Drug Development & Delivery

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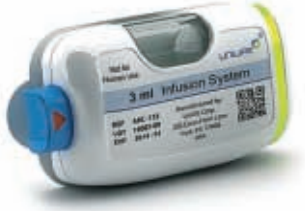

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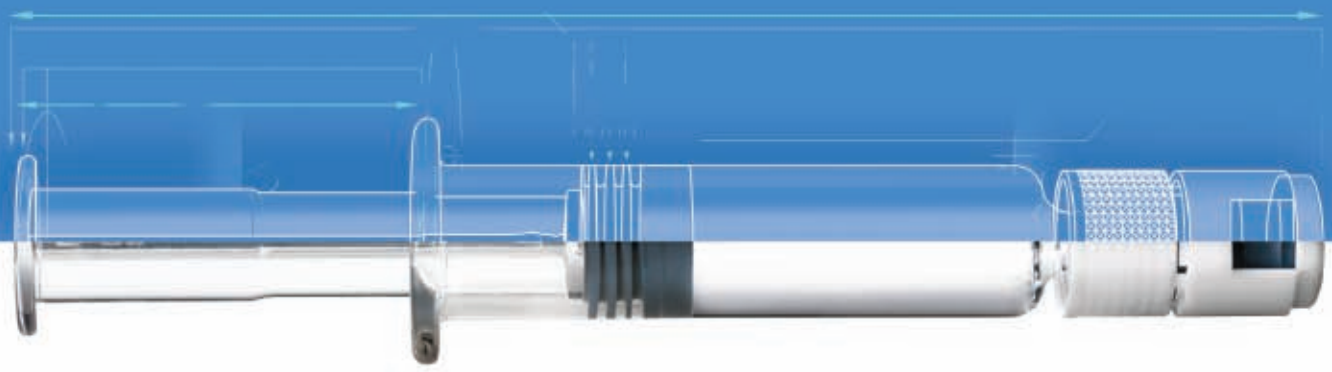

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Quinten Identifies Synergistic Markers; Predicts Favorable Response to TNBC Treatment

Quinten recently announced the identification of two discriminating biological marker candidates that are indicative of a favorable response to treatment in women suffering from triple-negative breast cancer (TNBC). In the sub-group with both markers in combination, 86% of women responded to treatment with Panitumumab plus Fec 100, followed by Docetaxel, with complete disappearance of the tumor (equating to a full pathological response on Chevallier's classification). Only 47% of women in the total population examined during Phase II testing showed a similar response to treatment.

Using its proprietary Q-Finder algorithm, Quinten analyzed 200 biological variables relating to samples taken from 47 TNBC patients, provided by the Centre Jean Perrin in Clermont-Ferrand, which is led by Professor J Dauplat. The biological markers that have been identified confirm and build on results already found by teams working at the center under Professor Nabholtz, who is responsible for the medical and clinical research departments and Professor Penault-Lorca, Head of Biopathology and Director of the 4677 ERTICa university research team (Equipe de recherche sur les traitements individualises du cancer [personalised cancer treatment research team]) at the University of Auvergne.

In cancers showing a mixed basal/luminal phenotype, among patients with an EFGR score of more than 80, combined with a cytokeratin 8/18 percentage in excess of 20, the response rate to treatment is almost double (1.83 times) the overall rate for women suffering from TNBC. These patients represent approximately 30% of women with TNBC.

TNBC accounts for around 15% of breast tumors. A breast tumor is said to be triple negative if less than 1% of its mass is made up of estrogen and progesterone receptor-carrying cells, and it exhibits no HER2 overexpression or amplification. These are found in around 13% of breast cancers. This type of cancer affects mainly younger women under the age of 50. In older women, it is often known as an 'interval' cancer, which is discovered between two routine screening mammograms, in which the most recent showed perfectly normal results. It is known to be an aggressive cancer, with 10-year survival rates of just 5% for basal phenotype TNBC (75% of all TNBC cases) and 62% for other TNBC cases. It is not unusual to see a rapid spread of pulmonary and cerebral metastases following conventional treatment, as the cancer cells spread through the bloodstream rather than the lymph ducts. There are few specific or targeted treatments available for TNBC at present.

"As far as we know, this is the first time that prognostic biological markers for a favorable response to this type of treatment have been discovered for TNBC. This discovery once again illustrates and confirms our ability to identify synergistic variable interactions that define specific high-benefit or high-risk sub-groups within a given population," explains Alexandre Templier, CEO of Quinten. "This approach to personalized medicine has long been of interest to pharmaceutical laboratories. More recently, we have seen growing interest from academic teams. We help them to make the best possible use of their data."

"We are delighted to have discovered this interaction between two markers that individually provide no information. It gives hope to women suffering from TNBC, as there are still very few treatments available. We will be able to select patients who have the greatest chance of responding to the treatment that we have implemented," added Professor Jean-Marc Nabholtz of the Centre Jean Perrin. "A scientific paper is being drafted, and we are discussing the commencement of work to confirm this discovery."

BASF & Bend Research Sign Bioavailability Agreement

BASF SE and Bend Research Inc. have signed an agreement to jointly evaluate and develop novel excipients to enhance the solubility and bioavailability of poorly soluble drugs.

The companies plan to combine their world-leading expertise in the development of new excipients and drug formulations to provide customers from the pharmaceutical industry with early access to the latest polymer innovations. The aim of this collaboration is to meet increasing challenges of poorly soluble APIs (BCS Class II and IV compounds); the initial focus will be on optimizing new vinylpyrrolidone-based copolymers being developed for the solubilization of poorly soluble APIs.

"We are excited about the opportunities this collaboration brings to us and our customers," said Rod Ray, CEO of Bend Research. "It offers early access to a different set of chemistries and allows us to develop and test customer formulations based on new polymers. BASF has an impressive track record developing and launching novel excipients. This deal complements our recently announced collaboration on cellulosics because it gives us access to completely different chemistries."

"We are glad to bring our in-depth knowledge of polymeric excipients into this collaboration - to jointly extend the current toolbox already comprising innovations like Soluplus," said Ralf Fink, Vice President Global Marketing at BASF Pharma Ingredients & Services business unit. "Coupled with Bend Research's outstanding strengths in formulation development, including spray-drying and hot-melt extrusion, we are in a unique position to address urgent solubility challenges. With this partnership, we help our customers with the development of drugs with poor bioavailability."

BioCellChallenge Launches First Universal Delivery System for Transporting Antibodies Into Live Cells

BioCellChallenge SAS recently announced the launch of a new delivery system, ImmunoCellin, which is designed to transport antibodies into live cells even in the presence of additives. The company has recently filed a patent for this pioneering technology.

Without a suitable nanocarrier, antibodies cannot cross the plasmic membrane of live cells unaided and reach their potential intracellular targets. ImmunoCellin delivers antibodies directly into live cells, without any particular advanced preparation. This system is especially effective in identifying new targets for future therapeutic treatments.

"Until now, cellular biology research projects have made little use of antibody transport into live cells largely because all the tools are not sufficiently effective to be used without a lot of preparation or re-engineering. However, there is particular benefit in introducing therapeutic antibodies to target the intracellular proteins involved in certain diseases, particularly in certain cancers," explained Dr. Meunier, CEO of BioCellChallenge.

ImmunoCellin is a much more potent protein function inhibitor than siRNA. Using siRNA to prevent a protein from playing its role in the cell inhibits all the functions of that protein. With ImmunoCellin, however, monoclonal antibodies can be directed to a single region of the protein to interfere with a single molecular mechanism, meaning that a specific function of the protein can be determined with certainty. ImmunoCellin is therefore a powerful tool for developing a broader understanding of the inter-protein interactions, which form the basis of cell function.

ImmunoCellin is also particularly suitable for use in kinetic studies of intracellular protein localization in response to different stimuli. It can also directly interfere with protein traffic in the cytosol or the nucleus by targeting a localization signal, for example.

The reagent is very simple to use: a few microlitres of the reagent are mixed with a few micrograms of antibody and this mixture is then added to the cells. No other preparation is required. The lipid-based formulation encapsulates the antibodies, facilitating their passage through the membrane.

There is no covalent interaction between the transport system and the antibody. Once inside the cell, the system does not retain the antibody, which can then diffuse freely through the cytosol until it reaches its target. Beacuse no chemical coupling is required, there is no impact on the activity of the antibody. Finally, as this system is not inhibited by the presence of serum, in vivo approaches are also possible.

This new system is aimed particularly at pharmaceutical and biotechnology industry R&D teams working on therapeutic antibodies. Accordingly, BioCellChallenge is keen to develop partnerships with players in the pharmaceutical and biotechnology industry. The ImmunoCellin system is also particularly relevant to cellular and molecular research biologists worldwide.

Capsugel Launches New Dosage Form Solutions Business Unit

Capsugel recently announced the launch of its Dosage Form Solutions (DFS) business unit to address growing customer demand for innovative product development and commercial manufacturing in the healthcare industry. The DFS business unit will focus on the company's growing expertise in lipid-based formulations, while continuing to expand its offerings in targeted release capsules.

"With the launch of the new DFS business unit, Capsugel builds on its heritage of delivering innovative, quality products and services in hard capsules, by advancing our expertise in product formulation and commercial finished product manufacturing," said Guido Driesen, President & CEO of Capsugel. "DFS is well-positioned to help address our customers' most pressing dosage form challenges of existing and new nutritional and pharmaceutical products."

Amit Patel will serve as President of the DFS business unit from Capsugel's headquarters in Morristown, NJ. Mr. Patel has extensive experience in the pharmaceutical industry, including generics and specialty pharmaceuticals. "Continuing to innovate and develop cutting-edge healthcare products is essential to maximizing the potential of the industry," said Mr. Patel. "The DFS business unit uses our proprietary technology platforms to help bring improved products to the market faster for our customers. The platforms can enable various solid oral dosage product improvements, including bioavailability enhancement, optimal dosing for potent APIs, controlled release, stability improvement, and taste-masking."

Over the past decade, Capsugel has developed a world-class portfolio of products, technologies, and intellectual property. DFS will leverage its proprietary technology platforms of lipid-based formulations and targeted release capsule formulation, R&D capabilities, and commercial manufacturing infrastructure to develop and manufacture products for customers. The business unit has operating sites in North America, Europe, and Asia, and has been involved with hundreds of products and projects for leading and emerging specialty, branded, and generic pharmaceutical customers, as well as those in the consumer health and nutritional segments.

Dow Chemical & Cambrex Collaborate to Manufacture Drug Solubility Solution

Cambrex and The Dow Chemical Company recently executed an agreement for Cambrex to contract manufacture Dow Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS) for Drug Solubility Enhancement.

This is the final step in building on the solubilization partnership that Dow and Bend Research announced in October 2012, and it will help Dow to commercially supply solubility enabling excipients. Construction has already begun on the new operational facility at Cambrex Karlskoga with commercial product availability set for year-end 2013.

"Dow's polymer science and application expertise, coupled with Cambrex's capabilities positions Dow for rapid entry into the market. The AFFINISOL product platform has excellent manufacturing flexibility to match the diverse excipients needs of our customers' pipelines," said Bob Maughon, Senior R&D Director for Dow. "We are enthusiastic about bringing the first solution of our AFFINISOL product range to the market," added Marc van Gerwen, Business Director for Dow. "This agreement demonstrates our ability to promptly address with material science the pharmaceutical industry's most pressing need: advancing poorly soluble APIs to become therapeutically beneficial oral drug products."

"We are proud to be part of this collaboration with Dow," said Eric Neuffer, VP of Sales and Business Development for Cambrex. "This agreement between Dow and Cambrex further validates Cambrex's commitment to finding solutions that offer our clients quality products and services to meet a market need. This has been a great partnership with both the Dow and Cambrex teams focused on achieving project goals and objectives in a timely manner."

ProBioGen Signs Major Technology Deal for Therapeutic Antibody Platform

Another global pharma company has licensed ProBioGen's GlymaxX ADCC-enhancement technology. The license covers the modification of the pharma's antibody production platform for the generation of antibodies with enhanced potency. The continued licensing success demonstrates the industry's endorsement of GlymaxX. The GlymaxX technology is highly versatile because it can be applied to any starter or production cell line. It allows both, the robust permanent modification of established antibody expression platforms, as well as the rapid conversion of existing antibody producer clones to produce ADCC-enhanced molecules.

The GlymaxX technology is based on the stable expression of a heterologous enzyme in the antibody producing cells. GlymaxX prevents antibody fucosylation almost completely, but moreover allows the exact adjustment of any desired fucosylation level through the controlled addition of fucose into the culture medium.

The license with an option for a commercial license covers the modification of the company's antibody production platform and the generation of multiple antibodies with enhanced ADCC potency. Financial details are not disclosed. The technology can be licensed royalty-free, based on milestone-dependent license fees only.

The GlymaxX technology, developed by ProBioGen, prevents the addition of the sugar "fucose" to the N-linked antibody carbohydrate part by antibody producing cells. The absence of fucose is known to greatly enhance ADCC. The GlymaxX technology is based on the introduction of a gene for an enzyme that deflects the producer cells' pathway of fucose biosynthesis. GlymaxX is universally applicable to different CHO hosts and other eukaryotic cell species, and it is simple and potent. GlymaxX can be rapidly applied in a few weeks to any existing antibody producer cell line, or can be introduced into entire animal cell expression platforms by modifying host cell lines. ProBioGen offers this technology royalty-free as service or as license to third parties.

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PROGRAM REVIEWS

"Very much enjoyed both the 1st and 2nd PODD meetings - and looking forward to the 3rd in Boston. Great forum for anyone interested in drug delivery for the biopharma industry."

Baruch Harris, PhD, Chief Business Officer,
Enlight Biosciences

"I thoroughly enjoyed the conference, the meetings, and the presentations."

Monica Fernand, Senior Strategic Marketing Manager,
BD Medical – Pharmaceutical Systems

"Overall, outstanding conference, well done!"

Ralph Solarski, Director, Business Development & Strategy,
Kimberly-Clark Corporation

"It was a great event and my thanks to you and your excellent team."

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Biosimilars Market Expected to Soar

Top representatives from the healthcare industry were confirmed to attend the 2nd Biosimilars Congregation which took place in London on February 19 and 20. Ranjith Gopinathan, Frost & Sullivan Program Manager for Life Sciences, Europe Practice participated on the event's Keynote Panel Discussion focusing on challenges and opportunities in the global biosimilars market.

"Experience in biosimilars development, manufacturing, and commercialization in regulated markets, such as Europe and the US, is limited. Furthermore, reluctance from some physicians and patients to adopt biosimilars due to perceived efficacy and safety issues could have an adverse impact on market penetration. Such uncertainties, in addition to the complex regulatory pathway, compound the risks for biosimilars manufacturers," said Gopinathan

Initially, manufacturers of biosimilars will focus on the three protein classes of erythropoiein and human growth hormone due to their recent patent expiry. In the long run, insulin, interferon, and more complex proteins like monoclonal antibodies are likely to emerge. However, some companies may concentrate on certain therapeutic classes depending on their capabilities and strategic fit.

Europe has the highest number of biosimilars approvals in the regulated market and will continue to increase in the near future. Further patent expiries of biologics will likely increase the number of approved biosimilars and players in the market and thereby will bring in a greater number of products that will increase the market size. Biosimilars are currently priced at about 20% to 30% below the original product price.

Third Rock Ventures Launches Cancer Immunotherapeutics Company With $47 Million

Third Rock Ventures, LLC recently announced the formation of Jounce Therapeutics, Inc. with a $47 million Series A financing of the company. Jounce is focused on the discovery and development of first-in-class cancer immunotherapies designed to harness the patient's immune system to seek out and attack cancerous cells and tumors. This transformational approach, as compared to more traditional approaches of targeting the tumor directly, has the potential to drive durable responses to treatment, extending and improving patients' quality of life for years. Jounce was founded by world leaders in the fields of immunobiology, cancer biology, and clinical and translational medicine.

"This is an exciting time as the promise of cancer immunotherapy is beginning to be realized. With key recent advances in cancer immunotherapy, we have gained invaluable insights into how the immune system recognizes tumors and a better understanding of effective cancer immunotherapy discovery and development," said James P. Allison, PhD, Chair, The University of Texas MD Anderson Cancer Center Department of Immunology, whose research led to the clinical development of ipilimumab (Yervoy). "Jounce has brought together an expert team and powerful capabilities to discover and develop novel treatments that harness the power of the immune system, marking a significant step forward in the way we treat cancer."

Jounce's proprietary product engine enables the exploration of multiple mechanisms of action and a broad spectrum of targets. The company's capabilities and expertise include tumor immunobiology, antibody discovery and optimization, and integrated translational science capabilities, including novel in vivo tumor model systems and other clinically based approaches. Jounce is leveraging these capabilities to build a robust pipeline of first-in-class biologic product candidates. The Series A financing enables the company to build its product engine and rapidly advance its lead programs to the clinic.

Management Insight

Business Lessons From the Salamander

By: Derek Hennecke, CEO & President, Xcelience

Part 2 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.

When business models break, management teams get out the band-aids. I've done it myself. We take the scalpel to org charts, swallow pills to get the financial blood flowing again, and splint or amputate damaged business units. It's not our fault. We're mammals. It's instinct.

We *should* repair our business models like a salamander would. When a salamander loses a leg, the reptilian body immediately loses a flood of stem-like cells to the area. Genetic coding contains a positional memory of the location and type of the missing body part. Tissue, bone, and blood form not only in the right place, but in the correct sequence to avoid defective regeneration.

I'm not going to argue with my ancestors. Mammals chose this evolutionary path for a reason. The theory is that to our bodies, the sudden rapid cell growth of regeneration is eerily similar to that of cancer growth. Faced with a choice, our genetic ancestors favored tumor suppression over regeneration. The result is that when we lose a limb, the body rushes in with scar tissue; a durable long-term band-aid. But do we have to deal with all of our problems with band-aids? In the business world, we could do with some out-of-the-phylum thinking.

This is the argument put forth by author Saul Kaplan in his book, *The Business Model Innovation Factory*. With the shelf-life of business models shrinking every day, Kaplan argues that today's most successful businesses respond to trauma by regenerating new business models, not splinting the old one.

It's a provocative assertion, and one that the pharma industry needs to hear. Under a full-scale assault of slowing R&D, generic competition, and declining profits, our industry is responding to this unending assault by throwing its entire rather well-stocked medicine cabinet full of pills and patches at the problem.

Getting netflixed

Let's start with an illustration. How could a business like Blockbuster go from a market cap of $5 billion at its height in 2002, to bankruptcy 8 years later? Blockbuster saw Netflix coming, writes Kaplan, but management was so infatuated with their own bricks and mortar business model that they refused to let it go. They struggled to create a finer, better balanced sword, when Netflix had just introduced gun powder.

It wasn't a new technology that took the movie rental behemoth down. The DVD itself, invented in 1995, was in fact a sustaining technology; one that would help Blockbuster deliver their model at a higher level. What took Blockbuster down was the new business model Netflix created around the DVD.

Netflix noticed that DVDs were small enough to stick in an envelope, so they began offering a mail order service. At first, the upstart company followed Blockbuster's pay-per-rental business model, complete with late fees. It did only moderately well. But in 1999, Netflix launched a single flat fee for unlimited rentals, no late fees, shipping charges, or due dates. The new model rocketed out of the gate, quintupling sales to $5 million in a single year. In the same 8 years that Blockbuster went from peak to valley, Netflix subscriber base grew from 1 million to 14 million.

Inside the corporate hallways of Blockbuster, CEO John Antico moved in with an online offering that offered credible competition, albeit Johnny Come Lately. Given the resources Blockbuster wielded in those early days, this approach, called Total Access, might have had a shot, but for the iconic investor Carl Icahn, then a major shareholder of Blockbuster, who moved to protect the storefront business model, effectively keeping the band playing even as the ship listed and descended into frigid black waters. Icahn fought for a strategy of more stores, and succeeded in pushing Antico out as CEO. With Antico gone, so too were the forces of change, and the lights rapidly went out.

