and medical device contract manufacturer providing web-based (flexible roll goods) manufacturing for Drug, Device, and Combination Products. Supported single-use drug delivery formats include active and passive transdermal patches, oral and transmucosal soluble film, topical patches and pads, and Tapemark's patented Snap! and SnapplicatorTM unit-dose packaging for semi-solids. Tapemark is cGMP-compliant, ISO 9001, and 13485 certified, and FDA registered as a Drug, Device, Food, Cosmetics, and Dietary Supplements contract manufacturer. In addition, Tapemark is DEA registered as a Schedule III-V Manufacturer of Controlled Substances. Supporting its expanding global reach, Tapemark's quality system has been successfully audited by the European Union, Japan, Australia, and Korea, with CE mark certification. Contact Tapemark at **www.tapemark.com**, or call (800) 535-1998.

Development Services

UUPM Pharmaceuticals® is an independent provider of contract formulation development, analytical services, and cGMP manufacturing. We continue a legacy of intellectual distinction and uncompromising performance with every new project. The talent and experience of our team, our dedication to science-based formulation design, and our commitment to communication and timeliness enables us to offer the highest level of customized drug development services. Our 40,000-sq-ft main facility in Baltimore features cGMP pharmaceutical manufacturing and packaging suites as well as analytical and R&D laboratories staffed by industry veterans. Whatever form your product takes, we ensure rigorous and technically sound product characterization, methods development, and QC release. Our clients enjoy service that is highly responsive and fast with total quality management characteristic of a customer-focused business. For more information, contact UPM Pharmaceuticals at 410-843-3738 or visit **www.upm-inc.com**.

West PFS Solutions

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Development Services

Xcelience® Formulation Development

Xcelience is a premier provider of formulation development and manufacturing solutions with a solid reputation for accelerating early phase small molecule development. Our outstanding quality record, significant drug development expertise, willingness to customize, and disciplined project management enable us to deliver real advantages to clients needing to speed potential drugs to clinical trials. Since 1997, Xcelience has been renowned for reliably expediting drug development. Our formulation development scientists have considerable experience overcoming challenges associated with physical and chemical properties of drug substance, or limited quantities of API, in a manner that results in compounds with improved solubility and bioavailability. Partnering with a specialist like Xcelience for early phase development can significantly reduce product risk and accelerate development timelines. For more information, contact Xcelience at (813) 286-0404 or visit **www.xcelience.com**.

Predictive Modeling

Predicting Price Changes of Oncology Drugs in the US: Can Proportional Hazard Models Predict the Timing & Percentage of Changes?

By: Bruce Wang, PhD, MA, Director, Alliance Life Sciences Consulting Group

Introduction

In recent years, the Life Sciences industry has been moving toward outcomes-based approaches due to rising legislative and operational pressures. In this environment, Health Economics Outcomes Research (HEOR) has come to the forefront as a way to measure the effectiveness of therapies and their competitive nature in the market.

One major factor in determining the competitive standing of your product is the price point. Predicting the price change percentages and timings of drugs is important to policy-makers, pharmaceutical companies, and even investment firms, to aid in sound policy and product decision-making. If it were possible to use advanced modeling to predict these changes, informed decisions could be made based on these forecasts.

Methodology

To test this theory, Cox Proportional Hazard Models were applied to a set of oncology drugs in the United States to perform predictions. Hazard models are a class of survival models in statistics. Survival models relate the time that passes before an event occurs to one or more variables that may be associated with it. In this case, we are observing the events leading up to a price change in order to predict the timing and percentage of that change.

Using data from First DataBank (2003-2012), a panel of ex-factory drug prices for drug packs for 18 brand names was examined. The data was converted into

