Drug Development & Delivery

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Patient-Centric Design

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

Sarah Baer, MBA
Incorporating Patient-Centric Design Into a Novel Anti-Needlestick Safety Device

Brian Reilly
Elution of Dexamethasone Acetate Into Buffered Saline Solution Through a Silicone Elastomer Using Excipients

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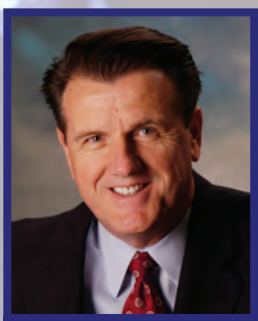

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Patient-Centric Design

"Historically, safety devices have been primarily added to prefilled syringes to meet anti-needlestick legislation around the globe. Today, we see a growing number of biotechnology drugs in pharmaceutical company pipelines that require devices to meet both healthcare practitioner and self-injecting patient needs. For example, patients with chronic diseases often suffer from impaired dexterity, making it difficult to perform an injection."

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Early-Stage Clinical Trials

"The successful transition rate from Phase I to Phase II was 60% in the period of 1991-2000. Insufficient or lack of clinical efficacy is the principal cause of program termination during development. Thus, strategies for risk mitigation have to focus on Phase II as that is where most failures occur. Achieving proof of mechanism in Phase II is one of the most important attributes of success. Drugs that achieved proof of mechanism in Phase II have the highest likelihood to be transitioned to Phase III and LOA."

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cGMP HEPES, MOPS & MES Available With Full Traceability & Secure Supply Chain

BioSpectra recently announced its cGMP, US-manufactured Zwitterionic Buffers are produced in its new FDA-registered facility in Bangor, PA. These buffers include HEPES, MOPS, and MES, which are suitable for end use as an excipient in drug products. BioSpectra's entire product line of buffers is offered with recognized or custom specifications and supported by necessary compliance. Each product is backed by a fully traceable, transparent, and secure supply chain, making it the highest quality ingredient for a variety of biopharmaceutical formulations.

"We are very proud to announce BioSpectra's newest Zwitterionic Buffers, including HEPES, MOPS, and MES, from our new FDA-registered facility in Bangor, PA," said Richard Mutchler, President of BioSpectra. "We continue to manufacture and provide the highest quality materials available to the biopharmaceutical industry."

BioSpectra's Zwitterionic buffers are ICH Q7-compliant excipients, available in high-purity crystal or solution forms. Offered in a full range of packaging sizes, BioSpectra's buffers are endotoxin-tested, particulate-free, and bioprocess ready. By providing a low molecular weight in combination with low reactivity, they maintain a stable environment for the end product into which they are formulated. These Zwitterionic buffers offer low UV absorptivity, minimal reactivity, stable pH, and high solubility in water for use in various biological applications.

BioSpectra is a FDA-registered cGMP-compliant contract manufacturer and commercial producer of amino acids, biological buffers, carbohydrates, pharmaceutical excipients, and active pharmaceutical ingredients. BioSpectra manufactures products for the biopharmaceutical industry in its state-of-the-art Pennsylvania facilities. Excipients offered by BioSpectra are produced in accordance with cGMP guidelines to provide the highest quality materials available to the biopharmaceutical industry.

Volume Rises, Value Falls for M&A Deals in Global Pharmaceutical & Biotechnology Industry

The challenges posed by expiring patents, the global economic slowdown, and price premium pressures are forcing the pharmaceutical and biotech industry to restructure and streamline strategies to boost profitability. Mergers and acquisitions (M&As) have become the preferred approach to counter low margins as they give access to new markets while creating more revenue pools and, to some extent, compensating for depletion in the research and development pipeline.

New analysis from Frost & Sullivan's Merger and Acquisition (M&A) Trends in the Global Pharmaceutical and Biotechnology Industry reveals that oncology, one of the largest and fastest-growing therapeutic domains in terms of drug development, is expected to remain the hot pick for buyers looking to strengthen their portfolio. North America will continue to be the most active region in terms of both number and value of deals.