Now, to get "netflixed" is a verb in the urban dictionary. The dictionary defines it as "being taken advantage of, or getting swindled out of money," but that's not quite accurate. That definition implies that Blockbuster was a victim. There are no victims in the business world. Getting netflixed means your existing business model has just been trumped. Amazon netflixed Borders and Best Buy. Apple netflixed Tower Records. Craigslist is netflixing rapidly your local paper.

Some have argued that even Netflix is now in danger of getting netflixed, though I'm not sure the analogy works, because it's more of a self-flagellation thing. Despite strong earnings and a remarkable recovery in its stock price this past month, Netflix has been stumbling since the summer of 2011 when the company decided it was operating two business models (DVD subscriptions and online streaming) under one roof. By trying to separate the models and simultaneously sharply raising subscription fees, the company undertook a business model regeneration when it wasn't under threat of attack, and the market responded to the strategy like it would to a cancer - it fought back. I, for one, dropped my subscription in anger, though I reluctantly came back a few months later. No competitor proved capable of meeting my insatiable demand for obscure movies.

Like Lady Gaga goes through sequins, Netflix goes through business models. The latest ones are proving profitable again, as the company tries out content ownership, including the cult favorite Fox situational comedy Arrested Development and the hotly anticipated political drama House of Cards, which begins in February.

Introducing a new business model in a young, sapling company like Netflix is one thing, but changing business models in a mature corporation is quite another. Just imagine the excitement on the faces of the senior managers responsible for Apple's distribution channels (then Sears and CompUSA) as they eagerly embraced Steve Jobs announcement that he was going to create the Apple Store.

Just kidding. I sincerely doubt it went that way. Apple insiders would've done what most managers would do - vehemently defended their existing business model and fought tooth and nail against the new concept. The entire organization, Kaplan writes, was in fact structured around that traditional distribution system, from job descriptions through performance management systems to incentives. Introducing a new business model always meets with resistance from the entrenched business model and its proponents.

Regenerating the pharma business model

Pharma, in the opinion of many, is long overdue for a business model overhaul. In all the other examples trotted out by Kaplan (Netflix, Apple, Amazon, Craigslist, etc.), the existing business model for the given industry was not broken. It was working just fine, thank you very much, until a new business model came along and made it obsolete.

Our industry model is broken, and begging for a better model to allow it to descend honorably into obsolescence. Large Pharma converged long ago around the Blockbuster Business Model - in this case, not referring to the Blockbuster movie example, but rather to those blockbuster drugs that achieve sales over $1 billion. It's a lottery ticket strategy, and it worked well in the past, earning over $1 trillion for Big Pharma in the past decade. That was then, this is now.

Declining R&D productivity, increasing commercialization costs, growing payor influence, and shorter exclusivity periods have inflated the cost of the average successful launch to somewhere in the range of $1-1.3 billion, depending on the source cited. Expected returns on new investments are now a paltry 5%. Even a mediocre hedge fund can beat those numbers.

Most Big Pharma executives see what's happening, but they feel powerless to wrestle their companies away from the entrenched and powerful organizational proponents of inertia who call on them to maintain their immense investments in science and their 80,000 sales reps in the US alone, all geared toward maximizing sales of just a couple of products in the portfolio. It's hard to argue internally against a system that, until 2002, generated average annual revenues of 13%, argue Gilbert Henske and Singh in "Rebuilding a Better Business Model," in *In Vivo* magazine, published in 2003. This seminal article, while somewhat dated, remains no less relevant given how little business models have evolved since it was written, largely due to the recession of 2008 which put the brakes on business innovation.

Pfizer, GlaxoSmithKline, and Merck may, through their sheer size and resources, be able to outlast their smaller competitors, but market value is already beginning to shift to business model innovators like Novo Nordisk, Genentech, and Forest Laboratories. In these companies and others like them, Gilbert, Henske, and Singh see the stirrings of a new model (or maybe a number of models) in what they refer to as the four building blocks.

Block 1: Focus, Focus, Focus…

Lucky breaks–the discovery of a blockbuster drug from R&D in an unrelated area–happen, but not as often as the media seems to think. Only about 30% of all blockbusters fall into the Viagra category. The rest make their discoveries the old fashioned way - by building on knowledge and experience. The fact is, prior experience does help companies increase the likelihood of developing a successful product, and with the increasing costs of failure, the old scattergun approach in which every molecule is given a fair chance is simply not feasible for most companies anymore.

Genentech has focused on biologics, Gilbert, Henske, and Singh write. They have since added small molecules as well. Vertex Pharmaceuticals uses a structured approach to drug design. Nova has zeroed in on particular patient/physician groups in diabetes. Big Pharma generally stays away from specialists, but these smaller drugs don't require primary care sales forces, and that can significantly boost their profitability.

Block 2: Partnerships

The move toward more partnerships is a trend I see growing so quickly and providing such obvious advantages over in-house offerings that it's practically unstoppable. Rapidly disappearing in the rear view mirror is the fully integrated pharma company, dependent on in-house specialists who have seen only a couple of products in their careers. In its place is a much more nimble industry, choosing from a range of specialists in each stage of product development. The choice is no longer whether or not to use a specialist, but how to partner with a chosen specialist - through a single, short-term contract? Through multiple contracts? Or joint ventures?

At a conference I was at in January, a speaker said he believes sixty percent of all products in development today are in-licensed. Actual stats are hard to find, because once a product comes inside it gets a new number and it becomes hard to trace back to its roots.

Gilbert, Henske, and Singh argue that pharma is headed the way of the movie industry, in which many blockbuster movies are made by partnerships of multiple studios and individual contractors who provide everything from screen writing and acting to directing and special effects.

Numerous other industries made the move toward partnerships years if not decades ago, most notably the car industry, but also fashion and information technology.

At Xcelience, we focus primarily on preformulation and formulation. Our scientists deal with new molecules every day and operate a broad variety of equipment. When dealing with a new drug, there is no substitute for this breadth of experience. Other specialist companies can say the same about their own services in other stages in the pipeline.

The more we work with Large Pharma, the more they recognize this specialist value. Not only is our business growing at a steady rate, but I've been

approached with more joint venture opportunities in the past few weeks than in the past few years, combined.

Block 3: Sell Customer Solutions

This building block, while advanced in other industries, is still in its infancy in the pharma market, and I find the idea particularly exciting. The premise is much like what we've seen in the computer industry, in which technology companies focus on selling solutions rather than products. The sale of products and ancillary products become part and parcel of the overall solution. In the pharma industry, instead of just selling the drug, the focus would be on selling the complete package required for the individual patient to manage his or her condition. This could include specific delivery methods, such as we are seeing developed for the diabetes markets, but it could also include products that improve compliance, nutritional requirements, over-the-counter products, and more.

Kaplan took this idea a step further in *The Innovation Factory* when he proposed to a pharma client in the diabetes market an outcome-based business model in which the company would structure its rewards based on patient success, rather than on providing a product. Such a model would represent a radical shift from selling drugs, to selling patient outcomes.

Kaplan writes that his team wasn't particularly surprised when the CEO - despite having asked for "out of the box solutions" - quietly thanked his team for their input and then implemented only those ideas that supported the company's current business model. Convinced the new model could be revolutionary, Kaplan begged the CEO, "Give me Rhode Island." Rhode Island represented a tiny portion of the company's overall market, and with it, Kaplan promised to test the patient-outcome business model, design a prototype, and demonstrate how it could make money. Still the company declined, and the model remains, to my knowledge, untested.

Block 4: Build a Business Unit

Pharma has generally operated along functional lines, organizing itself into units that reflect the different phases of the drug development pipeline. Other industries have moved away from this model, turning to a business unit model that focuses on a single product from birth all the way to marketing and sales. In the business unit model, IT and administration is generally shared or outsourced. Decision-making becomes tighter and quicker; more customer-focused. The profit contribution of an individual molecule/product is easily measured, making return transparent. It's a more flexible model. Novartis is experimenting with specialty business units such as oncology. In Large Pharma, Elily Lily has set up its promising 'Chorus' proof of concept business units.

I'm sure there are many more building blocks out there that have yet to be discovered, but I feel certain that our industry is on the cusp of radical change. We simply can't go on patching our rickety old blockbuster model. Industries all around us have learned the skill of regeneration while our industry has stalwartly refused. Our turn will come. The question is, who will lead the change? That will be the subject of my next installment. ◆

BIOGRAPHY

Derek G. Hennecke is a Founding Member, CEO, and President of Xcelience. He has a long history of growing strong businesses around the world. Blending a scientific and business background, he has nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner, having launched a management buy-out from MDS Pharma Services in 2006. The newly-formed company immediately embarked on a robust pattern of growth. Before founding Xcelience, Mr. Hennecke spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250-staff Biologics plant for more than 2 years. In Cairo, Egypt, as GM, he oversaw a turn-around in an anti-infectives plant that had been slated for closure. He spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke has a BSc in Microbiology from the University of Alberta and an MBA from the Erasmus University in The Netherlands.

Intranasal Saline: Can a Spray Per Day Keep the Doctor Away?

By: Degenhard Marx, PhD, and Georges Bouille

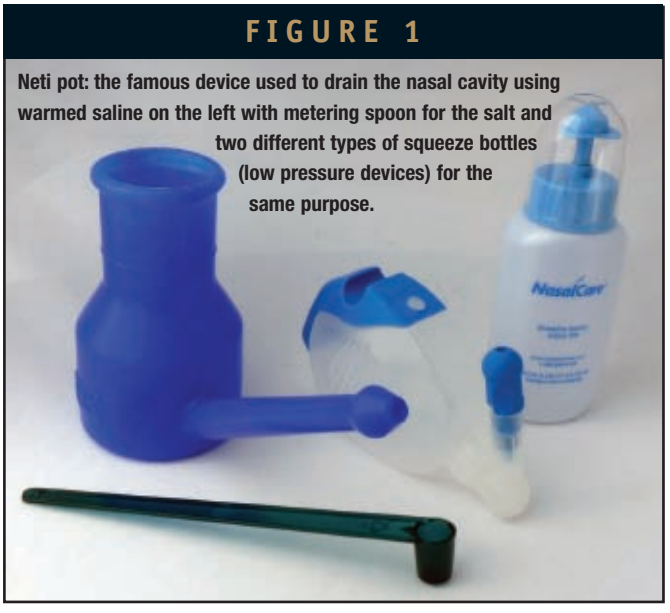
The use of intranasal saline to wash the nasal cavity, its use as nasal decongestant, or for moistening has a long tradition going back to the Ayurvedic medicine in India. Here, the roots of the famous Neti pot can be found: an item used to pour between 250 and 500 ml of warmed saline trough the nasal cavity to wash away thickened mucus. This procedure is a real "nasal lavage" or nasal wash, which may reach even the sinus cavities. On the other side - speaking in terms of volume - we find nasal droppers and spray pumps, which deliver roughly 50 microliters per drop or 100 to 140 microliters per stroke, used to moisten the nasal cavity. This moistening will relieve nasal congestion when suffering a cold and is useful to keep the nasal mucosa wet in a dry environment (eg, air conditioned offices). In this overview, the benefits of using intranasal saline, and a range of different devices on the market allowing administration into the nose, will be discussed.

BACKGROUND ON NASAL SALINE

Under resting conditions, an adult breathes about 10,000 L of air per day, in and out. Humans are designed by nature to be "nose breathers." So the air should go its way through the nasal cavity, where it is warmed and moistened close to 100% relative humidity. Dust particles and microbes are trapped there and bound by the mucus layer. This mucus layer is continuously renewed, and mucociliary clearance mechanisms bring it into the throat portion, where it is swallowed. This is a very effective mechanism and prevents dust and microbes from reaching the lower respiratory tract. It is also a well balanced system, and everyone will recognize when it is disturbed due to excess mucus production, swollen mucosa, nasal polyps, or foreign particles. So when you consciously realize you are breathing (eg, due to a blocked nose), it is most likely because something is going wrong, and you should see a doctor. But how can saline help here?

The activity of nasal saline within the nasal cavity is mainly physical action. The saline will help to remove the excess mucus and improve mucociliary clearance. This will support nasal breathing in acute upper respiratory tract infections, including the common cold and rhinosinusitis.[1] In addition to these cleaning effects, there may be other benefits coming from trace elements in sea water or intentionally added minerals to create so-called "enriched waters." According to some clinical studies, prophylactic use of moistening sprays can reduce the number of viral infections when taken regularly.[2] The mechanisms behind this observation are not clear, but regular saline sprays may prevent drying out of the mucus layer and help to maintain the aforementioned natural defense mechanisms. Also, the action of trace minerals may play a role here. Nasal saline reduces swelling of the nasal mucosa and is therefore recommended as a nasal decongestant in response to an infection or allergy (hay fever). Lower volumes of saline administered as drops (often used for toddlers) or sprays will dilute the highly viscous mucus, which may be enough to improve or to re-start the mucociliary clearance mechanisms. Higher volumes of saline will actually wash away the largest part of mucus and debris from the nasal cavity. This is a recommended procedure for people suffering from chronic rhinosinusitis.[3]

FIGURE 1



Neti pot: the famous device used to drain the nasal cavity using warmed saline on the left with metering spoon for the salt and two different types of squeeze bottles (low pressure devices) for the same purpose.

Based in Freiberg/Germany, teamtechnik has been making intelligent and reliable automation solutions for medical and pharmaceutical industries and for the automotive and solar technology for over 35 years. teamtechnik is considered an international leader in highly flexible automation technology. With a total of 750 employees throughout the world, the company achieves sales of over €145 million. The teamtechnik Group has production sites in Germany, Poland, China and the USA.

teamtechnik develops innovative process-optimized production solutions for medical technology that meet customers' requirements right up to serial production. The systems are designed with a modular approach, a highly flexible concept which allows the manufacturers of medical devices to adapt their production quickly and economically to changes in the market.

For cost effective production from Start-Up to High-Speed production the company has brought to market three different platforms: START-UP, the platform for prototype production to verify processes early in their final execution and for clinical trial production; TEAMED, a highly flexible and upgradeable platform for assembly and testing; and RTS, the high-speed platform for economical mass production.

These platforms are realizing almost 80% of all customer solutions in the medical technology sector. Superior process technology, SPC test systems and 100% end-of-line testing can be integrated specifically for the production of medical devices and pharmaceutical products. The teamtechnik production systems allow production compliant with global guidelines and monitoring systems such as GAMP5, FDA and CE and meet class 6 clean room specifications.

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PRODUCTION TECHNOLOGY

There are different saline solutions available that differ in the concentration of the main ingredient sodium chloride. A 0.9% solution is called physiological saline because the osmotic pressure is similar to the human blood (~300 mOsm/L). Higher concentrations up to 2.5% to 3% (~ 1 Osm/L) are called hypertonic and are preferred for decongestant purposes due to their osmotic effect. However, too high of a concentration could irritate the nasal mucosa. Sea water offers an interesting alternative due to a wide range of bioavailable elements. The desired osmolarity can be adjusted by means of dilution, as sea water often has a high salinity. Another well-known product for nasal rinsing is the so called Ringer solution: an isotonic salt solution with added bicarbonates or lactate as pH buffer. Clinical studies on the influence of different salt concentrations on symptom relief are not very conclusive. So it is the choice of users to decide on their osmotic preferences.

NETI POT & LARGE-VOLUME SQUEEZE BOTTLES

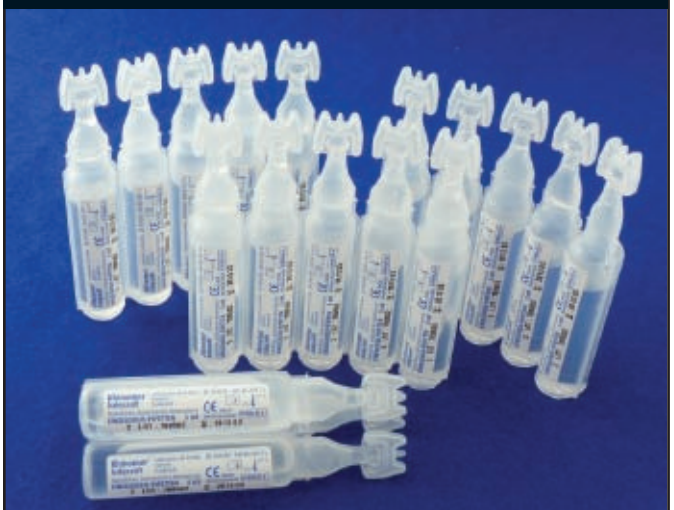
There are many ways to deliver a saline solution into the nose. The Neti pot may be one of the oldest devices to rinse the nasal cavity. The pot is filled with warmed saline and then poured into one nostril, finding its way through the nasal cavity and allowing it to drain out of the other nostril. Due to the comparable high volume, mucus and debris are washed out, and even the sinus cavities may be reached. It sounds simple, but the procedure needs some exercise and may be not everyone's preference. It is recommended by physicians as an efficient way to relieve symptoms of rhinosinusitis. On the other hand, some clinical studies suggest that a too intensive use of the Neti pot is linked to higher rates of bacterial and viral infections. Ready-to-use saline preparations appear to be expensive in relation to volume-consuming Neti pot. Prepacked concentrates or self-prepared saline solutions offer a cost-effective alternative but bear the extremely rare risk of microbial infections if the hygienic standards are neglected.

Large squeeze bottles used to instill high quantities of saline solution, again as a constant rinse, are using a "low positive pressure" and can be considered quite similar to the Neti pot.

NASAL DROPPERS FOR CHILDREN

Cleaning or blowing toddlers and young children's stuffy noses are highly facilitated by the use of nasal saline, reducing complications due to infections of the upper respiratory tract. Some parents and physicians are reluctant to use active drugs, such as xylometazolin in patients of that age group. Saline drops or sprays for these little noses are a great help to restore normal nasal breathing. Unpreserved saline mono-dose droppers manufactured with blow-fill-seal technology are widely used. Also, squeeze bottles or bottles supplied with pipettes are common. From a packaging point of view, this simple technology is relatively easy to use but does not meet the highest hygienic standards because mucus may be sucked back unintentionally. For this reason, such multi-dose drops are often preserved (eg, containing benzalkonium chloride, BAC).

FIGURE 2



BFS monodose for toddlers/kids filled with unpreserved saline solution.

NASAL SPRAYS FOR MOISTENING

There is a wide range of nasal saline sprays commercially available on the market. Their rather small packaging size (20 to 30 ml) is also highly convenient for on-the-go use. The delivered dose varies typically between 50 to 140 microliters per actuation, and the product is physiological or hypertonic saline, sometimes enriched with minerals or herbal extracts for specific use. Preserved and non-preserved products can be found on the market. In the first case, the saline solution contains benzalkonium chloride to prevent bacterial contamination of the bottle content. Metered pumps used for preserved formulations are well known and proven. Such spray pumps have an actuator with an open swirling chamber, so there is some remaining risk of sucking back small amounts of nasal mucus. So preservatives offer here a safety margin in terms of product purity. It is a mistaken idea that the preservative in the saline or the saline itself will knock out viruses and bacteria in the nose. A potential issue for the user, however, is the high incidence of local side effects attributed to preservatives. The discussion is controversial, and published data is not always consistent. It seems to be clear that short-term use of preparations containing preservatives at low concentrations is well tolerated, but preservatives can cause serious inflammatory effects with long-term use. The responses may include chemical irritation, hyperreactivity, and true allergies.[4] The German Authorities (BfArM) addressed the use of BAC for nasal sprays in 2003, which pushed preservative-free systems for this administration route.[5] Today, PFS pumps are one of the most sophisticated technologies for moisturizing nasal sprays.