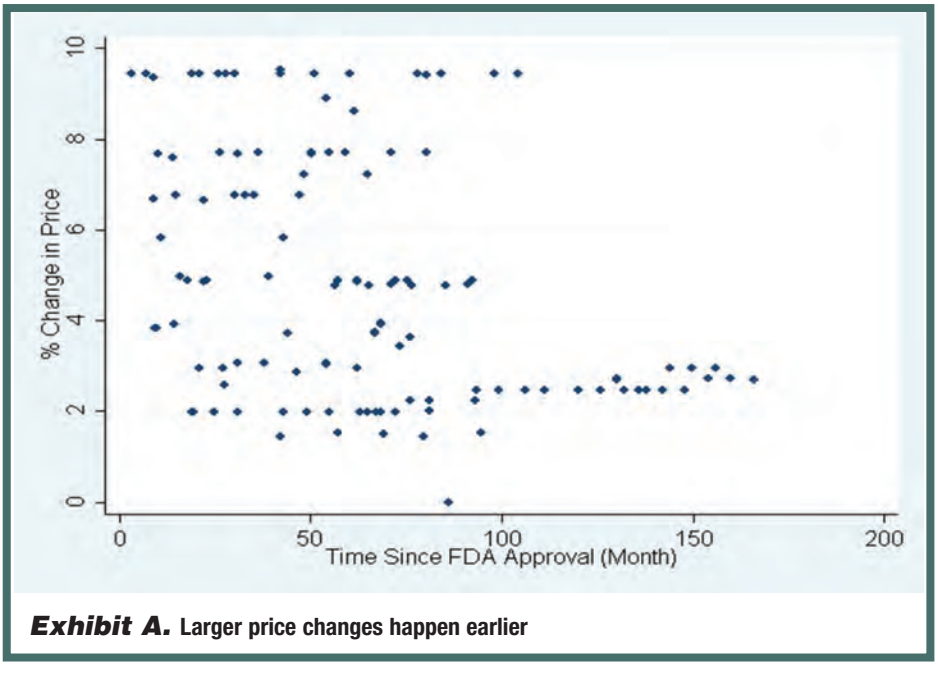


Exhibit A. **Larger price changes happen earlier**

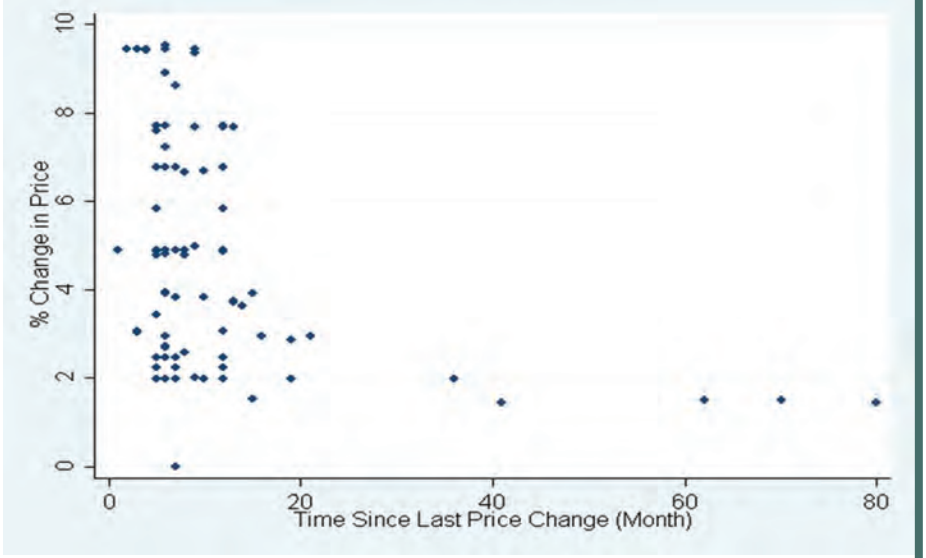


Exhibit B. **Prices typically change within 12 months**

survival time data by calculating the time duration between each price change, which results in a total of 200 price increases and 38 censored outcomes.

The hazard models include the FDA approval date for each drug as a variable to answer the following questions: 1) how is the percentage change in price related to the time since the last price change and the time since FDA approval; 2) does the probability of a price change depend on the time since FDA approval?

Results

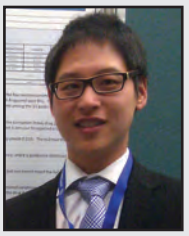
Using the proportional hazard model, the average "event" is a price increase of 5%. For percentage changes in price, for each additional month of constant price, the subsequent price increase drops by 0.08%.

For a second order effect, the negative effect of time since last price change is decreasing. Also, time since FDA approval has a large and significant effect: for each additional month since FDA approval, the subsequent price increase drops by 0.03%.