"Big pharma's contribution to M&A deal value has been decreasing, and the trend toward more low-value deals is likely to persist," noted Frost & Sullivan Financial Analyst Dr. E Saneesh. "However, with a good number of drugs expected to lose patent in the near future, and balance sheets showing more than adequate cash, big pharma will set in motion mega deal activities to replenish its portfolio."

Major drug companies are also exploring M&A opportunities in parallel sectors, such as nutritional supplements, over-the-counter products, and cosmetics in a further bid to expand their product range and make up for shrinking profits.

Other sectors in healthcare, like diagnostics and medical technologies, will be particularly attractive as they have higher scope for innovation and fewer regulatory hurdles. Acquiring companies in these segments could help drug manufacturers diversify risks in the primary pharmaceutical sector.

"The presence of financial investors in deal-making also increased in the first three quarters of 2013, indicating improving investor confidence in the industry," explained Saneesh. "This can lead to joint deals with pharmaceutical and biotech companies that are also on the verge of raising funds for deal-making."

A Rise in IPOs Revive Investments for Global Pharma & Biotech Industry

The heightened private equity and venture capital (PEVC) deal activity in the global healthcare industry during the recession years, 2008-2010, witnessed a decline post-2010. However, the fall in deals was not uniform among the constituent sectors, with the pharmaceutical, biotechnology, and healthcare equipment sectors experiencing a much sharper decline in investor interest than the healthcare technology and provider segments. Investors started to bet on providers based with the conviction they can provide quicker and safer returns than the pharmaceutical and biotechnology space, which is ridden with regulatory challenges and patent expiries.

New analysis from Frost & Sullivan's Private Equity and Venture Capital Investment in the Global Pharmaceutical and Biotechnology Industry reveals the total number of PEVC deals in the pharmaceutical and biotechnology industry decreased from 1063 in 2010 to 480 in 2013. Though the returns from the pharmaceutical and biotechnology industry have been dwindling, they are better compared to the performance of other industries.

"PE deals in the pharmaceutical sector have been relatively stable over the post-recession period, whereas activity in the biotechnology segment began to decrease after reaching its peak in 2010, due to the uncertainty caused by healthcare reform in the US, long incubation periods, and delayed approvals," said Frost & Sullivan Financial Analyst Dr. E Saneesh. "VC deals across both these sectors also started to plummet from 2011 due to risks associated with regulatory uncertainty, long gestation periods, and increased cost of production."

However, the strong comeback of initial public offerings (IPOs) in 2013 signals a positive outlook for investment in the pharmaceutical and biotechnology industry. The number of IPOs in the global biotechnology sector surged by 100% between 2012 and 2013, primarily on account of the 26 IPOs that took place in the US. IPOs in the pharmaceutical industry also rose with 11 deals in 2013, after the volume of IPOs declined to almost one-sixth of the sector's value between 2011 and 2012.

As a result of the rise in IPOs, exit opportunities are expected to increase for investors. The trend will be further fuelled by the anticipated growth of corporate investor-backed IPOs.

"PEVC investors in the global pharmaceutical and biotechnology industry have demonstrated maximum interest in oncology drugs, followed by anti-infective drugs and pharmaceutical contract laboratories," stated Dr. Saneesh. "They have also concluded the maximum pharmaceutical- and biotechnology-related PEVC deals in the US and are expected to continue to do so in the forthcoming years. Industry players most aligned with these trends will be well positioned to obtain financial support from PEVC investors."

GlycoMimetics Receives $15-Million Payment From Pfizer

GlycoMimetics, Inc. recently announced that Pfizer has made a $15-million payment to GlycoMimetics under the terms of the parties' collaboration for the development of rivipansel (GMI-1070). Under the collaboration, Pfizer plans to initiate a Phase III clinical trial of rivipansel, which will trigger an additional $20-million milestone payment to GlycoMimetics upon the dosing of the first patient in the trial.