A significant risk of contamination obviously comes from the orifice of the spray system, as it is potentially in contact with the infected nasal mucus. Some marketed systems use the oligodynamic

FIGURE 3

Classic line: On the left side is a rendering of a nasal spray pump for preserved formulations; the spray insert and valve ball are depicted in blue. The picture in the middle shows the way of the saline solution (blue arrow) when the pump is activated from the dip tube through the metering chamber and the actuator. The red arrow shows the way of the venting air. In both paths, the system provides no measures to prevent bacterial contamination.

activity of a silver wire in the open tip of the actuator.[6] These components release silver ions into the saline, which remain inside the actuator in between the dosing intervals. The system is able to keep concentrations of microorganisms at a low level between long dosing intervals, even when the tip is immersed into bacterial-contaminated fluid.[7] Silver ions are widely used for their antiseptic properties, and even when used for wound dressings, it is safe with no adverse effects attributed to this treatment.

The most recent preservative-free systems follow a purely mechanical approach. One technical solution to prevent contamination via the orifice is referred to as "tip seal technology." A spring-loaded valve is located directly below the opening of the tip orifice and does not allow any sucking back of liquid and consequently keeps microbes from migrating into the system. Under resting conditions, the orifice is "sealed." The tip seal keeps the system closed until a defined pressure (for nasal sprays, it is more than 3 bar) is reached by actuating the system. Then the system will open, and the saline solution is forced through the orifice with a higher pressure than needed to open the valve. When the pressure drops at the end of the actuation, the tip seal will immediately close the orifice with an outward movement, preventing any nasal mucus back flow into the device.

Unless equilibrated, throughout the use of product, the pressure within the packaging is decreasing gradually. To avoid product contamination via the venting air, different technical solutions are used. One solution consists of sterile filtration of the venting air using build-in filters or filter gaskets. Also, so-called depressed systems are used. These pumps are designed in such a way that the entire system is air-tight, resulting in an up to 300 mbar under-pressure building up during use in the bottle.

Today multi-dose preservative-free devices, capitalizing on advanced and proven technologies, offer a real alternative to preserved formulations. Independent of which technology is used, all will work best in an upright position when the dip tube is submersed into the saline solution. This is no problem for self-treatment. However, caregivers will face problems when administering the product to lying down patients or to children, babies, or toddlers. To overcome this issue, specially designed pumps or containers (eg, systems with collapsing bags) are used to enable spraying in any position (so-called 360° pump systems). Discussing such technologies cannot end without considering a system spraying in any angle: the bag-on-valve (BOV).

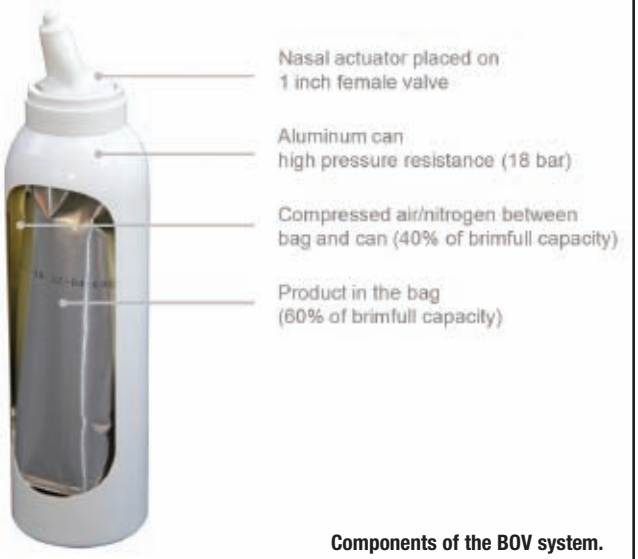
BOV

The BOV system consists of a continuous aerosol valve connected to a welded bag. The bag is placed in a can in most cases made of aluminum. A mounting cup will close the bottle and hold the valve and actuator. Prior to product filling, the container is pressurized using an under-the-cup gassing station, providing compressed air or nitrogen into the space between bag and can. Then the product is filled via the valve into the bag. When pressing the nasal actuator, the saline is dispensed by the pressure the compressed gas provides by squeezing the bag. It is important to understand that the compressed air is at no time in contact with the product dispensed. Furthermore, the system does not require any pumping, and its continuous valve allows determining the amount of product needed for each actuation. Depending on the nasal actuator's type, spraying will result in a gentle mist or jets of different flow rates for specific cleaning/rinsing purposes. For nasal saline, bag sizes are usually between 30 and 200 ml. The system is a real 360° device: it will work in any position independent from the level of remaining content. In addition, BOV technology is preservative-free technology (PFS) and environment friendly due to the use of compressed air rather than any harmful propellant. The same applies for the aluminum aerosol container that can easily be recycled.

FIGURE 4

Tip seal technology and sterile filtration of venting air are key features of APF nasal spray systems for unpreserved saline sprays.

FIGURE 5



Components of the BOV system.

Similar concepts exist on the market using various material and bag designs as well as low-pressure systems. For example, the low pressurized POWER ASSEMBLY (ATMOS) system using the power of a rubber sleeve around a specially designed flexible bag. Another system (eg, NOATECH® flexpack) uses a flexible bag made of silicone. When filled with product, the tension force of the silicone bag is sufficient to dispense the content. Various accessories will ensure the desired intensity of the spray. For these systems, plastic bottles are generally used as secondary packaging as not exposed to pressure. Filling process of such devices generally requires the use of a dosage cylinder unit, quite similar to BOV systems.

SUMMARY

Today, nasal saline is a well-established market that continues to grow with sustainable rates. Ways of use, prevention, and treatment have convinced an increasing number not only of consumers, but also experts in the pharmaceutical field, such as ENT specialists and scientists. The choice of the right saline solution, ranging from physiological saline to sea water and even enriched water is in the hands of the users, who have to find out what is best for their noses. The same applies for packaging technologies offering a wide range of dispensing systems dedicated to nasal saline. Considering the title of this article, claiming that "a saline spray a day keeps the doctor away" is not that unwise. Among various products, the market has fully adopted nasal saline as an adequate and effective product for itself, but also as an adjunctive therapy in combination with medicated products. Those who can see further than the tip of their nose, will recognize the high potential of nasal saline. ◆

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BIOGRAPHIES

Following the study of veterinary medicine and the successful completion of his thesis at the University of Leipzig, **Dr. Degenhard Marx** joined the Arzneimittelwerke Dresden/Asta Medica co-operate research in 1992. In 2001, he took over a senior research position at Altana Pharma/Nycomed in Constance, Germany. During this time in the pharmaceutical industry, he collected ample experiences in the drug development of anti-inflammatory and cardiovascular drugs. In 2008, he became Business Development Manager at Ing. E. Pfeiffer, Pharma Division, which became Aptar Pharma in 2010. Currently, he is Director of Scientific Affairs within the Aptar Pharma Consumer Health Care Division.

Georges Bouille is Vice President of Business Development - Consumer Health Care Division - Aptar Pharma. In the frame of Aptar Global Market Development organization, Mr. Bouille is in charge of both Nasal Saline and Wound Care application fields and strategy, capitalizing on over 20 years of experience in dispensing and spray technology. From 1991 and onward, he challenged and succeeded the introduction of the new EP Spray Systems' dispensing technology - Bag-on-Valve (BOV). Today, he is known as one of the leading WW specialist in that field. After graduating in Economics in 1987 in Neuchâtel (Switzerland), he started as a business consultant before joining an internationally renowned company in the packaging industry for aerosols. Mr. Bouille is based in Switzerland and has an excellent technical aptitude inherited from a Swiss watch manufacturing origin, with a unique passion for marketing and innovation.

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Bioavailability Enhancement Strategies & Opportunities

By: Frost & Sullivan Technical Insights Senior Research Analyst Ruplekha Choudhurie

INTRODUCTION

The therapeutic efficacy of a drug is mainly determined by its bioavailability (BA), which can be simply defined as the rate and extent of absorption of the drug at the target site. Solubility in water, permeability across membranes, resistance to enzyme degradation, as well as stability in different pH ranges are some of the key factors that determine a drug's BA, though solubility is the top parameter that correlates to the drug's BA. Generally speaking, a hydrophilic drug has a higher chance of achieving the desired pharmacologic response, when compared to lipophilic ones. Low aqueous solubility might require administration of higher levels of drugs at frequent intervals, which in turn can lead to systemic toxicity for drugs with a narrow therapeutic window.

Because a majority of the drugs in development are hydrophobic (estimated at more than 40%), they need to be modified using chemical, physical, and biological methods to improve the aqueous solubility, and hence, BA. Optimization of drug solubility and BA of therapeutics stands as one of the top challenges faced by the pharmaceutical and biotech industry today. A number of new chemical entities (NCEs) and new biological entities (NBEs) in clinical development are facing challenges in late phase of development (Phase II) due to a poor release profile and inability to achieve the desired BA. This can result in high costs, longer development timelines, and delays in regulatory approval. Issues with BA are especially critical for orally administered drugs, as the fraction of drug at the target side is generally much lower in this mode of administration when compared to the intravenous route.

Improvement in BA at the target site is achievable by either delivering the drugs in a form that is more soluble, controlling the release and degradation of the drug (stability), or by deploying active targeting mechanisms for delivery of drug cargo in the tissue/organ of interest. In certain cases, the drugs cannot cross the biological membranes due to the large molecular size, and in such cases, it is important to adopt "trojan horses," or stealth particles that can cross the barrier by receptor mediated endocytosis. Biological targeting agents, such as cell penetrating peptides, functionalized nanoparticles, monoclonal antibodies, and others are being deployed for active targeting, and this is especially critical for drugs in oncology and neurological applications. A number of drugs act on intracellular targets and require efficient endocytis and permeation to the site of action in a specific organelle in order to exert their pharmacological effects, and poor BA is a key issue for such drugs. Organelle-specific targeting to the mitochondria, endoplasmic reticulum, lysosomes, and so on is a nascent area of research garnering interest from academia and drug developers. By minimizing systemic exposure and maximizing concentration at the target site, smaller doses can be given at less frequent intervals to achieve the same therapeutic effect.

A number of BA-enhancement strategies, such as drug dispersions, self-emulsification, liposomal formulations, size reduction (nanoscale), chemical complexation, and the use of nanocarriers, excipients, and targeting carriers were developed to address issues

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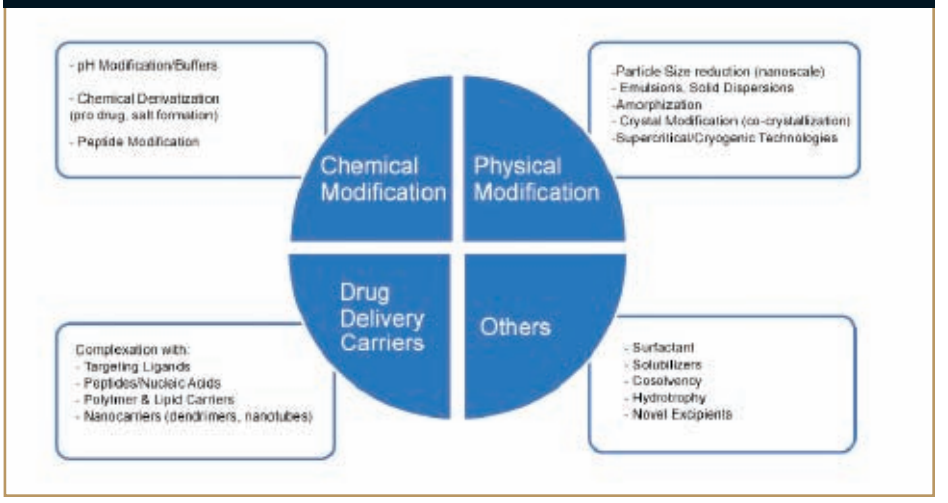
with specific drugs, and the industry is now striving to develop an integrated range of formulation and delivery strategies that can be cost effectively implemented as a complete toolkit in the drug development process for a wide range of drugs.

Approaches that can mitigate the biological, physical, and chemical barriers for effective delivery of poorly soluble and permeable drugs are being developed by a number of companies working closely with drug developers. Catalent; Merck Millipore; SEPS Pharma; Dow Pharmaceutical Sciences, Inc.; BASF; Aptuit LLC; and Alkermes plc are some of the key technology developers and contract service providers aiding in drug formulation development and manufacture. Enhancement in the BA of a drug cannot only improve patient compliance due to better therapeutic performance and reduced toxicity, but can also aid drug developers in significantly reducing the time and cost of development, while also easing the regulatory approval process.

OPPORTUNITY FOR PRODUCT LINE EXTENSION & PATENTING

Bioavailability boosting technologies not only support product development for new NCEs and NBEs, but also for generic versions of existing drugs and biosimilars. Companies that have developed innovator molecules for specific disease segments can expand their patent and product portfolio by improving the pharmacokinetic profile and dosing parameters of these drugs and also by developing novel formulations that are administrable via different routes. BA and solubility enhancement could also be used as a patenting strategy by companies that are working on generic formulations and biosimilars development. Achieving bioequivalence with alternative routes of administration, such as oral, dermal, mucosal, and pulmonary, with the use of delivery carriers and drug modification techniques could enable biotech and pharmaceutical companies to bring their drugs to the market at a faster pace, while also preventing the failure of drugs in late stages of development.

FIGURE 1



LIMITATIONS WITH DELIVERY OF PROTEIN-BASED DRUGS: TECHNOLOGY DEVELOPMENTS TO ADDRESS NEEDS

Biologics and other protein-based drugs have emerged as the primary class of drugs for several serious and chronic diseases like cancer, neurology, genetic disorders, and metabolic diseases, in which small molecules have generally not been successful. However, delivery is a challenge with biopharmaceuticals as they are larger and have a more complex molecular structure (when compared to small molecules), which makes it more difficult to administer biopharmaceuticals orally, or via alternative routes.

In spite of the increase in discovery and market approval of NBEs and other protein therapeutics, the issues with poor bioavailability of orally administered proteins and peptide drugs is still a major challenge. Most proteins and peptides undergo rapid degradation and have a very short plasma half-life that makes dosing and delivery difficult. The inflexibility of delivery of biopharmaceuticals has prompted a number of biopharmaceutical, drug delivery, and formulation development companies to explore formulation strategies and drug modification techniques that can improve the efficacy of the drug, and also reduce the dosage required for delivery via oral, pulmonary, and mucosal routes.

With a number of biopharmaceuticals coming off patent, development of novel delivery technologies and formulation techniques can be effectively leveraged by drug developers to carve a niche and gain an edge over others in the competitive biopharmaceuticals industry. The current

focus area is on oral and intranasal delivery of complex protein therapeutics, which is still challenging. Some of the key companies working on novel delivery and formulation technologies for protein and peptide drugs are Novozymes Biopharma, UniGene, Aegis Therapeutics, Flamel Technologies, and Aileron Therapeutics. Aegis Therapeutics was awarded several patents for its proprietary technology platforms in 2012. The Intravail technology that enhances transmucosal absorption and protein stabilization excipients (ProTek) technology has also been leveraged by many pharmaceutical companies to develop and commercialize protein-based formulations. Aileron's Stapled Peptide technology to improve the stability of peptide drugs has garnered interest from the industry, backed by market and pharma majors like Roche, who have entered into a collaborative agreement to leverage the platform.

Novozymes Biopharma's Albufuse (fusion) and Recombumin (conjugation) technologies using recombinant albumin variants to modulate and optimize the half-lives of drugs and Tier 1 companies like GlaxoSmithKline and Teva Pharmaceuticals are taking their peptide drugs forward into late clinical development with this technology platform.

A COMPREHENSIVE PORTFOLIO/ESTABLISHMENT OF ALLIANCES

Though there are a number of companies working in specific technologies and strategies for specific drug types, there is a lack of companies that offer integrated formulation and BA boosting techniques that can be offered seamlessly to customers. There is a need to address BA from a more holistic perspective rather than merely addressing it as a solubility issue. Research needs increased focus on combining solubility enhancement along with drug stabilization and targeting techniques to improve BA. Many companies are working toward this by combining individual expertise and developing an integrated solution that can be leveraged by drug developers.

Pharmaceutical and biotech companies are on the lookout for effective manufacturing and formulation technologies for their drug candidates. The number of collaborations between pharma and drug delivery companies, as well as particle engineering organizations, has been on the rise in the past 2 to 3 years. Oncology and central nervous system (CNS) targeted drug delivery are two key areas in which drug solubility enhancement, along with targeted delivery, has gained predominance for existing drug candidates and the development of NCEs. A good example is the partnership between Allergan, Inc. and MAP Pharmaceuticals, Inc. (2011) for development of the orally inhalable formulation LEVADEX for migraine treatment.

While most of the collaborations are research focused and aim to leverage both the companies' expertise in the area to develop a portfolio of products that can address BA and solubility issues faced by pharma/biotech companies, some of the collaborations have also been in the area of contract manufacturing. The past few years alone witnessed some major deals, such as BASF and Catalent in April 2012, which combines BASF's expertise in excipient development and formulations with Catalent's lipid-based delivery systems for BA enhancements. Another example is the more recent collaboration between Hovione and Solvias (December 2012), which is aimed at leveraging both the companies' strengths to address drug formulation and delivery challenges faced by the industry. This combines Solvia's solid state chemistry expertise with Hovione's particle engineering, enhancing solutions they can offer to the pharmaceutical industry.

In addition, Bend Research possesses strong capabilities in formulation development (such as spray-dried dispersion/SDD for low solubility compounds) and has entered into several agreements to capitalize their technology expertise. The collaboration between Bend Research with Dow Chemical (October 2012) and work with other companies like Quotient Bioresearch, Xcelience, Catalent, and Hovione toward integrated solutions for accelerated drug development are some of the most notable recent collaborations. Tier 1 pharma companies and vaccine developers, such as Eli Lilly and Company and PATH, have also leveraged the SDD technology for drug and vaccine formulation development.

BIOAVAILABILITY ENHANCEMENT & DRUG DELIVERY CARRIERS/TARGETING

Liposomes and other lipid-based systems, such as emulsions, have been widely

used to improve the BA of hydrophobic drugs for many years and are now being investigated from a different standpoint for targeting. Nano, conjugated, and functionalized liposomes are emerging as advanced solutions for targeted delivery of poorly soluble drugs.

Additionally, cell-penetrating stealth particles, cell targeting homing mechanisms, and environment-sensitive particles are being developed, which is resulting in targeted delivery and, in turn, better BA. Another approach to improve BA is the use of biomimetic particles.

A number of delivery technologies that combine permeability enhancers, protease inhibitors, and solubilizers (BASF) have been developed in the past couple of years. Other methods include particle engineering (including GenSyn Technologies, Inc; Liquidia Technologies; and Enavail), and formation of amorphous dispersions (eg, Veloxis Pharmaceuticals and Catalent) of the drugs, or formation of self-emulsified suspensions to improve oral BA. Because amorphous forms of drugs have better BA (several fold) when compared to crystalline forms (more common), the methods for formation of the same is still a challenge. Acoustic levitation (Argonne National Laboratory) is a new method that has been developed to form amorphous forms of some common APIs to improve BA.

In addition to physical and chemical methods of modification, biological methods, such as conjugation or fusion with targeting ligands/carrier molecules, can improve half-life of a drug or help target the drug to tissue of interest. Oncology is probably the most critical area for targeted delivery. Delivery systems that specifically accumulate in tumors (stimuli responsive, tumor-specific receptors) can improve the efficacy of chemotherapeutics. Delivery to the CNS is also a major challenge due to the presence of the blood brain barrier (BBB).