The average duration between events is 8.8 months. The Cox model shows that for each additional month since FDA approval, the "risk" of a price increase increases by 0.7%. Similarly, there is a second order effect showing this risk diminishing over time. Exhibits A and B illustrate some of the modeling results in graph form.

This case study suggests that Cox Proportional Hazard Models can be used to predict price change percentages and timing of prescription drugs in the market. This information is extremely valuable to decision-makers in the Life Sciences industry, as it enables more informed insights through predictive modeling and analytics on the lifecycle of a drug.

This is just one example of the many possibilities that exist through HEOR studies that aid in the guidance of new treatments and technologies to better manage the rising costs of healthcare both on a national and global level. ■



Bruce Wang, PhD, MA

Director
Alliance Life Sciences Consulting Group

Dr. Wang is the Practice Lead of the Health Economics and Outcomes Research Practice at Alliance. He joined Alliance in 2011, and leads his practice in work across the globe. He brings deep expertise in applied economics with a particular focus on health economic models. He has published papers on cost-effectiveness, methodology, pricing, and policy. Dr. Wang was a Senior Fellow in the Pharmaceutical Outcomes Research & Policy Program at the University of Washington. Prior to that, he was an Economic Strategist at Goldman Sachs in New York. He earned his PhD and MA in Economics from the University of Washington and his BA from Columbia University.

Rapid Action Therapy in Pain Relief: Potential for Nasal Delivery Systems

By: Shunji Haruta, PhD

Introduction

Improvements in therapy for pain management have the potential to be realized through the utilization of rapid action. Currently, the most effective pain management therapies achieving rapid action are those in a hospital or healthcare-professional setting with the use of injections, which provide fast onset of relief. However, such settings are typically limited to emergency and/or surgery situations, which often require the patient to regulate pain therapies on his/her own after leaving the clinic. Furthermore, a major allotment of pain management is not the result of an extreme precipice (such as an accident), and the pain management required can be on a daily basis for indefinite periods of time. A survey based upon a random sample of 28,902 working Americans found that "[p]ain is an inordinately common and disabling condition in the US work-force. Most of the pain-related lost productive time occurs while employees are at work and is in the form of reduced performance." Further conclusions derived from this survey found that $61.2 billion per year is lost due to pain conditions. The most common pain conditions resulting in lost productive time were headache, back pain, arthritis pain, and musculoskeletal pain.[1] This survey, along with information regarding acute and chronic pain conditions, demonstrates that there is a great need for improved rapid action pain therapies.

As a whole, the management of acute and chronic pain stemming from conditions such as migraine, cancer-induced breakthrough pain, neuropathic, post-operative, sports, and injury pain shows a

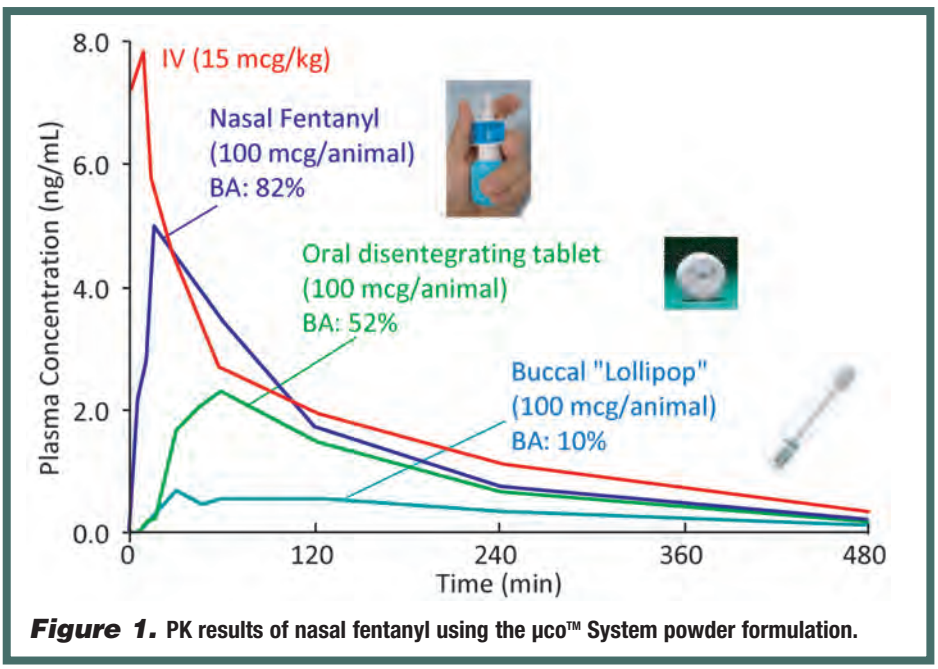
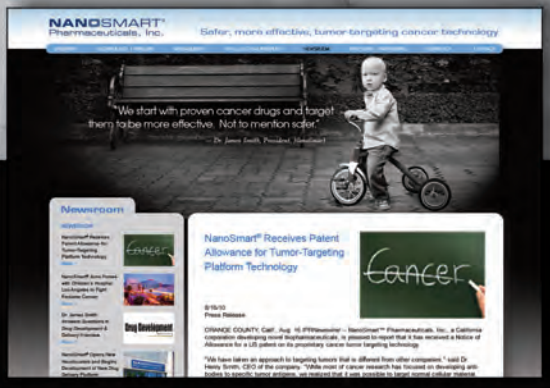