"Moving into Phase III will be a significant step forward in our effort to potentially address the unmet needs of individuals with sickle cell disease. With the commitment of our collaborator, Pfizer, we hope this will enable us to bring to patients, caregivers, and physicians an important new medication for treatment of vaso-occlusive crisis or VOC of sickle cell disease," said Rachel King , Chief Executive Officer, GlycoMimetics.

GlycoMimetics entered into a collaboration and exclusive license agreement with Pfizer for rivipansel in October 2011. The companies are currently developing rivipansel as a potential treatment for VOC of sickle cell disease. GlycoMimetics conducted a Phase II randomized, double-blinded study examining the efficacy, safety, and pharmacokinetics of rivipansel in hospitalized sickle cell disease patients experiencing VOC. GlycoMimetics reported top line data from the trial in April 2013 and presented full data from the clinical trial in two oral presentations and one poster presentation at the December 2013 meeting of the American Society of Hematology (ASH.) One of the oral presentations was selected as Best of ASH.

In the Phase II trial, patients treated with rivipansel experienced reductions in time to reach resolution of VOC, length of hospital stay, and use of opioid analgesics for pain management, in each case as compared to patients receiving placebo.

Vaso-occlusive crisis of sickle cell (VOC) is a condition that represents a significant unmet medical need. Sickle cell disease is one of the most prevalent genetic disorders in the US, affecting over 90,000 people. It is a chronic condition causing substantial illness and death.

GlycoMimetics is a clinical stage biotechnology company focused on the discovery and development of novel glycomimetic drugs to address unmet medical needs resulting from diseases in which carbohydrate biology plays a key role. Glycomimetics are molecules that mimic the structure of carbohydrates involved in important biological processes. Using its expertise in carbohydrate chemistry and knowledge of carbohydrate biology, GlycoMimetics is developing a pipeline of glycomimetic drug candidates that inhibit disease-related functions of carbohydrates, such as the roles they play in inflammation, cancer and infection.

Adamas Pharmaceuticals Receives $25-Million Milestone Payment From Forest Laboratories

Adamas Pharmaceuticals, Inc. recently announced it has received a $25-million milestone payment from Forest Laboratories Holdings Limited related to the development of MDX-8704. MDX-8704, a fixed-dosed combination (FDC) of memantine HCl extended-release capsules and donepezil HCl, is being developed as a once-daily therapy for the treatment of moderate-to-severe dementia of the Alzheimer's type in the United States.

The $25-million milestone payment was paid to Adamas as a result of the FDA's acceptance of the NDA for MDX-8704. Pursuant to the license agreement between Forest and Adamas, Forest paid Adamas a $65-million upfront payment in November 2012 and $40 million in the fourth quarter of 2013 for work related to the development of MDX-8704. Subsequent to this most recent $25-million payment, there is up to a $30-million milestone payable upon FDA approval. Also under the terms of the license agreement, Adamas will receive royalties on US net sales of Namenda XR and MDX-8704 beginning 5 years after their launches.

Leveraging Adamas' know-how and intellectual property, the companies are collaborating on the development of MDX-8704, for which Forest has exclusive US commercialization rights. Forest is also responsible for all US regulatory-related activities. Adamas retains exclusive commercialization rights outside the US. MDX-8704 is covered by a Forest patent and multiple Adamas patents that extend up to 2029.

Adamas Pharmaceuticals, Inc. is a specialty pharmaceutical company driven to improve the lives of those affected by chronic disorders of the central nervous system (CNS). The company achieves this by modifying the pharmacokinetic profiles of approved drugs to create novel therapeutics for use alone and in fixed-dose combination products.

Viking Signs Broad Licensing Deal With Ligand

Viking Therapeutics, Inc. recently announced it has obtained an exclusive worldwide license to five novel therapeutic programs from Ligand Pharmaceuticals Incorporated. The license includes programs targeting type 2 diabetes (Phase IIb) and cancer cachexia (Phase II) that Viking is currently preparing to advance into mid-to-late stage clinical trials. Viking is solely responsible for all development activities under the license. Ligand has also agreed to invest $2.5 million in Viking to fund operating expenses.