Improving BA at the target site can significantly reduce drug loads and side effects. Drug delivery systems that can cross primarily include nanoparticles with targeting ligands and CNS-targeting vectors. ◆

BIOGRAPHY

Ruplekha Choudhurie is a Senior Research Analyst for Frost & Sullivan's Technical Insights practice. Her functional expertise includes technical intelligence and competitive benchmarking, in addition to tracking and road-mapping emerging technology trends in the life sciences and biotech sectors that are primed for growth. Ms. Choudhurie also has academic research experience in genetics and microbiology projects. Her knowledge base encompasses genetics/molecular biology, bioprocess engineering, drug discovery, and clinical diagnostics. Prior to joining Frost & Sullivan in 2010, she worked with ABL Biotechnologies and the Children's Hospital of Philadelphia. She earned her MS in Biotechnology, with a specialization in Biopharmaceuticals/Bioengineering, from the University of Pennsylvania in Philadelphia.

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Oral Delivery of Peptides by Peptelligence™ Technology

By: William Stern, PhD; Nozer Mehta, PhD; and Stephen Carl, PhD

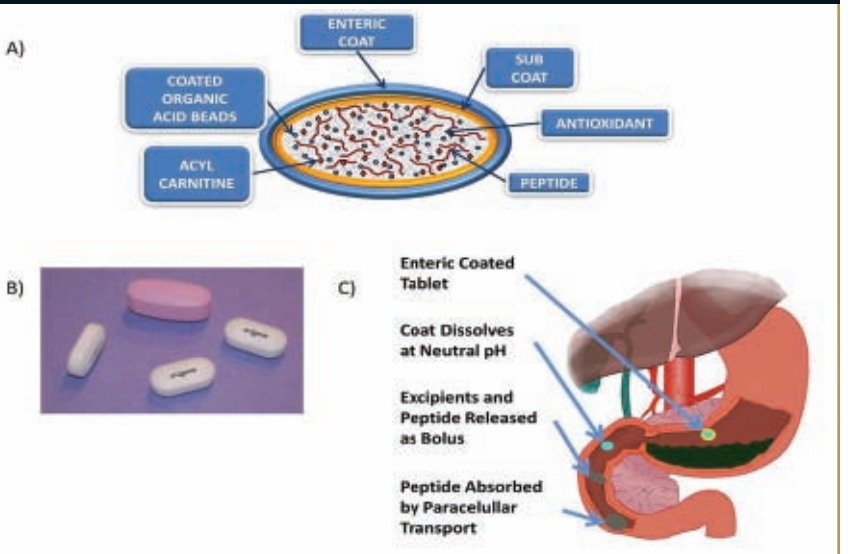
INTRODUCTION

Peptelligence™ is a highly developed, clinically proven platform technology that enables the oral delivery of peptides. It overcomes the hurdles inherent to oral peptide delivery and has been clinically successful with multiple peptides, including a Phase I trial conducted by Cara Therapeutics for the kappa agonist, CR845, a Phase II trial of a PTH analog, and a pivotal Phase III trial for the oral delivery of salmon calcitonin (sCT).[1-4] The obstacles to oral peptide delivery include 1) enzymatic and acid degradation in the stomach, 2) enzymatic degradation in the intestine, 3) an intestinal mucus barrier that prevents peptide diffusion, and 4) an intestinal lining of epithelial cells that resists peptide absorption. Unlike small molecule drugs, peptides are susceptible to hydrolysis, have an unfavorable partition coefficient for passive transcellular absorption, and are generally too large to be designed as substrates for influx transport systems. Furthermore, the molecular radius of peptides limits their ability to be absorbed through tight junctions between cells via simple, passive paracellular transport. In order to overcome these obstacles, a solid dosage form was developed that protects peptides from acid hydrolysis, enzymatic degradation, and also enhances paracellular transport. Figure 1A shows a cross-section of the tablet that was designed to fulfill each of these requirements.

The tablet consists of lyophilized peptide, coated organic acid granules (preferably citric acid), an acylcarnitine, an antioxidant (to prevent methionine and tryptophan oxidation), microcrystalline cellulose, a disintegrant, a dry binder, and a lubricant. These ingredients are dry blended and compressed into a tablet. The tablet core is then coated with a water-soluble polymer-based subcoat, followed by an acid-stable enteric-coating, which is designed to remain intact in the stomach and dissolve upon rise of the pH to above 5.5 in the duodenum.

The tablet weighs approximately 900 mg and is smaller than a widely used multivitamin tablet (Figure 1B). The coating of the organic acid granules forms a thin barrier that prevents acid

FIGURE 1



Mechanism of Peptelligence™ Oral Drug Delivery Technology in Enteric-Coated Tablets

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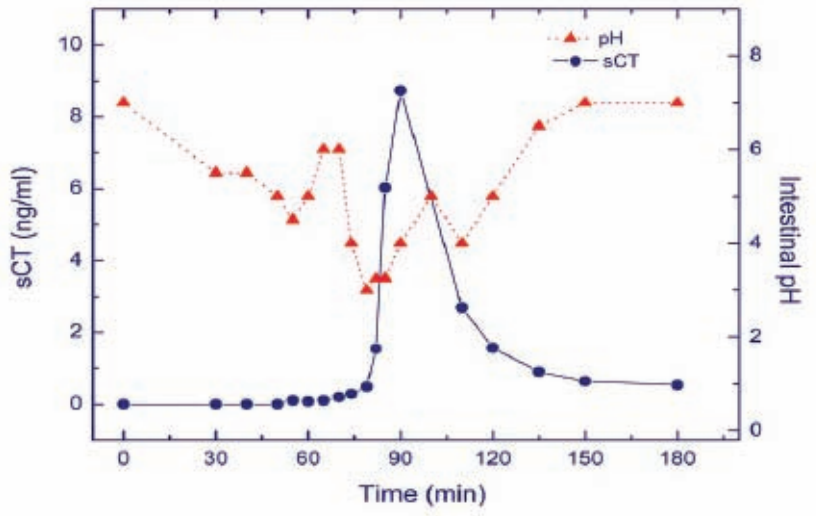
degradation of the peptide in the tablet during storage. Peptides tested in these tablets have been found to be stable for at least 9 months at room temperature. Thus, the medication can be stored at room temperature once in the hands of the patient.

The tablet's enteric coating allows it to pass through the stomach without releasing its contents (Figure 1C) and prevents food from affecting the peptide's efficacy.[5] Once the tablet is emptied into the duodenum, the neutral to alkaline liquid in the duodenum (Figure 1C) dissolves the enteric coating. The water-soluble undercoat sequesters the contents of the tablet core, allowing for complete and rapid enteric coat dissolution. Subcoat performance is a critical pharmaceutics design feature and acts to prevent the acid core from reducing the pH of the intestinal milieu and interfering with complete dissolution of the pH-sensitive enteric coat. Once the coatings dissolve, the tablet's contents are rapidly released into the duodenum with the assistance of the disintegrant. The released citric acid granules rapidly dissolve and quickly reduce intestinal pH transiently in this localized microenvironment. This in turn prevents degradation of the peptide by intestinal proteases and peptidases, which generally have a neutral to alkaline pH optimum.

The simultaneous release of the acylcarnitine, preferably lauroyl-L-carnitine (LLC), enhances peptide absorption by increasing passive paracellular transport. LLC acts by transiently loosening tight junctional complexes, resulting in a net increase in the paracellular pore radius between adjacent gastrointestinal epithelial cells (Figure 1C).

FIGURE 2



pH & sCT Concentration-Time Profiles After Oral Administration of Enteric-Coated Formulated sCT Tethered to a Heidelberg Capsule in Normal Beagle Dogs

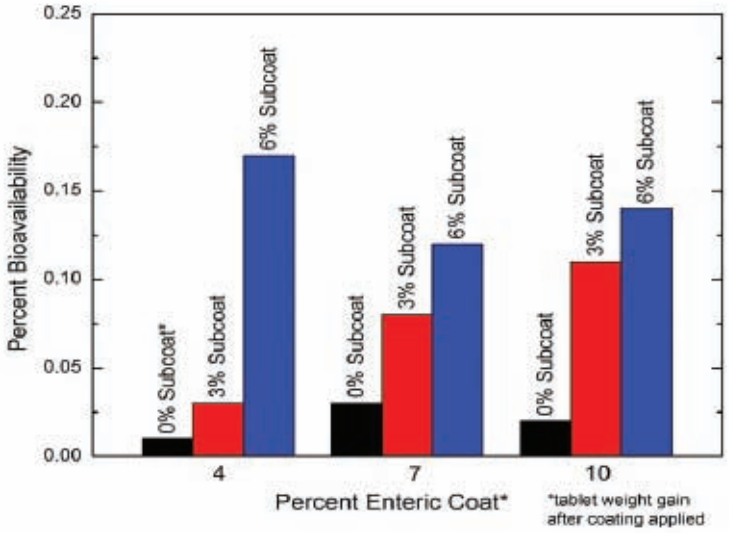
PRECLINICAL DEVELOPMENT

Early *in vivo* studies with anesthetized rats demonstrated that the bioavailability of salmon calcitonin (sCT), a peptide composed of 32 naturally occurring L-amino acids, could be increased 32-fold by lowering the vehicle pH, when administered by direct intraduodenal injection into rats.[6] By varying the ratio of citric acid and sodium citrate to control the vehicle pH, the bioavailability of sCT increased from 0.02% at pH 5 to 0.64% at pH 3 and to 0.69% at pH 2. A similar observation was made in dogs equipped with modified vascular access ports that were implanted into the duodenum of male beagles.[6,7] The inclusion of citric acid in the vehicle injected through the port into the duodenum increased the absolute bioavailability of sCT in dogs 25-fold from 0.015% to 0.37%.

In addition to inhibiting intestinal proteases, it was found *in vitro* that the addition of agents that reversibly increased intestinal permeability could also improve the bioavailability of sCT. The permeability of rat jejunal tissue to sCT in diffusion chambers increased up to 5- and 14-fold in the presence of 1% LLC and 1% sodium taurodeoxycholate, respectively, and to a lesser extent in the presence of other enhancers.[7] This change was accompanied by a decrease in transepithelial electrical resistance (TEER) of intact tissue, a measure of tight junction permeability and resistance to the paracellular transport of ions.[7] Importantly, from a drug safety perspective, upon removal of these enhancers, TEER returned to near baseline values within 10 minutes.[7]

In vivo, the bioavailability of sCT administered with LLC directly into the duodenum of anesthetized rats increased from 0.096% to 0.17% which further increased to 4.53% when citric acid was also included in the formulation.[6] In dogs equipped with modified vascular access ports attached to the duodenum, the bioavailability of sCT in a solution containing citric acid increased from

FIGURE 3



Effect of Tablet Subcoat & Enteric Coat Thickness on Oral sCT Bioavailability in Dogs

0.37% to 0.81%, when taurodeoxycholic acid was added to the formulation.[6] The *in vivo* results indicated that the inclusion of an enhancer in the formulation was not sufficient to significantly increase the "oral" bioavailability of sCT without the addition of a pH-modifying agent as a protease inhibitor. This observation was confirmed with beagle dogs that were orally administered enteric-coated capsules containing sCT, LLC, and increasing amounts of citric acid (up to 565 mg/capsule). The absolute bioavailability of sCT in the presence of LLC and no citric acid was 0.02%, which increased to 0.86% in the presence of 565 mg of citric acid.[8] By tethering sCT containing capsules with surgical string to Heidelberg capsules, which transmit pH by radio telemetry, it was possible to monitor intestinal pH at the time the enteric-coated capsules released their contents. The resulting pH and sCT absorption profile is shown in Figure 2. The first decrease in pH is caused by capsule residence in the stomach. When the capsule entered the duodenum, the pH increased to between 6 and 7. As the capsule dissolved in the duodenum, the pH decreased to 3 because citric acid was released. At the same time the pH decreased, the concentration of sCT in plasma increased. It should be noted that thereafter, the pH rapidly increased to 7, which indicates that the decrease in pH resulting from citric acid release is transient and rapidly reversible.

In addition to the inclusion of an acid and enhancer to the tablet core, it was found that the thickness and composition of the subcoat and the enteric coat had a significant effect on the bioavailability of the tablet formulation. Using sCT as a model peptide in LLC-free tablets containing CA, experiments were carried out to determine the optimal thickness (expressed as the percent weight gain of the tablet after coating) of subcoat and enteric coat on sCT bioavailability. As shown in Figure 3, in the absence of the subcoat, the bioavailability of sCT was 0.01% for tablets coated with a 4% enteric coat. The bioavailability increased to 0.03% and 0.02% for tablets coated with 7% and 10% enteric coat, respectively. The inclusion of a water-soluble non-ionic polymer as a subcoat increased the bioavailability of sCT up to 17-fold to 0.17%.

Using an approach similar to the development of enteric-coated capsules and tablets for sCT, studies were undertaken with several other sponsors or partners to determine if a formulation containing citric acid and LLC would improve the oral bioavailability of other peptides in development for therapeutic use. Peptides ranging in size from 4 to 39 amino acids and exhibiting a range of physico-chemical properties were tested in rat and dog models. The peptides were initially tested in anesthetized rats by injecting peptide into the duodenum in a formulation-free solution (unformulated peptide) or in a solution containing buffered CA and LLC (formulated peptide). This intra-duodenal delivery procedure is designed to mimic an enteric-coated tablet formulation that would pass through the stomach intact and dissolve and release its contents in the duodenum. Under these conditions, the bioavailability of unformulated peptides ranged from 0.35% to 6.0%, whereas the bioavailability of peptides that were formulated with citrate buffer and LLC was significantly increased to as high as 29%. The peptides were then tested in beagle dogs with either enteric-coated capsules containing a blend of peptide and inert filler, such as microcrystalline cellulose (unformulated) or a blend of peptide with citric acid and LLC (formulated). Under these conditions the bioavailability of unformulated peptides ranged from undetectable to 0.38%,

whereas the bioavailability of peptides that were formulated with citric acid and LLC increased up to 22.8%. In all cases, the bioavailability of the formulated peptide was significantly enhanced compared to that of the unformulated peptide. As expected, the absolute bioavailability depended largely on the size, charge, hydrophobicity, and stability of the peptide being tested.

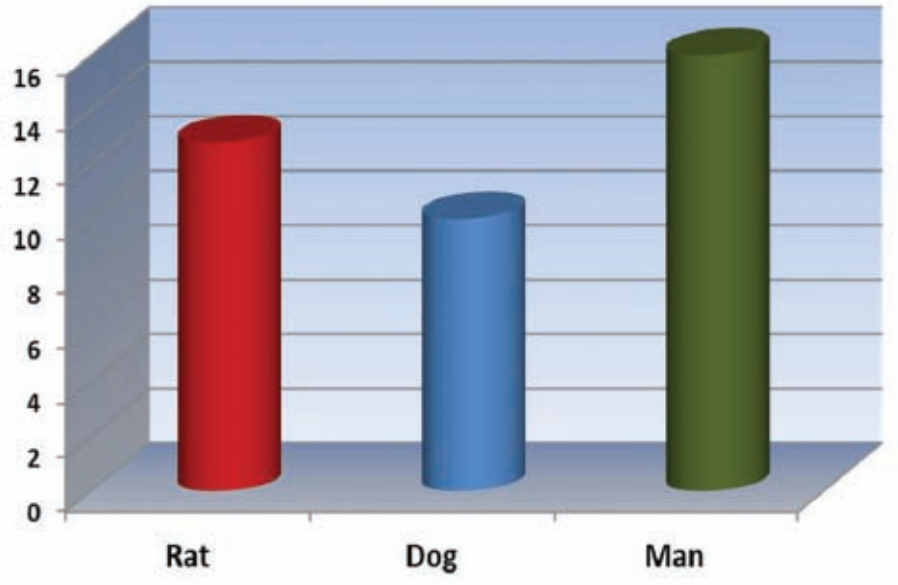
CLINICAL STUDIES

Figure 4 summarizes the results of feasibility studies in rats and dogs that culminated in a Phase I clinical trial. The bioavailability of formulated CR845, a kappa opioid receptor peptide agonist, in rats and dogs was greater than 10%. The results in dogs were deemed to be encouraging enough by the sponsor, Cara Therapeutics, to test the formulation in humans. In an oral Phase I study, 50 individuals were randomized to receive either placebo or one of four single ascending doses of an enteric-coated, capsule formulation of CR845 using the Peptelligence™ technology. The mean oral bioavailability was 16% across all groups under fasted conditions, with peak and total exposures proportional to each dose. Peripheral kappa opioid receptor activation was seen at all doses tested as measured by a standard biomarker. Orally administered CR845 did not produce any dysphoric or psychomimetic side effects and appeared to be safe and generally well tolerated across all doses tested.[1]

As part of a two-period clinical study, Peptelligence™ was used to orally deliver a 6-mg dose of PTH(1-31)NH_2 to postmenopausal women.[9] This two-period replicate dose pharmacokinetic (PK) study was carried out to evaluate the safety as well as the inter- and intra-subject variability of delivering 6-mg PTH(1-31)NH_2 to postmenopausal women. Blood samples were collected over a 6-hour period following dosing, and PTH levels were quantified using a specific sandwich ELISA. The mean Cmax values were in the 200 to 300 pg/mL range, and hence achieved or exceeded blood levels that have been shown to be anabolic with an existing injectable formulation. The PK profiles were consistent with the requirement for bone anabolic activity, with an elimination t½ of 13 to 21 minutes. The study also demonstrated low inter- and intra-subject variability (Figure 5). In a subsequent Phase II clinical trial, Peptelligence™ was used to test the bone anabolic efficacy of orally administered PTH(1-31)NH_2. The study was a 24-week double blind, randomized, repeat dose parallel group study of rhPTH(1-31)NH_2, or placebo tablets, compared to open label Forsteo® (teriparatide) in 97 postmenopausal women with osteoporosis. The primary endpoint was to characterize percent change from baseline in bone mineral density (BMD) at lumbar spine (LS) after 24 weeks of once-daily oral treatment with 5 mg PTH(1-31)NH_2. The trial met the primary endpoint with an increase of 2.2% in LS BMD with PTH(1-31)NH_2 compared to baseline ($p < 0.001$). This study also showed consistent exposure of the PTH(1-31)NH_2 at the beginning and end of the study [week 0 and week 24].[2,3,10]

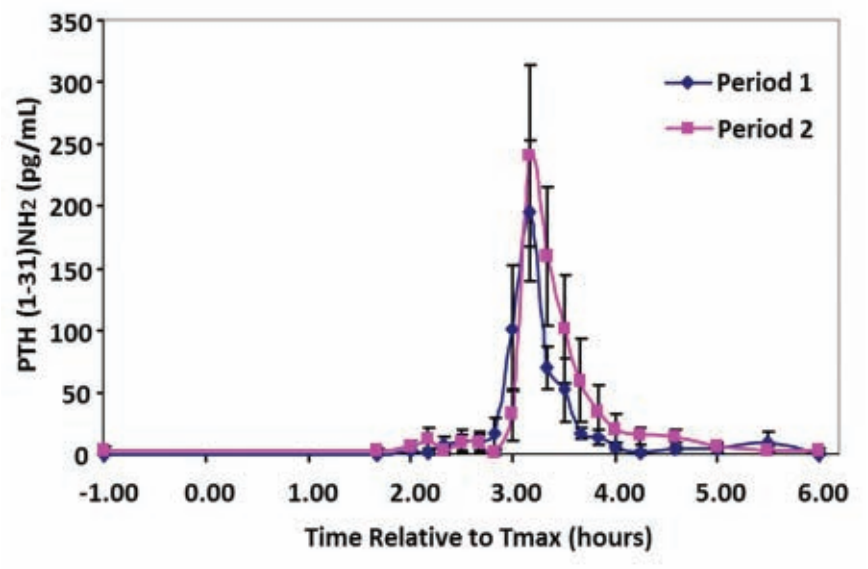
The clinical efficacy of Peptelligence™ technology has been further validated by a Phase III non-inferiority trial comparing oral calcitonin to an approved nasal calcitonin spray for the treatment of postmenopausal osteoporosis.[4] A total of 565 women aged 46 to 86 years were randomized to receive oral recombinant salmon calcitonin (rsCT) tablets (0.2 mg/day), synthetic salmon calcitonin (ssCT) nasal spray (200 IU/day), or placebo, respectively for 48 weeks. Although no PK measurements were carried out in this study, the efficacy of orally delivered sCT was

FIGURE 4



Mean Bioavailability of Formulated CR845 in Rats, Dogs & Humans

FIGURE 5



Mean Absorption Profiles of PTH(1-31)NH_2 (6 mg) Following Oral Administration on Two Separate Occasions

demonstrated by the finding that women randomized to oral rsCT had a mean 1.53% increase from baseline in LS BMD that was greater than those randomized to ssCT nasal spray (0.78%) or placebo (0.47%). Oral rsCT treatment also resulted in greater improvements in trochanteric and total proximal femur BMD than ssCT nasal spray. It is also of interest that oral sCT resulted in significantly fewer women having anti-sCT antibodies than women receiving nasal sCT (6.5% versus 32.5%, $p < 0.001$).[4] Oral rsCT was safe and as well tolerated as ssCT nasal spray or placebo.