Figure 1. **PK results of nasal fentanyl using the µco™ System powder formulation.**

"The opportunity to help millions of cancer patients doesn't happen too often in one's lifetime."

— Dr. Henry Smith, CEO, NanoSmart



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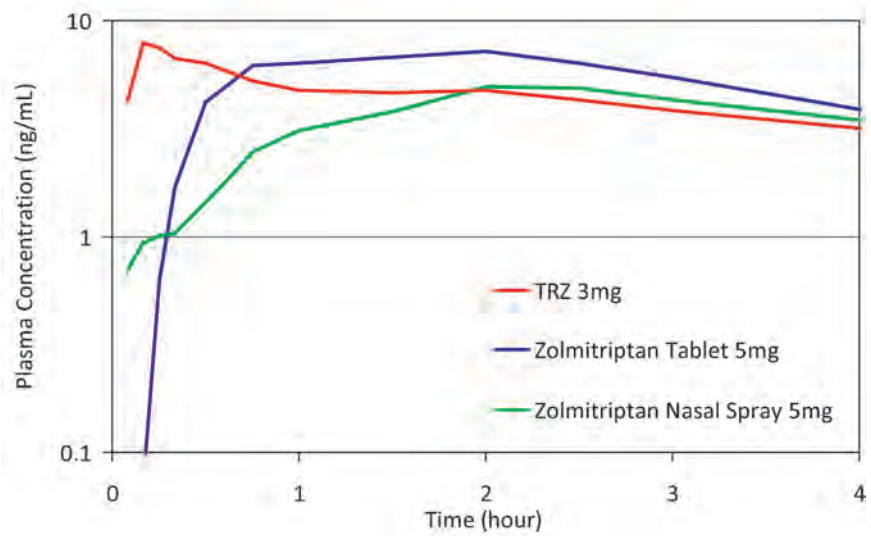

Figure 2. **PK of nasal zolmitriptan (TRZ) utilizing the µco™ System in Phase I clinical trial.**

great deal of room for improvement in terms of rapid action. As the approach to acute pain treatment underwent a significant evolution throughout the 90s, it was recognized that the effects of early control during episodes of pain on the subsequent evolution are of critical importance.[2,3] Patients suffering acute pain have been shown to become increasingly more sensitive to painful stimulus the longer the pain is uncontrolled; in other words, patients feel more pain than normally expected after an initial period of untreated acute pain. There is even risk that this change in sensitivity can become permanent, which is reason enough to aggressively pursue relief of pain as soon as symptoms present.[4] Furthermore, treatment at early onset of pain has been shown in some instances of shingles and amputation pain, respectively, to decrease subsequent pain, in turn reducing the need for further treatment. It is also notable that the prompt and complete relief of pain from migraine has been correlated with the reduction of migraine recurrence within 24 hours.[3,4] The benefits of at-home, reliable, and fast-acting pain management options are undeniable, and advancements in pain therapies are necessary.