The programs covered in the license agreement include Ligand's FBPase inhibitor program for type 2 diabetes, a Selective Androgen Receptor Modulator (SARM) program for muscle wasting, a Thyroid Hormone Receptor-b (TRb) Agonist program for dyslipidemia, an Erythropoietin Receptor (EPOR) Agonist program for anemia, and an Enterocyte-Directed Diacylglycerol Acyltransferase-1 (DGAT-1) Inhibitor program for dyslipidemia.

"Along with our partners at Ligand, we have created through this license an excellent vehicle to develop several promising new therapies for patients, while unlocking potential value for stakeholders," said Brian Lian, President and CEO of Viking Therapeutics. "Each of the licensed programs has what we believe to be first-in-class or best-in-class characteristics and a differentiated therapeutic profile. Importantly, the portfolio fits well within Viking's focus, as our team has an extensive history in diabetes and endocrine drug development, including two recent drug approvals. At all levels, from preclinical through pharmaceutical development, and including our chief medical officer, we have well-aligned development expertise to bring these programs forward."

"Ligand has been exploring opportunities to increase the investment in certain of our research programs in order to advance them to major inflection points. This is a creative transaction that establishes a bold portfolio of early- and mid-stage assets that have the potential to generate substantial news flow over the next 12 to 24 months and to be the basis for important new drugs in major therapeutic categories," added John Higgins, President and CEO of Ligand Pharmaceuticals. "A relationship such as this one with Viking gives Ligand the opportunity to entrust valuable internal programs to a dedicated team with the operational resources to take them to the next level."

Ligand is a biopharmaceutical company with a business model that is based upon the concept of developing or acquiring royalty revenue-generating assets and coupling them to a lean corporate cost structure. Ligand's goal is to produce a bottom line that supports a sustainably profitable business. Ligand's Captisol platform technology is a patent- protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs.

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EMD Millipore Expands Provantage Upstream Bioproduction Services to North American Market

EMD Millipore recently announced the expansion of its upstream services into North America as part of its Provantage Biodevelopment and Clinical Supply offering. The company's Massachusetts facilities will now offer upstream capabilities, including media and feed screening, small-scale material production, and optimization of conditions for scale-up and technology transfer. This expansion allows EMD Millipore's North American customers to access the same services European customers have long received at the company's GMP biodevelopment center in Martillac, France.

Provantage upstream services enable customers to improve yield and productivity, and reduce costs while ensuring consistent critical quality attributes. The Provantage team leverages years of experience in media and feed screening, defining parameters and assessing robustness to optimize conditions for specific cell lines, leading to enhanced upstream manufacturing processes.

Provantage services offer a great deal of flexibility for customers. Upon completion of upstream services, customers can elect to have the Provantage team provide GMP drug substances. Alternatively, for customers who wish to transfer production, a global network of engineers and scientists can seamlessly transfer the new process and associated equipment to any facility, providing expert training and support to ensure a smooth and successful transition.

"Some of the largest gains in process productivity, consistency, scalability, and efficiency can be achieved during the clone to media and feed steps," described Oliver Klaeffling, Head of Integrated Pharm Solutions. "It is essential to identify the optimal upstream process at an early stage as once in the clinic, these parameters often prove difficult to alter from a regulatory and economic standpoint. Our team works with clients to review their upstream strategies and identify opportunities for improvement while maintaining the desired quality characteristics." EMD Millipore is the Life Science division of Merck KGaA of Germany and offers a broad range of innovative, performance products, services, and business relationships that enable its customers' success in research, development, and production of biotech and pharmaceutical drug therapies. Through dedicated collaboration on new scientific and engineering insights, and as one of the top three R&D investors in the Life Science Tools industry, EMD Millipore serves as a strategic partner to customers and helps advance the promise of life science.