CONCLUSIONS

The results from multiple preclinical as well as early and late-stage clinical studies have demonstrated the applicability of Peptelligence™ to the oral delivery of peptides. As mentioned earlier, the absolute bioavailability achieved largely depends on the physicochemical properties of the peptide, such as size, charge, stability, and hydrophobicity. The use of enteric-coated capsules or tablets minimizes food effects or dilution effects due to large volumes of simultaneously imbibed liquids. This has been recently demonstrated in a Phase II study investigating sCT for the treatment of osteopenia, where it was demonstrated that the percent increase in LS BMD was equivalent whether the tablet was administered to the patient with a meal, or at bedtime.[4] This clinically proven technology will increase patient acceptance and compliance for chronically administered drugs. It also expands the market for drugs that are or would be niche products if administered by daily injections, and offers the potential for life cycle management of older injectable products. ◆

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BIOGRAPHIES

Dr. William Stern is a Senior Director of Formulation Development at Unigene Laboratories, Inc. in Fairfield, NJ. He earned his BA in Chemistry from New York University in 1967 and a PhD in Biochemistry from the University of Michigan in 1972. Subsequently, he joined the research staff of the Public Health Research Institute of the City of New York, where he isolated and identified the neutralizing antigen for vaccinia virus. Since 1986, he has been with Unigene Laboratories, Inc. He was the lead scientist in the development of Unigene's first commercial product, Fortical®, is the inventor of Unigene's nasal peptide technology, and an inventor of Peptelligence™ technology.

Dr. Nozer Mehta earned his Masters from the University of Mumbai, India, and a Doctorat d'Université (equivalent to the PhD) with Honors from the Université Louis Pasteur in Strasbourg, France. He has worked as a staff scientist at the Cancer Research Institute in Mumbai and as a research assistant professor at the University of Nebraska in Lincoln. Dr. Mehta joined Unigene in 1982. He has played a key role in developing Unigene's therapeutic programs and platform technologies and is an inventor on several key Unigene patents. As the Chief Scientific Officer at Unigene, he oversees the scientific research and development of Unigene's therapeutic programs.

Dr. Stephen M. Carl is currently an Associate Director of Formulation Development at Unigene Laboratories, Inc., where he has been working on new formulation techniques as applied to oral peptide delivery. Prior to joining Unigene, Dr. Carl worked at Baxter Healthcare for 6 years in drug stability and analytical research. Dr. Carl completed his doctorate in Industrial and Physical Pharmacy with a focus on Biopharmaceutical Sciences, from Purdue University. He has published and presented multiple articles in national and international journals and conferences.

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PREFILLED SYRINGE MARKET

The New Industry Paradigm for Prefilled Success

By: Alan Shortall

INTRODUCTION

The prefilled syringe turns 40 next year. Since the filing of the first patents for a glass ready-to-fill syringe in 1974, this device class has attained an unrivaled position as the preferred choice for the delivery of parenteral drugs and vaccines. After a period of relative industry stability defined by peripheral innovation, a converging series of external and internal forces are set to reshape the prefilled syringe industry so that it will better serve the emerging needs of pharmaceutical companies, patients, and other stakeholders across the continuum of care.

More than 2 billion prefilled syringes are used worldwide each year. At least 60 drugs and vaccines are available in a prefilled format for use across more than a dozen therapeutic classes. These branded, generic, and biosimilar injectable therapies, collectively made by a who's who of pharmaceutical companies, generate combined annual revenues in excess of $50 billion. Due to the continued success of these and other pipeline drugs, more than 3.6 billion prefilled syringes are expected to be used in 2015, with compound annual growth rates in excess of 10% for the foreseeable future.

The simplicity of the prefilled syringe has been the primary foundation for its success to date. It is both a sterile primary drug container and a drug delivery system. Composed of a glass barrel with rigid needle seal, an elastomer stopper, and a plunger, the prefilled syringe has very well

FIGURE 1

The standard prefilled syringe has now replaced vials as the minimum starting point for managing the lifecycle of an injectable therapy.

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understood materials in the drug fluid path and fits seamlessly into high-volume fill-finish systems. When compared to multi-dose vials, it eliminates overfill and significantly improves the time, convenience, and accuracy of delivering a dose to a patient.

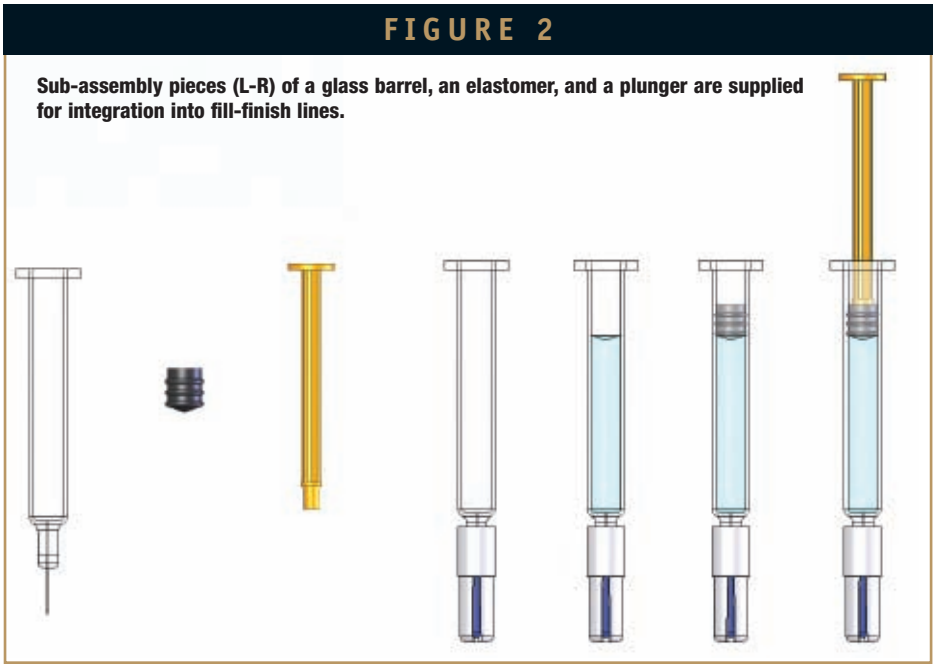
The difficulty of administrating large molecules non-invasively has led to the progressive launch of a series of biotechnology drugs and vaccines, such as monoclonal antibodies, that are ideal for the subcutaneous or intramuscular injection of doses 1 mL or less in volume.

A MATURE, PROVEN DEVICE CLASS

The pharmaceutical industry now considers the prefilled syringe to be a mature device class that has a proven track record. To help streamline costs and standardize filling and packaging systems, the standard prefilled syringe has become largely commoditized under a one-size-fits-all model. Regardless of the supplier, the components that compose a standard prefilled syringe and the filling and packaging systems used during the fill-finish process are largely identical. Indeed, if you were to compare a standard 1-mL long prefilled syringe made today with one from the 1970s, they would be largely identical in design, functionality, and handling.

The handful of incumbent device and material suppliers active in the prefilled syringe market have also invested heavily behind a business model reliant upon the high-volume production of commoditized components. There are few device manufacturers who take responsibility for the entire package of components that comprise a prefilled syringe. As a result, pharmaceutical companies may source glass barrels from one supplier and elastomers from another. While this traditional system has helped to reduce costs and standardize fill-finish systems, it can complicate the supply chain and create the potential for quality control challenges should problems arise downstream.

FIGURE 2



Sub-assembly pieces (L-R) of a glass barrel, an elastomer, and a plunger are supplied for integration into fill-finish lines.

Pharmaceutical companies with a long-term view are now displaying even greater concern about how the rigidity of this traditional model imposes restrictions upon them when they seek to leverage a prefilled syringe to optimize the delivery and commercial success of their injectable therapies.

A CHANGING LANDSCAPE

Where there has been prefilled innovation, it has largely been around the periphery. Examples include the development of elastomer coatings to enhance the suitability of prefilled syringes for use with complex biologics, or the attachment of secondary devices, such as ancillary safety products or auto-injectors. The industry has also made positive inroads towards improving component quality issues, such as glass breakage, and the removal of materials, such as tungsten from the fluid path.

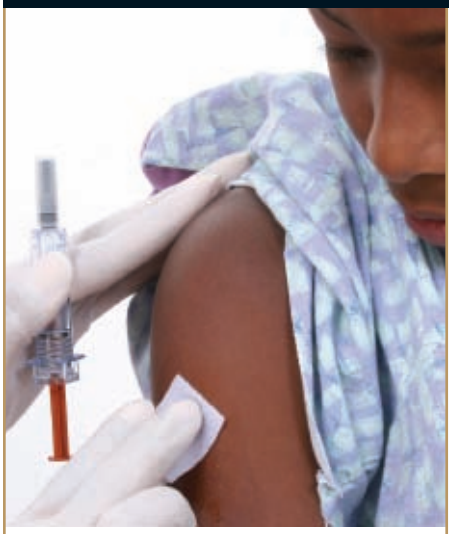
Such superficial improvements to the prefilled syringe have been something of a stop-gap measure to address immediate customer, patient, regulatory, or safety compliance needs.

With pharmaceutical and healthcare markets having evolved so rapidly throughout the past decade, many leaders within the industry now consider that it's time the prefilled syringe caught up with the injectable therapies they are designed to contain and deliver. Indeed, the 40th anniversary of the prefilled syringe may become something of a midlife crisis for those who remain entrenched in the status quo.

EMERGING MARKET NEEDS

Pharmaceutical companies now face a number of obstacles to their future growth

FIGURE 3



Many healthcare markets now mandate the use of prefilled syringes with safety features that can help protect those at risk of needlestick injury.

that industry players within the prefilled syringe market should be closely aware of, and highly responsive to.

At the macro level, the healthcare system is responding to rising costs associated with the treatment of an aging population and the growing prevalence of chronic diseases by imposing pricing and reimbursement cuts, driving the uptake of generics, and increasing regulatory scrutiny on new drug filings. These changes are pressuring pharmaceutical companies to showcase how their injectable therapies generate value to patients, payers, and prescribers across the entire healthcare system.

Patients in particular are evolving, and in many ways, becoming more like consumers. In a world full of smartphones and tablets, they expect their injectable therapies to be convenient, portable, safe, and highly intuitive in use. Today's patient generation is also highly brand-aware, and empowered to request that their physician prescribes the injectable therapy they believe is right for them.

Pharmaceutical companies are also acutely aware that the therapeutic markets in which they are active are becoming more crowded. Competition between brand-name, generic, and biosimilar drugs will continue to heighten. In response, pharmaceutical companies are seeking to streamline marketing budgets and diversify their clinical pipelines with a range of targeted therapies that can help offset the anticipated loss of revenues from the expiration of their aging blockbusters.

With novel pipeline drugs costing at least $1 billion on average to commercialize according to most industry estimates, pharmaceutical companies recognize that they must fully leverage the critical position of the prefilled syringe as the primary interface between their drug and the patient. In a world increasingly defined by bioequivalence, it will be the drug that is most differentiated from its rivals and preferred for use by patients that will beat the competition.

In speaking with many pharmaceutical companies, it is apparent that five trends are now converging together to redefine not only the composition of a prefilled syringe, but the entire industry landscape. These five emerging or unmet market needs for the delivery of prefilled therapies are 1) Device Customization, 2) Lifecycle Management, 3) Needlestick Safety, 4) Brand Differentiation, and 5) Combination Therapies.

Device Customization

Injectable formulations are becoming more complex, quality assurance controls more stringent, and patient populations more targeted. The traditional model whereby manufacturers of glass barrels, elastomers, and associated materials have invested in the high-volume production of rigid commoditized prefilled syringes is rapidly becoming outdated.

Instead of pharmaceutical companies being asked to adjust their formulation or manufacturing processes to conform to a standard prefilled syringe, device manufacturers must look to provide in the future have greater flexibility in customizing their primary container materials and the overall user-functionality of the delivery system to address specific customer needs. This new industry paradigm will require long-term collaborations between drug, material, and device manufacturers that can begin earlier in the clinical development process and extend through the regulatory approval and lifecycle management of the combination product.

With only a handful of glass barrel and elastomer suppliers within the prefilled industry, pharmaceutical customers do not wish to be constrained to only the proprietary materials, lubricants, or coatings available from one company. Instead, many now desire an open architecture supply chain system in which they can select their preferred configuration of components, materials, and coatings that will comprise the perfect prefilled syringe. Device manufactures should have the breadth and flexibility in their supply chain network to support customers with a preference between one fluid path material or another.

Another key requirement for prefilled customization relates to the growing

importance of human factors engineering. With prefilled therapies increasingly being targeted for self-administration by specific patient populations, the external design and functionality of the device must be tailored to specific user needs.

During the clinical development or lifecycle management of injectable therapies, drug and device companies must conduct user studies with the target patient group. Human factors that can be measured for patient acceptability include initiation force, glide force, and the activation force for a safety mechanism, the ergonomic design of finger flange, overall ease-of-use, and convenience of disposal. The data generated by these user studies can add significant value to the regulatory approval and commercial success of the combination product.

Lifecycle Management

The continuous enhancement of an injectable therapy throughout its commercial lifecycle is becoming a standard method of building market share and fighting off competition from current or prospective rivals. Traditionally, a pharmaceutical company would launch its therapy lyophilized in a vial, then transition a few years later into a liquid-stable format with a standard prefilled syringe, and then perhaps later add an auto-injector. The lifecycle management of Copaxone by Teva is an excellent example of lifecycle management in process. Today, however, the launch of an injectable therapy in a standard prefilled syringe is considered to be the absolute bare minimum required to compete.

With the standard prefilled syringe now widely acknowledged as a status-quo device, pharmaceutical companies are seeking access to best-in-class delivery systems that can improve therapy compliance and drive preference rates amongst patients and prescribers.

Potential may also exist for prefilled syringes to extend the commercial lifecycle of mature therapies. The conversion of a drug from a standard prefilled syringe into an enhanced, market-leading delivery system may allow the pharmaceutical company to retain some level of market share that would otherwise be lost to incoming generic or biosimilar rivals.

Furthermore, where there are proprietary primary container features within the prefilled syringe that can improve clinical outcomes, regulatory claims, or administration of a therapy, these advantages may potentially be utilized to obstruct the future entry of generic rivals that are unable to replicate these characteristics. Such device-related strategies may help a pharmaceutical company protect or regain significant revenue streams and operating margins during the mature years of a product's commercial lifecycle.

FIGURE 4

Innovative, differentiated devices such as the Unifill syringe can be leveraged by pharmaceutical companies to optimize preference rates and build market share for their injectable therapies.

Needlestick Safety

Europe and other international healthcare markets are now following the U.S. toward the mandatory use of devices with needlestick prevention features. These laws require the frontline staff of healthcare facilities to play a role in the evaluation, selection, and use of devices, including prefilled drugs that can eliminate or minimize the risk of occupational exposure to the lowest possible extent.

For pharmaceutical companies that must comply with these needlestick prevention laws, the selection of a prefilled syringe that can optimize levels of protection to healthcare workers can represent a significant competitive edge.

Traditionally, pharmaceutical companies have had two options for needlestick compliance. In the case of drugs and vaccines targeted for intramuscular injection, they can utilize a prefilled syringe in a needleless format. Such devices require healthcare workers to attach a safety mechanism, such as a needle guard onto the prefilled syringe, immediately before injection. However, data suggests that such manual safety products are frequently not activated by the

FIGURE 5

Unilife has a broad portfolio of platform-based prefilled technologies that can all be customized to address specific customer and target patient needs.

healthcare worker, or associated with needlestick injuries either during use or after disposal.

A more common approach has been to attach an ancillary safety product onto the prefilled syringe after it has been filled with the drug and prior to packaging. The process of attaching an ancillary safety product can require the purchase, installation, and operation of additional assembly systems within the pharmaceutical cleanroom. Any problems associated with the breakdown of these assembly systems or the subsequent breakage of the prefilled syringe can impact the financial efficiency of the entire fill-finish process. The bulky size of these ancillary safety products compared to a standard prefilled syringe also increases packaging, transport, and storage volumes by up to 60% to 70%.

OSHA, the FDA, and many healthcare associations cite a preference amongst healthcare workers for the selection and use of devices with automatic (passive) and integrated safety features that can minimize the risk of harm and best comply with routine injection procedures. Pharmaceutical companies that select such prefilled devices with automatic, integrated safety features will be in a strong position to leverage these protective and functionality benefits to build user preference rates and optimize market share.

Brand Differentiation

Devices that are differentiated and offer true benefits to the patient can be leveraged by pharmaceutical companies to optimize the commercial value of their injectable therapies. The insulin market is a perfect example of how the patient delivery system can be just as important as the drug itself when it comes to driving patient preference and building market share. However, when one standard prefilled syringe product looks much like any other, options to differentiate an injectable therapy from rivals can become extremely limited.

The challenge extends to ancillary products that are attached onto the standard prefilled syringe, such as ancillary safety products and disposable auto-injectors. In both these cases, the functionality and external shape of these bolt-on products are similar across available brands marketed by relevant manufacturers.

An elegant, sleek, and attractive device that is devoid of unsightly springs, compact in size, and has an external form factor that can be customized to specific drug brand or patient needs can generate powerful levels of differentiation. User opportunities for differentiation may include a more intuitive device that offers fewer steps of use, an unobstructed view of the drug, or the use of audible, tactile, and visual indicators to signal delivery of the full dose. Pharmaceutical companies that are able to access prefilled devices that can be customized to address the specific therapy needs and create the safest, simplest possible injection experience for the patient will have the best opportunities to generate powerful brand differentiation within competitive markets.

Combination Therapies

Prefilled syringes have traditionally been limited to the containment and delivery of liquid stable drugs and vaccines available in a single measured dose. Standard prefilled syringes are therefore unable to accommodate the needs of therapies that require reconstitution or mixing at the point of delivery.

Around a third of novel injectable drugs and vaccines launched in the U.S. during recent years have been in a lyophilized format, either because they cannot be made liquid stable or to fast-track time to market. Traditional reconstitution systems can require a dozen or more steps of use, and are largely unsuited for self-injection by patients. A new generation of injectable therapies supplied in a liquid-liquid combination for mixing at the point of use will also be launched onto a number of healthcare markets this decade.

Prefilled syringes with dual or multi-chamber configurations that can efficiently contain a combination of liquid or dry drug combinations in a system that is ready for efficient reconstitution or mixing at the point of delivery have significant potential to transform the treatment of countless chronic or acute conditions. Only a few such dual-chamber prefilled syringes are now available to pharmaceutical companies.

FUTURE OUTLOOK

A number of internal and external forces have led the prefilled syringe industry to a state where it is primed for change. In the future, the prefilled syringe is set to transition from being an off-the-shelf commodity device, to one in which component materials, functionality, and branding are fully customizable.