Pain therapies need to be available and feasible for the average person; API, formulation, and manufacturing costs need to be minimal in order to keep the drug affordable for the consumer. Under typical day-to-day conditions, formulations need to be stable, which allow medications to be carried with a person, such as in a pocket or a purse. This would be especially useful in instances of cancer-induced breakthrough pain or migraine pain when onset can be swift and is mostly unpredictable. Self-administration and ease-of-use (non-invasive delivery) are other key elements to effective at-home therapeutic treatment. Treatments that can be administered on-the-go or in public places are desirable, and historically, this is one reason oral pill therapies have enjoyed much popularity. Delivery methods that offer a level of comfort during episodes of dry mouth or nausea are also desirable when pills are difficult; nasal delivery offers a good solution to this problem. The therapeutic effect needs to be reliable, which hinges heavily on the dependable and consistent performance of the paired delivery device. It is expected that if a product can meet these needs (availability, stable formulation, easy self-administration, and reliability), that rapid action pain therapies can be a reality of at-home care.

Of the major alternative administration routes, a great amount of attention has come to nasal delivery. The nasal cavity has proven to be an effective route of administration for systemic delivery due to the high permeability of the nasal mucosa and great vascularization.[5] Nasal delivery is also made desirable by ease of administration, which enables high patient compliance, along with avoidance of gastrointestinal (GI) and hepatic first-pass metabolism which further contributes to rapid action.[5] Nasal delivery technologies are progressing, and attempts to mitigate the drawbacks of traditional nasal therapies, such a running liquids and use of locally irritating absorption enhancers, are being offered by several companies. SNBL, Ltd. is one such company, with the µco™ System. The system offers a dry-powder carrier technology and line of delivery devices that help formulations meet the aforementioned criteria for rapid action and successful delivery of pain therapies.

Cancer-Induced Breakthrough Pain

Cancer-induced breakthrough pain (CiBP) takes a significant toll on quality of life, and a number of surveys evidence the significant impact of CiBP on the lives of cancer patients. In one cross-sectional survey of 164 inpatients with controlled baseline pain, CiBP was present in 84 patients on the day prior to survey with a median number of 6 episodes (range 1-60).[6] Assessment tools for the measurement of pain and mood, pain-related interference with function, depressed mood, and anxiety were used, and the resulting multivariate analysis found that CiBP "independently contributed to impaired functioning and psychologic distress."[6] In another prospective survey with 218 CiBP-experiencing cancer patients, 361 pains were reported of which 38% were classified as severe or excruciating; 49% of pain episodes occurred suddenly, 59% of which were unpredictable. Another common disruption and factor impacting quality of life for cancer patients is incident-related CiBP. Incident-related CiBP is brought on from movement of the body, often associated with bone metastases. Patients prone to incident-related breakthrough pain often cope in a preventative manner by limiting movements, which leads to a significant reduction in autonomy.[7]

CiBP illustrates why some pain therapeutics not only require rapid action, but simply cannot be treated effectively otherwise. A quintessential example, CiBP is an area of patient need that struggles to be met through the use of traditional delivery routes. Slow onset associated with oral medications often results in therapeutic action when pain has already crested (therapeutic onset around 30 minutes), proximately followed by 3 to 6 hours of unnecessary analgesia.[6,7] Not to mention traditional oral medications are made further impractical by a patient's decreased salivary flow, a common characteristic found in cancer patients. The inconvenience and patient discomfort with administering at-home injection medications make such therapies unattractive, and they are sometimes viewed as a last attempt at pain control.

Compounding the need for better at-home CiBP treatments is the industry-wide shift in healthcare demands as hospitals and patients struggle to balance costs with needs. Treatment has historically included supplemental doses of oral opioids in combination with an analgesic regimen for the maintenance of baseline pain. As previously stated, these oral opioids lack the rapid action necessary for treatment, with a resultant prolonged and unnecessary analgesia. However, in recent years, non-parenteral therapies enabling rapid action for CiBP have been explored with the use of fentanyl.