Management Insight

Antifragile: Nassim Taleb on the Evils of Modern Medicine

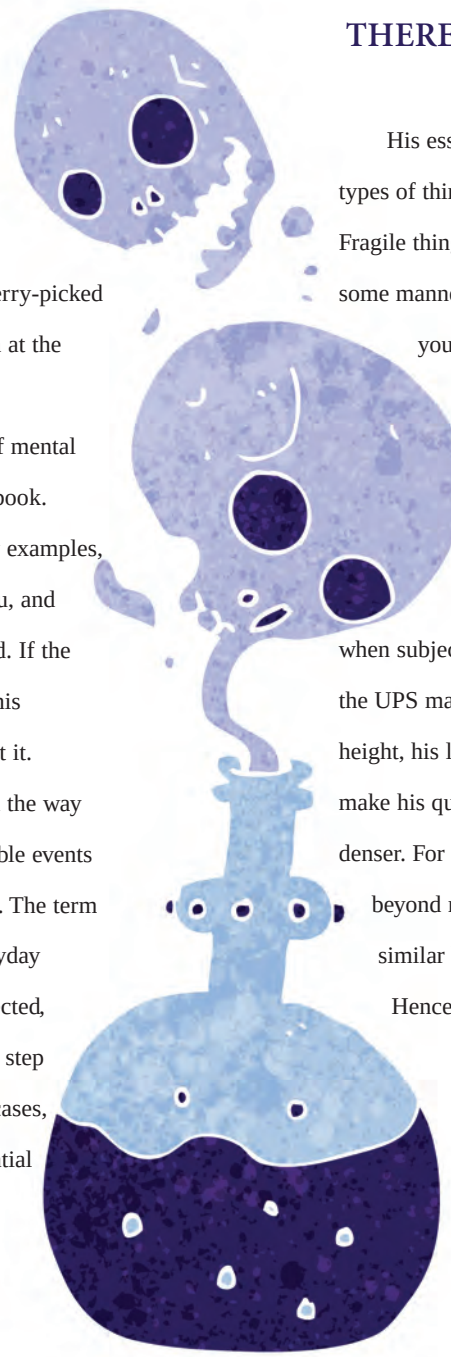
A review of Nassim Taleb's newest book, *Antifragile*

By: Derek Hennecke, CEO & President, Xcelience LLC

Antifragile, the latest book by Black Swan author Nassim Taleb, is a thoroughly maddening book. His writing style is pretentious and petulant. His points are overstated, full of trite stereotypes and cherry-picked facts. I agree and disagree with him, often at the same time.

Whether or not you enjoy this type of mental gymnastics, you need to know about this book. Taleb uses medicine as one of his primary examples, arguing that physical stress is good for you, and medicine is, with very few exceptions, bad. If the book gains anything like the notoriety of his previous books, you're going to hear about it.

Black Swan was a book that changed the way we think. Taleb showed us that unpredictable events underlie almost everything we do or think. The term "black swan" has even crept into our everyday vocabulary - a term for any totally unexpected, unprecedented event. Antifragile goes one step further, arguing that disorder is, in many cases, good and necessary. He makes three essential points;



THERE ARE THREE TYPES OF THINGS

His essential line of arguments is this. There are three types of things: the fragile, the robust, and the antifragile. Fragile things are those which, when subjected to stress, will in some manner be worse off than before. If the UPS man drops your package, the new Macbook inside will break. Macbooks are fragile. Robust things, on the other hand, are resilient and remain unchanged in the face of stress. If the UPS man drops your next package, the soccer ball inside will be no worse off than it was before. But what about things that, when subjected to stress, become stronger? Take for example, the UPS man. If the UPS man were to fall from a similar height, his legs would catch him, and the experience would make his quads and calves a little stronger; his bones a little denser. For this last circumstance, Taleb sought to create a word beyond robust. The positive affect on the UPS man is similar but opposite to the negative effect on the Macbook. Hence, the term antifragile.

…THINGS THAT ARE NON-LINEAR TEND TO BE FRAGILE…

The Macbook, dropped from the UPS man's arms, broke. But the same computer in the same box if dropped from just a couple of inches lower, would not have broken. The difference is only a couple of inches, and yet the outcome is drastically different. Put another way, the height of drop is not proportional to the damage the Macbook experiences. This is true of many things. A biotech stock may languish at the levels of a penny stock despite the fact that the company's lead molecule is making solid steady progress down the drug development pipeline. On the day the FDA announces approval of the drug, the stock explodes. The price of the stock is not proportionate to the progress of the underlying drug. When a thing is nonlinear, relatively small things can have a huge impact.