To succeed in this new environment, device manufacturers must follow a new paradigm for market success. They must be committed to serving pharmaceutical companies under long-term partnerships throughout the clinical development and commercial lifecycle of the drug-device combination. They must have the right balance between operational capabilities and business agility to ensure they are responsive and adaptable to emerging customer needs. They must have quality standards that exceed the industry benchmark and instill confidence and reliability into the pharmaceutical supply chain.

Device manufacturers must also possess management depth with strong levels of technical expertise so that their knowledge base can rival, and in some cases exceed, those of pharmaceutical companies. They must have a broad portfolio of flexible, differentiated device technologies that are platform-based instead of being rigid products. And they must be fully committed to working with their customers to enhance or enable the commercial success of their injectable therapies. Unilife is one such company that is ready to serve these emerging, unmet needs of customers seeking to enable and enhance their injectable therapies. ◆

BIOGRAPHY

Alan Shortall is the CEO and Founder of Unilife Corporation, a US-based company engaged in the design, development, production, and supply of injectable drug delivery systems. Unilife builds long-term collaborations with pharmaceutical and biotechnology companies seeking to utilize its innovative and highly differentiated devices to enable or enhance the clinical development, regulatory approval, and lifecycle management of their injectable therapies. Unilife has developed a broad range of highly innovative single and multi-chamber syringes that meet the needs of all drugs, vaccines, and biologics and are strongly accepted and preferred by users. In addition to prefilled syringes with USP compliant materials and integrated, automatic safety features, pharmaceutical companies can select from a broad portfolio of proprietary device technologies, including reusable and disposable auto-injectors, bolus injection devices, and targeted delivery systems. Each of these device platforms can be customized to address specific customer, drug, and patient requirements.

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SPECIAL FEATURE

Analytical Instrumentation Gets Faster, Smaller, and Easier to Use

By: Cindy H. Dubin, Contributor

FIGURE 1

Pall Life Sciences' Acrodisc® MS syringe filter is certified low in extractables using LCMS.

The world has witnessed a strong pattern of demand for analytical instruments and automation products in the past few years. Players in the industry have seen revenue boosts, marked by factors such as high investments, strict regulations and compliances, and product innovations. Though the economic slowdown impacted the market in 2009, the post-recession period is likely to bring increased spending from end users. By 2014, the U.S. analytical instruments market may reach $7.3 billion, according to a study on Reportlinker.com, *U.S. Analytical Instruments Market Forecast*. Market growth is largely dependent on the spending patterns of several industries, such the life sciences, and their demand for quality driven analytical instruments may propel the overall market.

Several leading analytical instrument companies recently sat down with *Drug Development & Delivery* magazine to discuss how they are developing devices that address key trends in today's pharmaceutical industry: the need for faster sample prep, more user-friendly equipment, and smaller but more sophisticated instruments. These companies are B&W Tek, Pall Life Sciences, and Shimadzu Scientific Instruments.

B&W TEK—GEARING PRODUCT TO THE LESS TECHNICAL

With an understanding that a current trend in analytical instrumentation is high-performance, portable instrumentation with sophisticated software, and an easy user interface, B&W Tek has introduced products to the market that address that direction. "Analytical instruments have moved out of the lab, and the hand of experts, to the place where inspectors, operators, and other less technical users need them to test the material they work with, be it verifying material identification, detecting counterfeits, or a rapid screening of products and materials in the field," says Dr. Katherine Bakeev, Director of Application Service at B&W Tek.

B&W Tek, founded in 1997, is a founder-owned company headquartered in Newark, DE. The advanced instrumentation company produces optical spectroscopy and laser instruments for the pharmaceutical, biomedical, physical, chemical, and research and manufacturing communities. With a strong vertical integration capability, B&W Tek also provides custom product development, design, and manufacturing. "Our analytical instrumentation is primarily Raman spectroscopy with a range of portable systems that we started providing in 2003," says Dr. Bakeev. "We have expanded our product family to also include handheld Raman instruments to serve the pharmaceutical and many other vertical markets."

In 2012, the company introduced the NanoRam, a handheld Raman spectrometer for rapid material identification. It has a touch screen and intuitive workflow, allowing for easy adoption of this technology into a QC environment and for use by non-technical operators, explains Dr. Bakeev. Also introduced was a portable Raman spectrometer, the i-Raman Plus, which comes with a complete software package for qualitative and quantitative analysis and has a higher sensitivity than the previous system and is the highest performance portable Raman in the marketplace, she claims.

FIGURE 2

i-Raman Plus (left) NanoRam (right) portable Raman systems for qualitative and quantitative analysis from B&W Tek.

But, improved performance does not equate to more difficult to use. "Analytical instrumentation continues to evolve and be simpler to operate, while also having increased ruggedness and sensitivity," says Dr. Bakeev. Much of the advancements, she says, are in the analysis of the data, which is more often being interrogated to a higher level using multivariate analysis techniques. Instrument vendors are adding simpler user interfaces that are often backed by powerful computational engines or providing users the ability to analyze the data in the instrument software or export it for analysis elsewhere. "The revolution is really in the harnessing of the data that comes from the instrumentation."

It is this revolution that is moving the pharmaceutical mindset from must-have technology to must-have support and documentation. "Many pharmaceutical scientists are well-versed in separation technologies, and there are also groups who specialize in spectroscopic techniques, so each of these groups have their preferred methodologies, which include HPLC, FTIR and NMR," says Dr. Bakeev. "But the pharmaceutical companies who are looking to purchase new equipment do not appear to demand new technologies and are often late adopters of new technology. What they do require is a high level of support from their

suppliers, and a full suite of documentation for the qualification and operation of instrumentation that they purchase."

Based on this evolution, she predicts that the future is in small, smart systems for analysis. This means that the work in the area of miniaturization will continue, as well the advancement of data analytical tools to enable robust data-driven decisions be made using such instrumentation. "Typically, instrument performance now is quite high, and the important aspect of instrument manufacturing is to make the instruments themselves so reproducible that data can be readily interchanged from one instrument to another, without much worry about calibration transfer and matching instrument responses." These developments will improve the global implementation of technology without the need for redevelopment of methods and procedures at each site to address the differences that may exist from one instrument to another, she adds.

"Though there is a large push to improve user interfaces and make instrument use easier for the non-expert, there will still be a need for technical expertise to get the most out of the use of analytical instrumentation," says Dr. Bakeev. "The trend seems to be moving from having the expertise at the user site to the vendor, but these are sophisticated, technical instruments, and someone needs to understand their capabilities, limitations, and performance for a given analysis."

PALL LIFE SCIENCES—FASTER ANALYTICAL SAMPLE PREP

Analytical sample prep is growing, facilitating a movement to analyses of smaller samples with more sensitive assays and a need to process more samples faster. To that end, Pall Life Sciences has introduced multiple new products that are used in HPLC sample prep.

"Pharma expects analytical sample prep to have low extractable contributions, low analyte adsorption, and the ability to filter very small samples," says Larry Scheer, Marketing Manager at Pall. "We are meeting this expectation with our newest Acrodisc® MS syringe filter line with WWPTFE membrane, which is certified low in extractables using LCMS."

Pall is a filtration, separation and purification company that provides solutions to meet the critical fluid management needs of the life sciences industry. The company's engineered products enable process and product innovation and minimize emissions and waste. Pall's products are used routinely in HPLC sample preparation.

Pall has also expanded its offering to include a smaller version syringe filter for filtration of samples as small as 25µL. Its AcroPrep™ Advance filter plates, and Microsep™ Advance and Macrosep® Advance centrifugal devices round out the offerings.

"Sample prep automation is moving forward with high throughput processing using both 96-well and 384-well plate filtration products," explains Mr. Scheer. "There are also systems available for simultaneously filtering a complete set of samples directly into a carousel for an HPLC system." These types of systems allow automation of the filtration process so it can be completed in batch or in process via automation.

FIGURE 3

Shimadzu's Perfinity IDP reduces sample prep time and enhances reproducibility.

SHIMADZU SCIENTIFIC INSTRUMENTS—SMALLER TECHNOLOGY AND FASTER SPEEDS

There is a concerted movement toward faster speeds, more automation, and smaller instruments in the analytical instrumentation market. According to Terry Adams, Vice President Marketing, Shimadzu Scientific Instruments (SSI). "The first two aspects are in a direct response to a need to do more in a shorter amount of time," he says. "More compact instruments reflects the lack of bench space available; in addition, there are more specialized instruments that customers want to utilize and bench space is at a premium."

SSI is the American subsidiary of Shimadzu Corporation, headquartered in Kyoto, Japan. SSI offers a full line of analytical measurement and testing instrumentation for a range of applications. Products include chromatographs (HPLC/UHPLC, GC); mass spectrometers (GC/MS/MS, LC/MS/MS, MALDI);

spectrophotometers (FT-IR, Fluorescence, UV-VIS-NIR); atomic spectrometers (AA, ICP); X-ray spectrometers (EDX, XRD, XRF); thermal analyzers; Total Organic Carbon (TOC) analyzers; particle size analyzers; balances; and materials testers.

In the past year, Shimadzu introduced several new products. Two key instruments are the LCMS-8040 triple quadrupole LC/MS/MS and the Perfinity IDP (Integrated Digestion Platform). Using proprietary high-speed technologies, the LCMS-8040 features ultrafast MRM transition speeds (555 MRMs/second), ultrafast polarity switching (15 msec), and an ultrafast scan speed (15,000 u/sec). Plus, newly improved ion optics, integrating two multi-pole RF ion guides, maintain signal intensity and suppress crosstalk, even for high-speed or simultaneous multi-component analysis. This increases sensitivity for MRM and scan mode measurements, significantly expanding the application range and ensuring high-throughput analysis at lower levels of detection.

The Perfinity IDP system automates key proteomics workflow steps to significantly reduce sample preparation times and enhance reproducibility. Traditionally, manual sample preparation techniques involving 18-hour tryptic digestion to reverse-phase HPLC and mass spec detection take three days to complete. Perfinity IDP, which features a customized Shimadzu HPLC, reduces time to 30 minutes or less. This is accomplished through automated integration of buffer exchange, digestion, desalting and reverse-phase separation. The automated process removes much of the equipment and labor associated with LCMS analyses of proteins, minimizing a potential source of error and improving laboratory productivity. Perfinity IDP can be used in multiple application areas, including assay development, protein purification, drug development, and biomarker discovery.

Mr. Adams says that all of Shimadzu's analytical instruments are built with the end user in mind. "They are pressed for time and pushed to do more with less. We understand these issues and continually strive to make our instruments easier to use, from hardware features to software functions. Our engineers have incorporated a variety of automated functions into instruments that save time, allowing end users to perform their experiments and other tasks more efficiently; and to do this without sacrificing the quality of the data."

For instance, the new UHPLC, Nexera X2 includes an Intelligent Peak Deconvolution Analysis (i-PDeA) function. This function extracts a single peak from co-eluted peaks and quantitates it by exploiting the differences in spectra between each compound. i-PDeA enables users to visualize and detect a minor single impurity even when the impurity is co-eluted with an analyte. Nexera X2 also features automated solvent blending and comprehensive method scouting, saving a significant amount of time during the method development process.

Another example is the open-access method toolbox software for LCMS. With the Method Toolbox, chemists can analyze up to 96 methods, 16 mobile phase solvents and six columns — all in one batch. This makes it easier to find the optimal separation conditions for fractionating synthetic compounds, thus increasing laboratory throughput for compound isolation. In addition, Method Toolbox software automatically manages vials, and fully cleans columns and flow channels, allowing multiple analysts to confidently screen different samples at the same time.

In addition, pharma customers are seeking specialized configurations and software to address specific applications, or the ability to use instruments from different vendors with one software platform. Shimadzu has ensured its HPLC instruments, for instance, can be controlled by other vendor's software.

As a specific example, Shimadzu developed an automated method development system, ProminenceMD. An automated system from injection to report generation, the system is designed to handle both large numbers of samples and a variety of users, eliminating concern about instrument operation while making the input of sample information possible with minimal mouse clicks. "The ProminenceMD system allows the user to observe various separation conditions by actually injecting samples onto a set of columns with different chemistries using multiple solvent systems," explains Mr. Adams. "In this way, the user has the best chance to detect hidden or co-eluting peaks from completely unknown samples. This serves as a critical step in early drug development, natural product isolation, synthetic reaction tracking and many other possible areas where sample constituents may not be totally identified." ◆

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Technology & Services Showcase

Drug Development Services

AAIPharma Services Corp. is a highly experienced provider of drug development, manufacturing, and analytical services that supports all phases of drug development. Our extensive expertise and wide array of capabilities include analytical development, formulation development, microbiology, oral solid dose and parenteral manufacturing (clinical and commercial), pharmaceutical packaging, stability storage, and analytical testing services. We are focused on providing the absolute best service and have a reputation for solving the toughest development problems - Your Results Become our Reputation®. To request a quote or learn more, contact AAIPharma at (800) 575-4224 or visit **www.aaipharma.com**.

CRO/CRM

Agere is the leading fee-for-service CRO/CRM for enhancing oral bioavailability of challenging APIs. From formulation design and development through cGMP manufacturing, Agere's commitment to excellent science delivers results that enable challenging compounds to get to the clinic. Our approach reflects the needs of our clients: a customized solution and solid results on schedule and in budget, and a partner they can count on from formulation into Phase II manufacturing. Multi-disciplinary teams ensure that each project benefits from the creative science that is only possible when challenges are analyzed from a diverse set of experience and expertise. The continuity of a project team along with excellent communication enhances client success. Agere is located in Bend, OR. If you are faced with challenging small molecule, low soluble compounds, we can help. For more information, contact Agere at (541) 639.8397 or visit **www.agerepharma.com**.

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**.

Biopharma Solutions

BioPharma Solutions, a business unit of Baxter, partners with pharmaceutical companies to support their commercialization objectives by providing scientific expertise, sterile manufacturing solutions, parenteral delivery systems, and customized support services needed to meet the unique challenges that parenteral products face. Experience makes the difference: with nearly 80 years of parenteral expertise, we can help to navigate the pathway of success for your molecule. BioPharma Solutions provides our clients with confidence of delivery, service, and integrity - we know the work we do is ultimately vital to the patients you serve. BioPharma Solutions offers resources to help solve the high-stakes challenges you face in today's complex parenteral marketplace. For more information, contact Baxter BioPharma Solutions at (800) 4-BAXTER or visit **www.baxterbiopharmasolutions.com.**

Technology & Services Showcase

Development & Manufacturing

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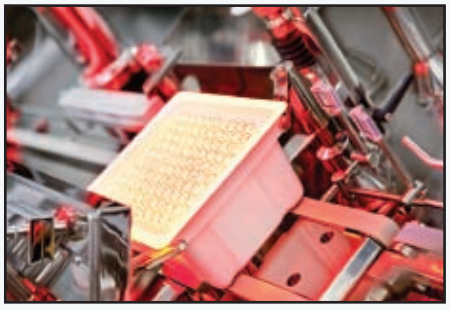
Bend Research is a leading independent scientific development and manufacturing company with more than 35 years of experience in the development of pharmaceutical delivery systems. To achieve its mission of improving health through the advancement of its clients' best new medicines, the company uses 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 Ivers of Bend Research at (800) 706-8655 or Phoenix.Ivers@BendResearch.com or visit **www.BendResearch.com**.

Pharmaceutical Solutions

Catalent

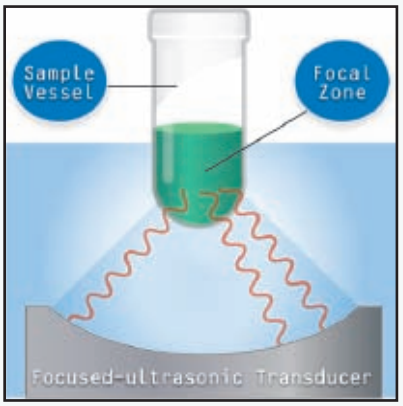
Catalent Pharma Solutions is a world leader in patented drug delivery technologies. For more than 70 years, we have developed and manufactured advanced drug delivery systems and partnered with nearly every major global pharmaceutical company. We continually work to advance the science of drug delivery and enhance the therapeutic and market performance of our customers' drugs. Our advanced drug delivery technologies bring new options to resolve the technical challenges development scientists face every day. These patented technologies can improve the odds of successful formulation by enhancing bioavailability, optimizing the rate of release, and targeting the site of absorption. Our technologies include softgel and Vegicaps® Soft capsules; Zydis® fast-dissolve dosage form; modified-release technologies; and a range of inhaled technologies, including MDIs, DPIs, nasal sprays, and solutions/suspensions for inhalation, nebulizers, and liquid inhalers. For more information, contact Catalent Pharma Solutions at (866) 720-3148 or visit **www.catalent.com**.

Integrated CDMO



Cook Pharmica is an integrated contract development and manufacturing organization providing the pharmaceutical and biopharmaceutical industries with drug substance manufacturing from mammalian cell culture; analytical and formulation development; parenteral manufacturing in vials and prefilled syringes; lyophilization; and secondary packaging. The small-scale train has capacity up to 250 L, featuring disposable technologies. Our large-scale train houses one 600-L and two 2,500-L stainless steel bioreactors, and disposable seed tanks up to 100 L. Cook Pharmica's parenteral drug product manufacturing has the capacity to aseptically fill product in vials or syringes for clinical or commercial supply. The current manufacturing lines are fully automated within barrier isolators. The high-speed syringe filling line can fill 600 units/minute, while the vial line can fill at a rate of 150 units/minute. For more information, contact our Business Development team at busdev@cookpharmica.com or visit Cook Pharmica at **www.cookpharmica.com.**

Faster to First-In-Human



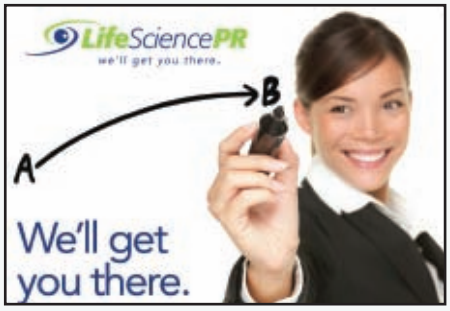
Accelerate the pace to First-In-Human (FIH) testing with an easy, scalable, and reproducible method to manufacture nanoparticles, nanoemulsions, nanosuspensions, and liposomes. Covaris Adaptive Focused Acoustics (AFA™) has the capability to produce a "Best in Class" particle size in a non-contact, self-contained vessel with 100% material recovery. AFA can allow an early stage compound to move forward into development that might have otherwise been dropped due to limited material availability. Covaris AFA is the method of choice to manufacture lipid-based nanoparticles for drug delivery. Liposomes are produced without the use of solvents and at low temperature, allowing for easy liposome formulation without degrading delicate molecules such as biologics. For more information, contact Covaris at (781) 932-3959 or visit **www.covarisinc.com**.