Fentanyl is a synthetic opioid characterized by high lipid solubility. A hundred times more potent than morphine, along with accelerated crossing of the blood brain barrier, fentanyl provides quick analgesic effect along with shorter duration of analgesia when administered transmucosally.[6,7] Studies have shown fentanyl is well absorbed through the nasal mucosa with peak blood concentration reached at 13 minutes and bioavailability of 70% to 90%.6 In one clinical study comparing efficacy of intranasal fentanyl against oral transmucosal fentanyl citrate, patients were titrated to an effective dose of either the nasal or transmucosal fentanyl preparations and subsequently treated for six episodes; the process was then replicated for treatment with the other formulation. The purpose of this study was to measure time to meaningful pain relief as recorded by the patient. Overall, it was reported that the nasal formulation provided a median time of 11 minutes to meaningful pain relief; meaningful relief was achieved at a median time of 16 minutes with the oral transmucosal formulation.[6] Additionally, pain intensity difference was measured at 5 minutes post-dosing and was significantly greater for the intranasally delivered fentanyl than that of the oral transmucosal.[6]

It is clear that non-parenteral delivery can provide the rapid action necessary for the successful treatment of CiBP. Self-administration and ease-of-use due to non-invasive delivery is key for CiBP therapies. SNBL, using their predictive intranasal PK animal model and animal pain model, has developed and tested an intranasal fentanyl formulation with similar preclinical results as previously stated. This type of formulation goes one step further in achieving the parameters of rapid action as it utilizes the µco System's dry powder formulation designed for greater stability, coupled with its reliable delivery device (Figure 1).

Migraine Pain

As previously discussed, migraine pain accounts for a significant amount of lost productive time in the workplace; specifically, survey results cited that 3.51 hours of productive work time per worker, per week was lost due to headache.[1] Additionally, the World Health Organization (WHO) has ranked migraine among the world's most disabling medical illnesses, and migraine has been shown to have a significantly negative impact on quality of life.[3,8] In one survey of 500 migraineurs, 93% reported moderate or severe headache pain, and in one study, 71% of migraineurs reported inability to think or concentrate when symptoms were severe.[9] Additional surveys and studies have shown that the most important and/or desired effect of treatment is quick and complete relief from headache.[9,10]

Patient preferences in the treatment of migraines is critically important due to the necessity of patient compliance in administration, and surveys often report that patients are most comfortable with the oral route of delivery. Market research conducted by SNBL, Ltd., including interviews of multiple migraine treating and prescription-writing Primary Care Providers and Neurologists, showed that the majority of patients have greatest comfort with oral pill medications across all aspects of treatment. It should also be noted that physicians reported one major reason existing marketed nasal products were not preferred by patients was bad taste and nasal irritation. Despite patient preference, oral pill medications often do not yield fast onset of relief, which is counter to the needs of patients as studies have also shown that fast therapeutic onset is of utmost importance to migraineurs.[9,10] Furthermore, it was revealed through physician interviews that one-third of the migraineurs treated were unable to accept oral treatment due to nausea and vomiting. As such, it is evident the needs of migraineurs are not being fully met, and alternative delivery routes, which enable rapid action therapies, have the ability to meet this need.

Traditional therapy options for migraines prior to the discovery of 5-HT 1B/1D agonists included analgesics, ergotamine, and dihydroergotamine. However, a significant revolution in the treatment of migraine pain came with the class of 5-HT1B/1D agonists, commonly known as triptans. Sumatriptan was the first to be used, and second generation triptan's, such as rizatriptain, zolmitriptan, and naratriptan, have also been found to be effective in migraine treatment. Studies conducted following the introduction of triptans found that the leading factor in patient satisfaction with triptan therapies during migraine was rapid therapeutic onset. So consequential was the time to relief that some patients have been reported as choosing a subcutaneous injection over traditional oral pill therapies for the purpose of fast relief.[9] Advancements in delivery of triptans for the purpose of decreasing time to relief have come to market. Products such as liquid nasal sprays of sumatriptan and zolmitriptan, respectively, have found some market share, and it has been reported that some patients experience relief in as little as 15 minutes, with 55% to 64% of patients reporting no-to-mild pain at 2 hours post-administration of said nasal therapies (it should be noted, however, that such nasal products continue to receive fewer prescriptions due to patient preferences discussed in the prior section).9 However, the pharmacokinetics of nasally delivered liquid products suggest that much of the formulation runs out of the nasal cavity and is absorbed by the GI, a common characteristic of traditional nasal liquid sprays, which also accounts for the bad taste often cited by patients. The initial therapeutic onset can be attributed to limited absorption in the nasal cavity with the remaining analgesic effect taking place after GI absorption. While treatment for migraine has made great strides with the use of 5-HT 1B/1D agonists, there is still ample room for improvements relating to rapid action. SNBL has developed an intranasal zolmitripan (TRZ) formulation, which is designed for rapid action utilizing the µco System's dry powder formulation and reliable delivery device (Figure 2). Thus far, TRZ in a Phase I clinical trial has shown rapid absorption as shown in Figure 2.