Technology & Services Showcase

Development & Manufacturing

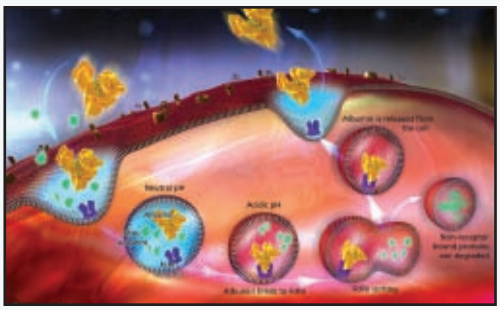
DPT is a contract development and manufacturing organization (CDMO), specializing in semi-solids and liquids for biopharmaceutical and pharmaceutical products since 1938. From virtual to large pharma, from concept to commercialization, from sterile to non-sterile - DPT offers the broadest range of capabilities in the industry. Drug development services include pre-formulation, technology transfer, formulation and biopharmaceutical development, analytical development, CMC preparation, and validation through process development, and regulatory support. DPT has a solid regulatory history, with production capabilities that include five world-class cGMP facilities, clinical trial materials, full-scale commercial production, controlled substance registration Class II-V, complete supply chain management, and expanding sterile product development and aseptic manufacturing facilities. Packaging services include packaging identification, specifications development, engineering, and procurement resources necessary for conventional and specialized packaging. For more information, contact DPT Labs at (866) 225-5378 or visit **dptlabs.com.**

Marketing & Communications



Get Noticed. Get Funded. Grow Faster. When you need to connect with investors, business partners, and regulatory agencies, LifeSciencePR can make that happen. Our integrated communication strategies and well-established industry contacts will help your life science company achieve its short- and long-term corporate objectives. We work seamlessly with your senior management team to develop the most effective communication initiatives to reach your prospective investors and partners. Our experienced staff knows what it takes to break through with your breakthroughs, powering your engine in your continued drive toward your success. LifeSciencePR will get you there smarter, faster, and easier than any other marketing and communications firm in the industry. For more information, contact LifeSciencePR at (800) 724-2372 or visit **www.LifeSciencePR.net.**

Tunable Half-Life 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. The technology also features long patents until at least 2030 and provides manufacturers with a unique competitive edge in current challenging markets. For more information on Novozymes' HLE technology, visit **www.halflifeextension.com.**

Knowledge Management

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.**

Technology & Services Showcase

Multidose Eyedropper

Rexam has developed Novelia®, a new preservative-free multidose eyedropper with a patient-friendly package. The key benefit for patients is that usage is similar to a "classic" multidose eyedropper. This device is able to calibrate droplets, which improves compliance. For ophthalmic pharma companies, Novelia® offers major advantages, including compatibility with existing filling lines, able to accommodate wide range of drug viscosities, more sustainable than unidose, and availability in a large range of bottles (from 5 mL to 20 mL). Novelia® represents a major innovation in ophthalmic drug delivery devices by providing patients a preservative-free alternative for chronic treatments with a patient-friendly package. For more information, contact Rexam Healthcare at www.rexam.com/healthcare, **healthcare.info@rexam.com**, USA: +1 (800) 537-0178, Europe : +33 1 58475676, or India : +91 80 40326500.

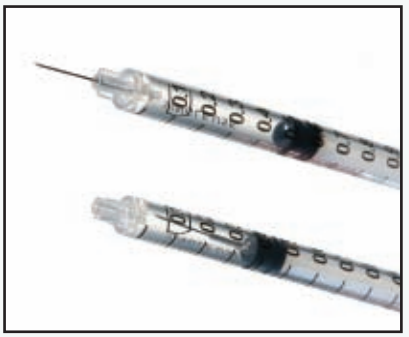
UV-VIS Spectrophotometers

Shimadzu's compact, high-performance UV-2600/2700 UV-Vis spectrophotometers feature advanced optical systems and Shimadzu's proprietary "Lo-Ray-Ligh" diffraction gratings to enable confident and convenient use for routine analysis and demanding research applications. The double monochromator UV-2700 achieves ultra-low stray light of 0.00005 %T at 220 nm, and offers an absorbance level to 8 Abs. Equipped with a single monochromator, the UV-2600 features a measurement wavelength range to 1400 nm. Both systems come standard with new UV performance validation software for applications requiring hardware validation. The software supports USP, EP, and JP test requirements. For more information, contact Shimadzu Scientific Instruments at (800) 477-1227 or visit **www.ssi.shimadzu.com.**

Automation Solutions

Based in Freiberg/Germany, teamtechnik has been making intelligent and reliable automation solutions for medical and pharmaceutical industries for over 35 years. The teamtechnik Group has production sites in Germany, Poland, China, and the US, developing innovative process-optimized production solutions for medical technology that meet customers' requirements right up to serial production. The systems are designed with a modular approach, a highly flexible concept, allowing manufacturers to adapt their production quickly and economically to market changes. For cost-effective production from Start-Up to High-¬Speed production, the company offers three different platforms: START-UP, the platform for prototype production to verify processes early in their final execution and for clinical trial production; TEAMED, a highly flexible and upgradeable platform for assembly and testing; and RTS, the high-speed platform for economical mass production. For more information, contact Chuck Mraz of teamtechnik at chuck.mraz@teamtechnik.com or visit **www.teamtechnik.com.**

Prefilled/Clinical Safety Syringes



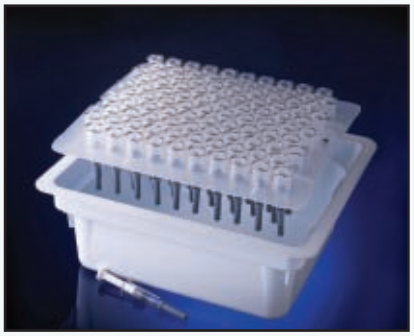
Unilife Medical Solutions has a range of prefilled and clinical safety syringes suitable for pharmaceutical companies, healthcare facilities, and patients who self-administer prescription medication. Our products incorporate passive and fully integrated safety features that can help customers comply with needlestick prevention laws and encourage single-use and safe disposal practices outside of healthcare settings. The products feature a passive (automated) needle retraction mechanism allowing operators to control the speed of needle retraction directly from the body into the barrel of the syringe. The Unilife Ready-to-Fill Syringe features a glass barrel and is compatible with the manufacturing procedures used to fill standard prefilled syringes. The Unitract 1-mL Insulin Syringe is FDA certified and now being manufactured in the PA facility. For more information, contact Unilife at (717) 938-9323 or visit **www.unilife.com.**

Technology & Services Showcase

Clinical Development Services

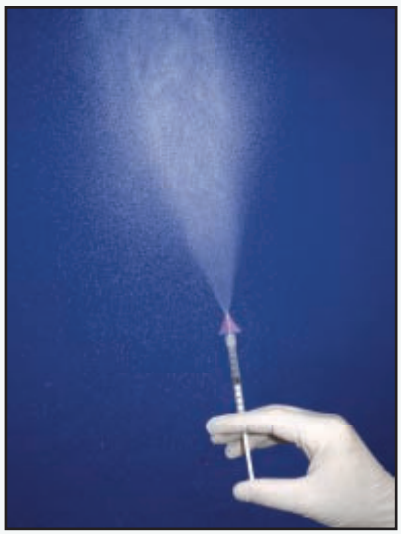
Vetter Development Service (VDS) provides expert support for your drug development projects, from inception to market launch. Our services include state-of-the-art clinical manufacturing at our facilities in Chicago and Europe, with scale-up and transfer to our large-scale manufacturing facilities. Due to the latest technology and innovative processes, we help increase your API yield. Vetter Development Service provides Formulation Support, Process Development, Clinical Trial Manufacturing, Analytical Services, and Regulatory Support. For US inquiries, please contact (847) 581-6888 or infoUS@vetter-pharma.com. For EU inquiries, please contact +49-751-3700-0 or info@vetter-pharma.com. For more information, visit Vetter at **www.vetter-pharma.com.**

West PFS Solutions



You need prefillable syringe systems and components designed to compete in an evolving industry. You need the management, expertise, and support of a manufacturer capable of creating systems and components that will mitigate risk and differentiate your product. You need West. Pharmaceutical and biopharmaceutical customers trust West to provide prefillable syringe systems and components that help bring products to market safely, reliably, and with the integrity you've come to expect from West. Our global technical expertise and services provide solutions that are true to our core goal of reducing regulatory risk while ensuring quality and patient safety. So you can rest easy. Pictured above is West's prefillable syringe solutions that include the Daikyo Crustal Zenith® 1-mL long insert needle syringe system. For more information, contact West at (800) 345-9800 or visit **www.WestPFSsolutions.com.**

Intranasal Drug Delivery Device



The LMA VaxINator™ Intranasal Drug Delivery Device offers a rapidly effective method to deliver vaccines or other medications to a patient without the need for a painful injection. The device features a precise 30- to 100- micron spray, has low dead space, attaches to any luer lock syringe, is ideal for lyophilized and liquid drugs, and is not manufactured with latex. For more information, contact Teleflex at (801) 281-3000 or e-mail mdenton@wolfetory.com, or visit **www.lmana.com.**

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**.

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DRUG DEVELOPMENT
AAIPHARMA® Executive

AAIPharma: Making the CDMO a One-Stop-Shop for Manufacturing, Development & Analytical Services

Patrick Walsh
CEO & Board Director,
AAIPharma Services Corp.

"We've seen growth rates for outsourcing, but throughout the next 3 to 5 years, we also predict increased consolidation, and thus, greater competition. Large and mid-sized pharma are actively looking at reducing the number of service providers they do business with and getting more intimate with those they choose as more of a full product offering. That obviously favors AAIPharma and our business model."

The global pharma outsourcing industry is on a fast growth track, likely to reach a market value of $360.6 billion by 2016, according to BCC Research. Making up the various legs of this market sector are contract research organizations (CROs), contract manufacturing organizations (CMOs), and contract development and manufacturing organizations (CDMOs). While each of these niche providers is experiencing rapid expansion in its own right, the CDMO is becoming a more integral part of a pharmaceutical company's development and manufacturing strategies. Patrick Walsh, CEO, and Board Director of AAIPharma Services Corp. (AAIPharma), a CDMO headquartered in Wilmington, NC, recently spoke with Drug Development & Delivery about the role of a CDMO in today's pharma and biotech space, why companies may choose to partner with a CDMO, and how the company has managed to maintain a leading position in the market.

Q: There is a bit of confusion in the industry about the differences among a CRO, CMO, and a CDMO. Can you help better define each?

A: Typically, the distinction is made based upon the company's core strength and focus. For example, a CMO is typically defined by its focus on manufacturing and/or packaging services only. With a CMO, one expects the ability to handle very large batch sizes efficiently. Supporting the drug development side, CROs consist of large global organizations whose main business is that of patient recruitment, data management, and clinical trial management. Some CROs also offer select analytical or manufacturing services.

A CDMO is defined by its broader service offerings that link product development (R&D) services, analytical support, and manufacturing into one integrated process. There are a lot of stand-alone analytical service providers in the industry as well. Across North America alone, there are more than 400 analytical services companies, the majority of which are small operations–less than $25 million in revenue–and won't have manufacturing attached to the analytical business. Our business, on the other hand, includes formulation, analytical capabilities, and manufacturing services.

Q: For our readers who may not know, can you describe AAIPharma's service offerings in a bit more detail?

A: AAIPharma has been around for more than 30 years, and the company has gone through several iterations throughout that time. Today, we have a full range of drug development and manufacturing services, which is composed of analytical testing, which could be compendial testing, raw material testing, finished product testing, and drug testing; analytical development, which would involve method development and validations; pharmaceutical formulation development; biopharmaceutical development, which involves protein and large molecule work; stability storage and testing, as well as multiple manufacturing options, such as parenteral and solid-dose capabilities. When you look at how AAIPharma has positioned itself and why we're doing so well in the sector, it's because all of those services create a one-stop-shop for the client.

We actually trademarked the phrase Compound to Clinic™ to describe our services. We provide the ability to go from a compound into the clinic by using our comprehensive service offerings. A virtual firm, early-stage company, or global pharmaceutical company can bring us a compound, and we can take it through to the clinical stage and commercial market.

Q: Why is the pharma community increasingly turning to CDMOs?

A: If you look at our client base, we have more than 600 active clients, so it's clear to see that many pharmaceutical companies are using CDMOs at this time. When you consider the changes in the pharmaceutical and biotechnology industries throughout the past 5 to 10 years, there's been a significant trend towards outsourcing earlier-stage analytical and formulation capabilities. Clients are looking to get products into the clinic more quickly and make a decision on those compounds at an earlier phase, so they rely on service providers to assist them in these efforts. However, at the same time, they are also consolidating the number of service providers to which they outsource.

Q: How has that service provider consolidation affected AAIPharma and the industry overall?

A: We've seen growth rates for outsourcing, but throughout the next 3 to 5 years, we also predict increased consolidation, and thus, greater competition. Large and mid-sized pharmaceutical companies are actively looking at reducing the number of service providers they do business with and getting more intimate with those they choose as more of a full product offering. That obviously favors AAIPharma and our business model. Those providers that participate in the sector that are small and regional don't have the capital infrastructure, lab automation, or ability to make necessary IT improvements due to of the large

expense. This gives us a competitive advantage.

Q: For those pharma companies choosing to work with a CDMO, what considerations should be part of their decision-making process?

A: Clients typically want to see four things in a CDMO. The first is obviously a high quality organization–the people, processes, and infrastructure to handle some of these very difficult projects. Second is responsiveness. Pharma is under tremendous timeline and financial constraints to move projects quickly. They need a CDMO that is responsive to their needs, understands their concerns, and is comfortable engaging in that kind of dialogue and timeline. Third is expertise. They are looking to obtain knowledge outside their own company to move the project forward. Fourth is a cost-effective partnership. Many clients are outsourcing capabilities that 5 or 10 years ago resided within their companies. So they're making sure that if they outsource, the project will be completed at a reasonable cost and still be delivered expeditiously to meet their stringent timelines.

Q: When is AAIPharma typically brought into a client's drug development timeline?

A: We can be brought in at any stage of the product development continuum. If the client has a molecule that requires formulation or solubility analysis to get it into a delivery system that would be amenable to a Phase I study, we can be brought in at that point. We also have clients who contact us at the end of the spectrum, where they've managed the product themselves, and would like to have somebody just manufacture and package it on a commercial scale.

There is not a one-size-fits-all scenario because there are so many ways to manage these processes. We also see large pharma companies formulating on their own and then outsourcing, or others who want to outsource the formulation and then bring the project back in house at Phase II. Virtual companies may have one compound they're running, and large pharmaceutical companies may have a series of compounds they are looking to narrow down and determine which one is most amenable to moving forward. Those are two different profiles; we do both and work well with each type of organization.

Q: AAIPharma made some announcements within the past few months regarding expansions to its service offerings. Can you explain what those entailed?

A: Within the company, we have three business units–manufacturing, pharmaceutical development, and analytical services. Each one is complementary and synergistic to the other, meaning there's overlap, but we believe each should stand as a leader on its own.

Our manufacturing sector is growing at a 20% year-over-year growth rate. We made the decision about a year and a half ago to increase our manufacturing capacity in both our Wilmington, NC, and Charleston, SC, facilities. Our parenteral manufacturing is one of the fastest growing segments within our portfolio.

To further improve our development and analytical service offerings, we built a 40,000-sq-ft, world-class Technology Center in Wilmington and recently added additional ICP-MS, GC-MS, LC-MS, UPLC, and HPLC systems to our list of instrumentation to meet growing market demands. New particle size testing equipment was added to support preformulation and material testing services.

We also expanded our bio-pharmaceutical development services by adding a micro-flow imaging system, a multi-angle laser light-scattering detector, and a dynamic light-scattering detector to support aggregate and particulate testing services. A capillary IEF was added to further support protein analyses.

AAIPharma also expanded its extractable and leachable testing services to evaluate and qualify the materials used in the manufacturing process and final product configuration. Our Technology Center that opened in May in Wilmington was part of a $15 million capital expansion program that included enhancements in analytical, microbiology, preformulation, and mass spectrometry resources.

Q: As the entire healthcare sector turns to electronic record keeping, how has this permeated the CDMO realm?

A: Project documentation will become virtually paperless with the rollout of an electronic laboratory notebook system. This further maximizes internal analytical processes and provides clients real-time accessibility to their project deliverables, which few contract pharmaceutical development companies have achieved. It's great to say that, but unless you're automating and providing online data access, you're not able to do that. The pharmaceutical industry is beginning to request immediate access to data because these are clinical projects that require online, real-time results, and it's important that we lead that pace to be a dominating company in the next 3 to 5 years.

Q: What challenges do you face as a CDMO doing business today, and what are your concerns as you look to the future?

A: We made a decision as a company to put our infrastructure in the US, while many of our competitors are offshoring these jobs and communicating electronically. We strongly believe there's a technically and scientifically trained workforce here that is as good as anywhere in the world, and we can invest in our infrastructure here to compete globally. The market is growing at a greater than 10% rate, so that has fueled a lot of opportunity for this sector. But, there is a high barrier of entry to create and organize a company like AAIPharma. There is the cost of capital, the cost of maintaining regulatory standards, and the cost of investing in lab automation. Couple this with clients who are actively reducing the number of service suppliers on whom they rely. We are always under pressure to get to, and maintain, the critical mass that allows us to have the infrastructure in place to be a leading presence in the space. A CDMO has to be willing to invest heavily in its business to be a top-tier provider. That's just a requirement of doing business.

Looking ahead, for me, it's keeping pace with the automation. Three to five CDMOs will emerge and dominate the marketplace. They will be paperless in their labs, have online client data access, run on electronic lab notebooks, and offer multiple manufacturing and analytical service options. So as clients become more selective in service providers, they'll have breadth and depth of service offerings to maintain and expand as the clients' needs expand. ◆

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Maximizing Yield in Transdermal Manufacturing

By: James Fenton, Plant Manager, 3M Drug Delivery Systems

Introduction

Maximizing yields is critical, not only to ensure maximum return on investment on existing products, but also to opening the possibilities of new markets. With improved efficiency, pharmaceutical companies can pursue markets that in the past have been a challenge from a cost-benefit standpoint. Additionally, by maximizing manufacturing yield, a transdermal manufacturer can help lower the final cost of a drug product, benefiting end users as well.

As outlined in this article, efficient transdermal manufacturing requires knowledge and experience in formulation, expertise in each component of the process, as well as the interactions between manufacturing operations. Pharmaceutical companies must thoroughly vet their potential manufacturing partners to assess their strengths and weaknesses and determine if the manufacturer's priorities align with the need for maximum yields. By working with a manufacturing partner who can provide proven expertise in every step of the process, pharmaceutical companies can give their products the best opportunity for high yields and profits.

Expanding Possibilities for New Markets

Passive transdermal drug delivery (TDD) offers a number of advantages to the pharmaceutical industry. This method of delivery is patient- and caregiver-friendly due to its simple method of self-administration. It is painless and non-invasive, and for patients with serious or chronic conditions, it offers an easy way to take one less pill each day. Transdermal delivery also offers several advantages in compliance, as sustained-release patches can deliver a drug for up to 7 days, and the patch's presence provides visual confirmation for patients or caregivers that the drug is being delivered (as opposed to having to wonder or try to remember if a pill was swallowed).

In terms of efficacy, administration of a drug via transdermal delivery allows the opportunity to avoid the first-pass metabolism of the drug in the liver. An additional advantage of transdermal delivery is the opportunity to reduce the chance of side effects, which can come from gastrointestinal exposure. Use of a patch also maintains constant therapeutic drug levels. Finally, an additional safety benefit provided by transdermal delivery is that it enables quick removal of the drug source in the event it becomes necessary.

These advantages of transdermal delivery highlight some of the reasons it is well received by patients. Unfortunately, in today's pharmaceutical market, transdermal delivery is still an underutilized tool. This can be attributed to a number of factors, including the inclination of pharmaceutical companies to think primarily in terms of oral delivery when developing a new drug. It may

also be related to a lack of understanding of how transdermal products are developed. However, many pharmaceutical companies are finding that with the right manufacturing partner, creating a product for transdermal delivery can be a smooth and predictable process. To give themselves the best odds for success in partnering with a manufacturer, pharmaceutical companies should be aware of the specific steps of the transdermal manufacturing process, as seen in Figure 1, and should challenge manufacturers to optimize their efficiency and yield.

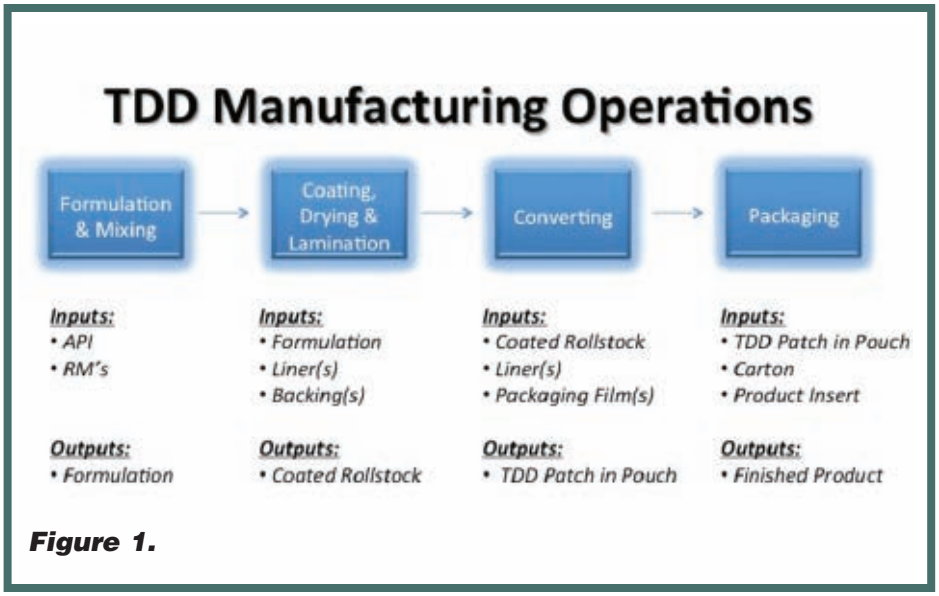

Figure 1.

TDD Manufacturing Overview

The transdermal manufacturing process is composed of several manufacturing operations, specifically including formulation, mixing, coating, drying, lamination, converting, and packaging. The equipment used in these functions includes a combination of isolators, mixers, coaters, web lines, ovens, lamination, converting, and packaging equipment. While some may assume these operations represent the entire manufacturing process, it is important to understand there are also critical quality control parameters and measures at each step, as well as final product testing, to ensure all of the product's requirements are met.

Optimizing the Process

In order to achieve the highest possible yields, manufacturers must first develop robust and predictable processes for each step of the operations. There are a number of tactics that can be used to achieve this. Broadly speaking, a manufacturer that leverages data-driven continuous improvement principles and methodologies such as Lean Six Sigma will be better prepared to achieve maximum productivity and yields. These methodologies go beyond the use of statistics and decision-making tools. It is really about the data-driven decision-making culture that is created in an organization that leverages these methodologies to make the on-going daily decisions that are critical to the quality of the product. Pharmaceutical companies should make inquiries to potential manufacturers about their formalized approach to continuous improvement.

There are a number of actions that manufacturers can and should take in relation to any given active pharmaceutical ingredient (API) and drug product to ensure high yields. These actions include optimizing procedures, training personnel, modifying existing equipment, and designing new equipment customized specifically for the requirements of the product and partner.

The overall goal in these endeavors is to ensure quality, improve productivity, reduce variation, and eliminate any non-value-added steps in the process, which consume valuable time and also increase the waste of raw materials. By engaging employees in open dialogue and hands-on training you can increase communication and understanding while harnessing their expertise to continuously apply best practices and optimize procedures. By designing and fabricating customized equipment for the specific process and product, manufacturers can help eliminate unnecessary steps, improving efficiency and yields.

As with any manufacturing process, it requires all process steps to hit yield targets to achieve the optimal rolled throughput yield for the product. However, this following will focus on formulation, mixing, coating, and converting operations to highlight how they can be leveraged to maximize yield.

For the formulation and mixing operation, a manufacturer must first understand the formulation requirements. This includes understanding if it is a solution or suspension, as well as other critical requirements, such as order of addition, percent solids, viscosity, potency, and batch size. This leads the manufacture to the

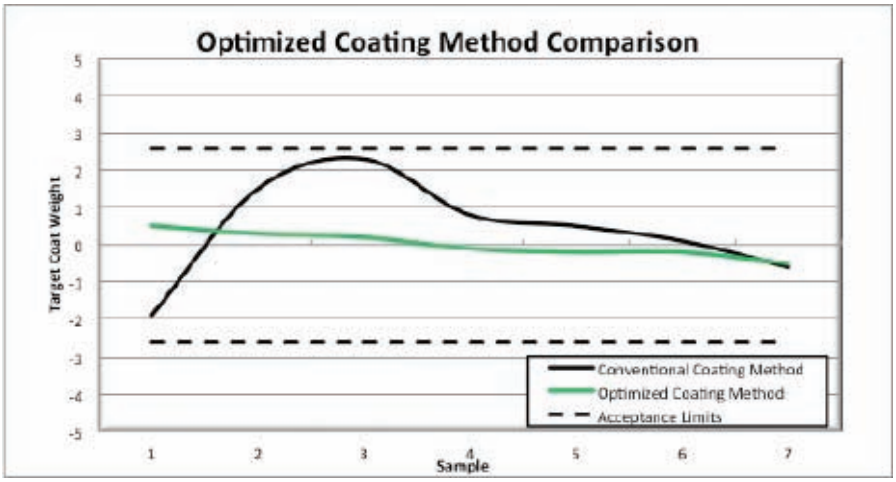

Figure 2.

selection of an appropriate mixing technology. To minimize waste and make sure employee health and safety are not compromised during formulation, manufacturers must examine how to properly mix, what kind of vessels to use, and how to minimize the amount of manual operation required. The manufacturer must consider any transfers or additions necessary when proceeding to the coating step. By considering not just the basic steps themselves but the intermediate steps between them, transdermal manufacturers can uncover additional opportunities for efficiency and improving yields. Selection of the optimal mixing technology directly impacts solvent and excipient use and concentrations, mix times, API yields, and ultimately wet mix homogeneity while protecting the safety and health of personnel. Optimizing the formulation and mixing process produces a stable, homogenous, and high-yield formulation that is fit for the coating operation.

Manufacturers often leverage commercially available coating methods, such as conventional roll-coating or die-coating methods. Oftentimes, these coating methods are part of the manufacturer's base capabilities, but they may not be optimized for the specific formulation rheology or the specific product requirements, which can often directly impact yield loss.

Coating processes are critical to the overall product quality and yield of TDD products. A non-robust coating process can often consume costly processing time and expensive raw materials to set up the process and achieve the proper coat weight. Once in operation, a non-robust coating process can have unacceptable cross-web thickness uniformity or down-web thickness variation that does not meet product requirements. This can result in a manufacturing process that necessitates stopping, continuous adjustment, and rechecking throughout a batch. This directly impacts product yield via poor formulation yield. In addition, a non-robust or poorly understood process may require extra in-process testing to ensure critical product requirements are being met. This causes further delays in the coating process and inefficient use of quality control laboratory personnel and equipment resources.

However, by performing thorough mathematical modeling in advance, a manufacturer can develop a customized coating method designed for and dedicated to a specific formulation. Figure 2 illustrates a direct comparison of a conventional and an optimized coating method using the same formulation. There are eight samples for each method comparing the coat weight versus target. The conventional coating method was adjusted to the desired coat width and thickness; however, despite these set-up and operational adjustments, it still displayed relatively high variation. The optimized coating method was mathematically modeled, and a die was designed and fabricated for the same specific formulation. It too was adjusted for coat width and thickness. However, in this case, the data demonstrates a significant improvement in the target coat weight compared to the acceptance limits. The optimized coating method delivers better coating uniformity, which directly impacts the manufacturing yield.

Specifically, by utilizing mathematical modeling, manufacturers can develop coating methods that reach the target coat weight more rapidly, enabling them to minimize formulation waste. Additionally, the steady coat weights throughout the coating run allow for excellent formulation and drug in adhesive (DIA) coated rollstock yields.

In the next operation, converting the process transforms the web-based DIA coated rollstock into a final converted patch system that is pouched and sealed in packaging film. As you can imagine, poor coating quality can result in downtime, splices, additional testing, and rejects at converting. This directly

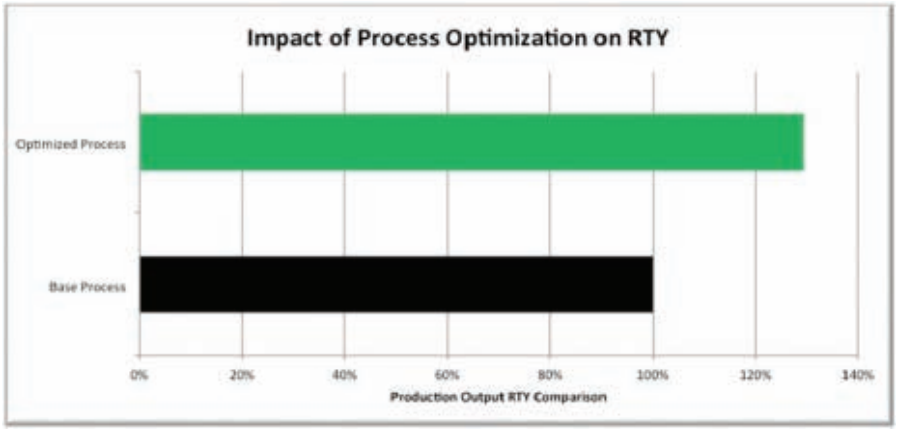

Figure 3.

impacts converting run time, rates, and yields. Furthermore, the manufacturer should have flexible yet optimized converting equipment to maximize yield. A manufacturer should have experience with a variety of TDD product constructions, patch sizes, and wide-range of materials. This level of experience offers a valuable insight into their equipment design and process capabilities as well as their process know-how. The manufacturer should have converting equipment that maximizes the utilization of coated DIA rollstock as well as liners and backings. Additionally, they should include inspection systems to continuously characterize the quality of the product being produced.

Figure 3 compares the rolled throughput yield (RTY) of a base TDD manufacturing process versus an optimized TDD manufacturing process. This rolled throughput yield improvement is ultimately realized in the converting process but is really a culmination of the improvements in the formulation, mixing, coating, and converting operations. For this specific product, it resulted in nearly a 30% rolled throughput yield improvement, which highlights the importance of process understanding.

These examples illustrate the importance of considering yields in each individual step of the manufacturing operation, but these steps are not the complete process. A manufacturer must also consider the interaction with the next step in the process, and how these interactions can be optimized as well.

Look for the Track Record

In seeking a manufacturing partner, pharmaceutical companies should look for one that has a history and expertise in each step of the manufacturing process. This includes assessing the vertical integration of the manufacturer. The manufacturer should also be able to optimize and customize its manufacturing processes for the company's specific transdermal needs.

While it is true that any number of organizations can procure commercially available equipment and components needed for transdermal manufacturing, pharmaceutical companies should apply higher standards in order to find a manufacturing partner who can add maximum value by optimizing yields. An experienced manufacturer will be able to apply intellectual property and process know-how in each step of the process. This kind of expertise is gained only from years of experience working with different types of formulations, whether they are solutions or suspensions, potent or non-potent compounds, and in various batch sizes ranging from small bench-top to large manufacturing campaigns. With this kind of history, a manufacturer can leverage its knowledge to optimize the process, determine best practices, and continuously apply new insights to the next program. A strong manufacturing partner provides not only a breadth of materials, but also a depth of knowledge that helps ensure success.

This depth of knowledge can be evidenced in a number of ways, including the use of statistical tools to perform tasks like modeling of coating methods based on specific rheology formulations, or modeling oven parameters to conduct designed experiments for optimization. Additionally, varied capabilities in lamination and web handling can allow a manufacturer to handle constructions from a monolithic adhesive layer to a multi-layer laminate construction. Intellectual property and process know-how help each step of the manufacturing process flow more smoothly.

It can be difficult to quantify the increase in yield that is possible with optimized procedures, and clearly this number will be different for every product. However, case studies exist that demonstrate double-digit improvements in yields when the

proper protocols and equipment are put into place. These improvements are made evident in the converting and packaging steps, but are the cumulative result of improvements throughout the entire process - not just the final process step.

Maximizing Yields in Pain Management Products

While there are many areas of the pharmaceutical market that have yet to widely adopt transdermal delivery, the pain management market has embraced this method. Transdermal delivery is appealing for pain management drugs due to its consistent delivery of the API, and the successes and trends seen there are illustrative of what is possible for the industry overall.

Manufacturing pain management products for any delivery method can inherently have many challenges, as these products use DEA Schedule II or III potent compounds. Because of that, there are many barriers and engineering controls that must be put into place in order to manage the environmental, health, and safety risks to workers producing or conducting the manufacturing steps. Additionally, even if the APIs being used are not in limited supply, they are often high in cost. Therefore, maximizing the yield of the API is critical - not only in the manufacturing stage, but also during the development process.

A reliable manufacturing partner can take steps to effectively use these valuable materials to obtain the best possible data from the development process, and can also lay the groundwork to deliver the best payback when the manufacturing stage is reached. This can be predictably accomplished via the aforementioned tactics by minimizing the number of operations, eliminating non-value added tasks in the process, designing and fabricating custom equipment, implementing the proper procedures, engineering controls, and bringing the knowledge and expertise of working with various potent compounds. Not only do these practices reduce risks for workers at the manufacturing site, but also for the pharmaceutical company itself. Taking care in these steps delivers maximum yield for both the manufacturer's and the pharmaceutical company's needs.

While the challenges presented by manufacturing pain management products can be significant for some manufacturers, for the right manufacturer, pain management products can present an opportunity. Those that can successfully identify solutions to allow manufacturing processes to take place safely and effectively, while still providing all the benefits customers need, can better compete and articulate the value they bring to the process. ■

James Fenton

Plant Manager
3M Drug Delivery Systems

James Fenton is the Plant Manager for 3M Drug Delivery Systems at the division's Process Technology Center (PTC), which is dedicated to the development and manufacture of transdermal and inhalation drug delivery products. Mr. Fenton has 15 years of experience at 3M in various technical and leadership roles within multiple divisions of the company, including process and product development. In addition, he has held a technical leadership position in a rapidly growing manufacturing operation and previously held technical leadership roles in 3M's Corporate Research and Development Process Laboratory. Mr. Fenton earned his BSc in Chemical Engineering from the University of North Dakota.

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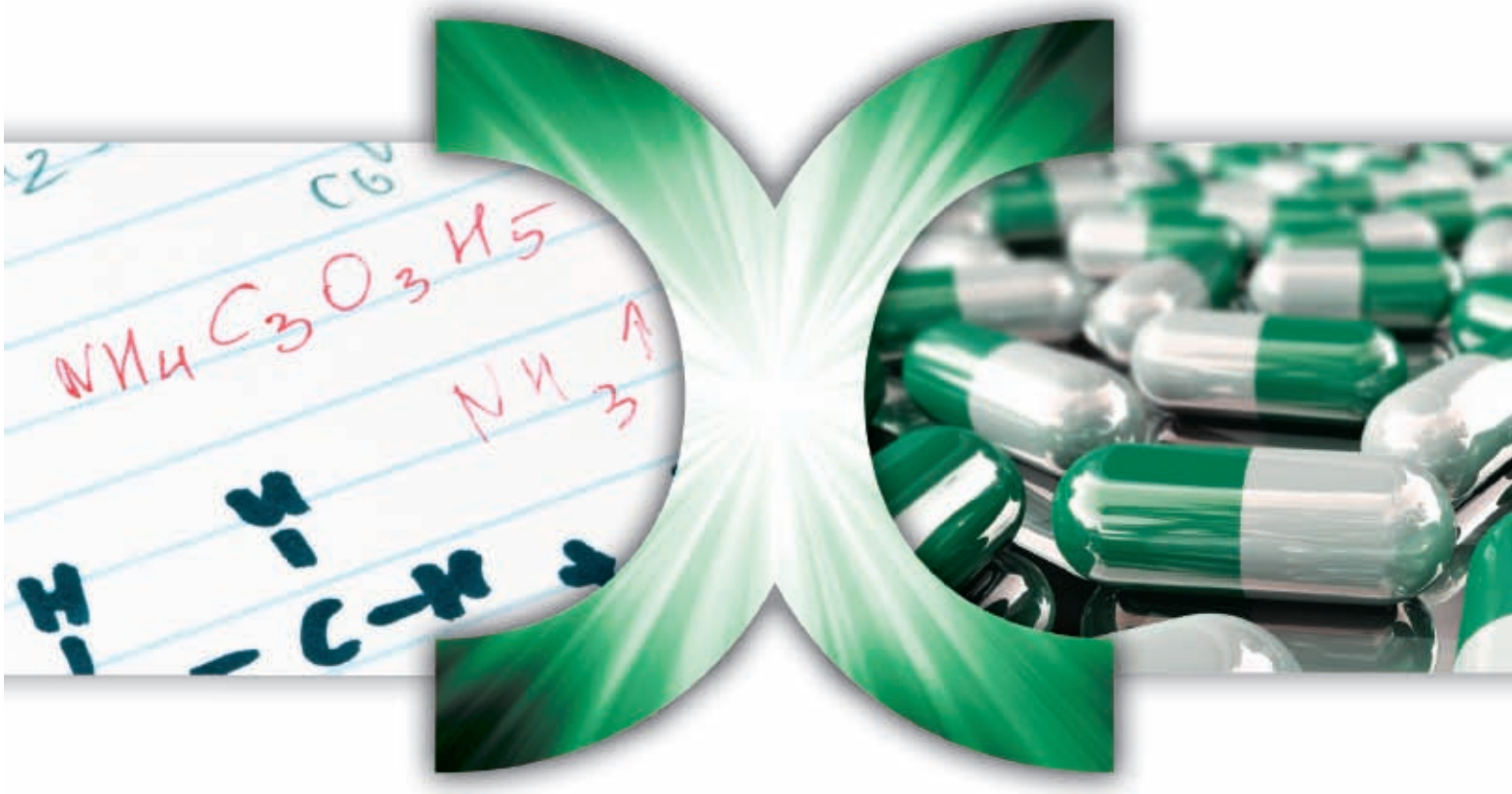

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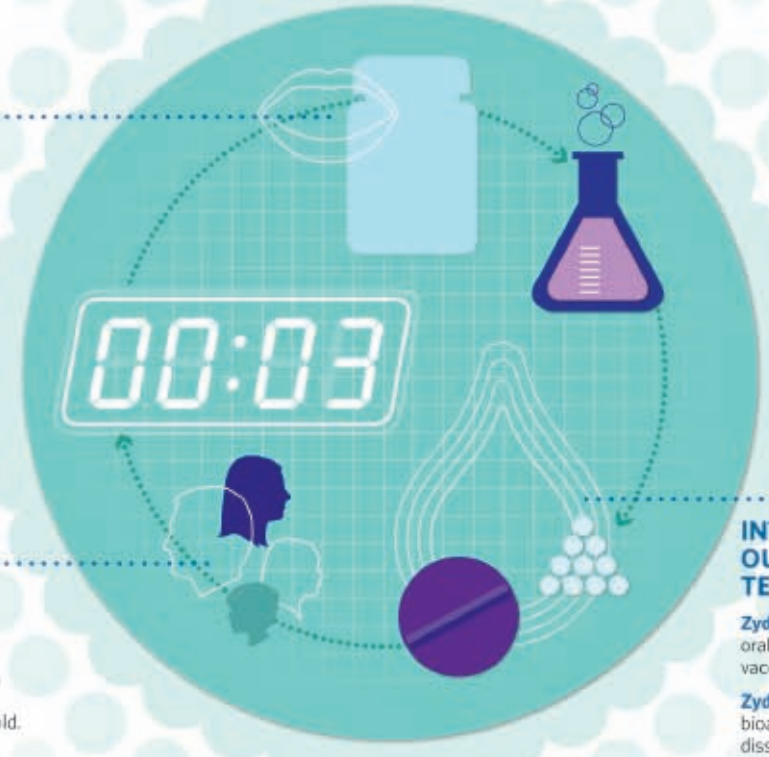

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