Summary

Pain has a major diminishing effect on quality of life and productivity, from episodes of acute pain to chronic, long-lasting conditions. In the past 2 decades, findings that rapid action in pain therapies help to avoid CNS wind-up has resulted in a paradigm shift in pain management.

Furthermore, rapid action pain therapies better address the needs of patients especially in regard to conditions such as CiBP and migraine pain. Alternate routes of delivery, specifically delivery to the nasal cavity, have shown a great propensity for success in rapid action onset. The µco System by SNBL is one such delivery system that has shown preclinical and clinical success in rapid action thanks to a dry powder carrier formulation and reliable delivery devices. Alternate route delivery systems such as the µco System are promising in the future of pain therapies and management.

Outside of the treatment of acute and chronic pain, there are many therapeutic areas that could benefit greatly from rapid action treatments. Treatments for life threatening conditions, such as seizure, including subarachnoid hemorrhage, and heart attack, would see obvious benefits from rapid action therapies. Other less dire conditions that could reap the discussed benefits are patients being treated for sexual conditions, such as erectile dysfunction and anorgasmia. Patients seeking sleep-induction therapies, sedatives, and/or anxiolytics also have the potential to receive better results with the use of nasal delivery enabling rapid action. ■

References

1. Stewart W, et al. Lost productive time and cost due to common pain conditions in the US workforce. JAMA. 2003;290(18):2443-2454.\
2. Carr D, Goudas L. Acute pain. The Lancet. 1999;353:2051-2058.
3. Antonaci F, et al. Meeting patient expectations in migraine treatment: what are the key endpoints? J Headache Pain. 2008;9:207-213.
4. Ducharme J. Acute pain and pain control: state of the art. Annals Emerg Med. 2000;35(6):592-603.
5. Grassin-Delyle S, et al. Intranasal drug delivery: an efficient and non-invasive route for systemic administration. Pharmacol Therapeut. 2012;134:366-379.
6. Leppert W. Role of intranasal fentanyl in breakthrough pain management in cancer patients. Cancer Manage Res. 2010;2:225-232.
7. Mercadante S. Managing breakthrough pain. Curr Pain Headache Rep. 2011;15:244-249.
8. Menken M. The global burden of disease study. Arch Neurol. 2000;57:418-420.
9. Ryan Jr. R. Patient treatment preferences and the 5HT1B/1D agonists. Arch Intern Med. 2001;161:2545-2553.
10. Worthington I. Delivery systems for acute migraine medications. Can Fam Phys. 2001;47:322-329.

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Dr. Haruta is an Executive Officer at SNBL, Ltd. and the General Manager of NDS Division, with focus on the R&D of the µco™ System. Dr. Haruta has been with the µco System since its inception over 10 years ago and continues to oversee the R&D and business operations relating to it. Dr. Haruta earned his PhD in Pharmaceutical Science from Okayama University, Japan. His scientific background includes pharmaceutics and specializes in drug mucosal absorption, formulation technology with mucoadhesive and controlled release, and the effect of gastrointestinal transition on drug absorption and pharmacokinetics. He formerly worked as a clinical pharmacist and researched drug absorption at Miyazaki Medical College Hospital, Japan.

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Big Brother/Little Brother

By: John A. Bermingham

On August 17, 1975, Senator Frank Church appeared on NBC's Meet the Press to discuss the results of his investigation into the United States' growing intelligence capabilities. He revealed shocking information and ended the interview with a warning to the citizens of the United States.

"America's intelligence gathering capability at any time could be turned around on the American people, and no American would have any privacy left. Such is the capability to monitor everything: telephone conversations, telegrams, it doesn't matter. There would be no place to hide."

After further comment, he went on to state in conclusion: "I don't ever want to see this country go across the bridge. I know the capacity that is there to make tyranny total in America, and we must see to it that (the NSA) and all agencies that possess this technology operate within the law and under proper supervision so that we never cross over that abyss. That is the abyss from which there is no return."

This was prior to the widespread use of the internet, cell phones, and social media, so you can imagine what Senator Church's reaction would have been had those technologies been in widespread use in 1975. While almost everyone reading this article has heard of George Orwell's famous novel, Nineteen Eighty-Four and Big Brother, the Inner Party's leader, not too many people think about Little Brother.

Who is Little Brother? Little Brother is someone you encounter multiple times per day almost every day. Little Brother is the great communications overseer who involves himself in many areas. Here's how he works.

When you are at work and you are using your computer, your company has the right to monitor the information that you send or receive because you are utilizing company assets, such as their computer, their WAN, LAN, WiFi, or servers. Your e-mail, including personal e-mail, is not private in this case. Even If you use your own personal device, such as an iPad, and utilize your company's WiFi network as an example, the company still has the right to monitor your information.

If your company supplies you with a company cell phone and pays for the service, they have the right to monitor who you are calling and who is calling you. The same thing holds true if your company reimburses you for your cell phone costs if you are using your personal cell phone for business purposes.

If you are in a coffee shop, restaurant, hotel, or airport and you utilize their WiFi network, that venue has the right to identify you and send unsolicited messages back to you.

So while there is great concern with Big Brother watching over you, you must be aware of Little Brother as well.

We have reached a point in technology where people must be very careful with their communications and be fully cognizant of the fact that others can access your communications and information, be it personal or business.

There is also the legacy issue. When you leave a company, your management will often access your e-mail account to look at past e-mails and to receive future e-mails. This is done to protect the business by monitoring and following up on key issues that might otherwise fall through the cracks. In addition, your personal e-mails sent and received, websites visited, and social media communications conducted via company assets are also viewed by management.

It all comes down to this. The word "anonymous" may soon disappear from our language, that is if Little Brother has anything to do with it! ◆

Biography

John A. Bermingham
Chief Operating Officer
1st Light Energy & Conservation Lighting

John A. Bermingham is currently the COO of 1st Light Energy & Conservation Lighting. He was previously Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc), as well as President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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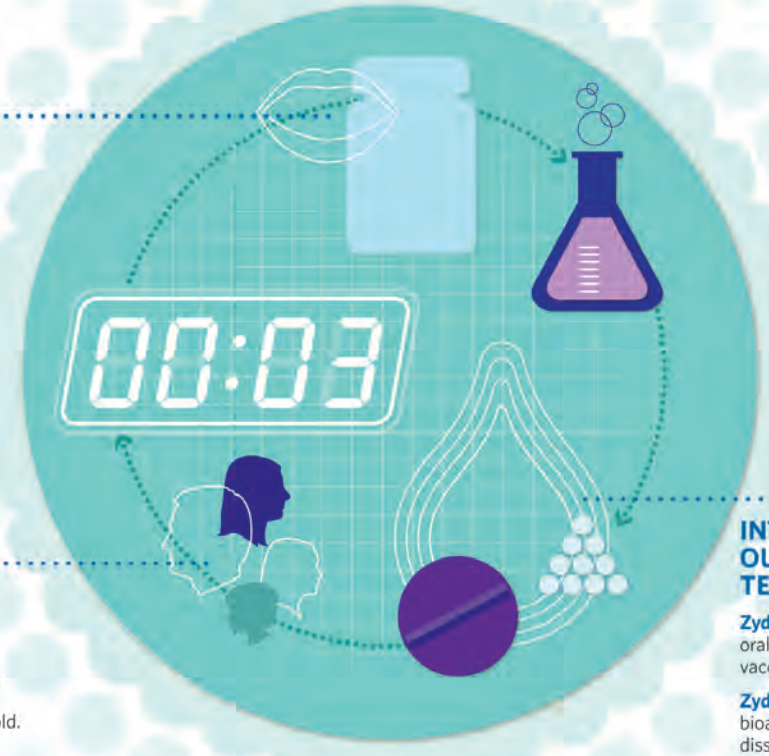

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