… AND THE PAST IS A LOUSY PREDICTOR OF THE FUTURE….

Any investor knows that past performance is not a reliable indication of future gains. The past does not factor in the real outliers. It can't. Many of them haven't happened yet; or at least not within recorded history. Events that cause the extinction of the human race are underrepresented in any prediction of future events, because this has never happened before. Future epidemics can't be predicted because they haven't arisen yet. Even our ability to predict the more mundane things is really quite stunningly bad. Our track record for predicting significant economic or political outcomes is, as Taleb says, not close to zero, but zero. Not one economic guru accurately predicted the crash of 2008.

…SO IT'S BEST TO BE ANTIFRAGILE.

Because the world is full of non-linear things, and because the past is of little help in predicting the future, your best shot at thriving is to be antifragile. You can influence your circumstances to accomplish this. If, for example, you have lots of cash in the bank and a closet full of tradable items like batteries and gold coins, you don't have to be able to predict the next imminent, non-linear catastrophe. Be it a hurricane, a recession, a revolution, or an earthquake, you are in pretty solid shape to get through it. If, on the other hand, you are in debt and your closet has only dust bunnies, then you're going to need to predict the future and with a lot more accuracy.

VIEWING THE WORLD THROUGH THE LENS OF FRAGILITY

Many things we think of as safe, when viewed through the lens of fragile/robust/antifragile, really aren't. Employment at a large company, for example, is often seen as a stable, conservative career path. In actuality, it's quite fragile. While it appears safe at first glance (a reliable salary every month), it is also fragile because it carries the non-linear risk of one day losing one's job. Through this lens, the Canadian economy is antifragile because it is debt free. The debt-ridden American economy is fragile, because even a slowdown can cause a financial catastrophe.

A LITTLE DISORDER IS A GOOD THING

For the antifragile, a little disorder and stress is a good thing. Cities, economies, biological species, and ideas are examples. Smaller units are more fragile than the larger communities of which they are a part. Skin cells die and slough off, while the organism from which they came adapts and renews. Individuals are more fragile than families, firms, or societies. Industries are no different. The last economic slowdown put some CDMOs out of business. Their clients' programs suffered, but the CDMOs (and

clients) that survived learned to adapt under stress, emerged stronger than before, and are far less likely to repeat the mistakes of others.

WHAT DOES THIS MEAN FOR ME?

We must each view our own lives through this filter. If I look at my company, I see a fragile entity. It is by necessity fragile, because it is such a small part of a large industry. But I can coax it toward antifragility. I can minimize debt, so that the company can better withstand unpredictable, non-linear shocks. I can broaden our base of services, to reduce our dependence on any one service, such as formulation or packaging. Even if the philosophy of antifragility doesn't give me a shopping list of new practical things to change in my business or my life, it does form a mental model in which to place my observations.

IS MEDICINE A THREAT TO YOUR ANTIFRAGILITY?

Here is the infuriating part of this book. Taleb's theory holds up well enough until he delves into specialized fields he knows less about. Biological entities fall squarely in his antifragile category. Because antifragile entities benefit from a little stress, he spends a great deal of time belaboring his wariness of "iatrogenic" effects (in which the treatment is worse than the original illness). To a point, most of us would agree. For example, if your blood pressure is only slightly outside of the range of normal, you might be wise not to choose medication as your solution. Slight stresses on the body are indeed natural. I'm not sure I'd agree that your higher reading will make you stronger, but certainly in this case the downsides of the medication may be considerable higher than the benefits it might provide.

Taleb argues that the side effects of medication are unpredictable. We simply don't have enough history to truly predict outcomes. Medicine is like tobacco, which when it first was introduced was purportedly good for you. There was no "proof" to the contrary as it took decades for the evidence to accumulate. Thalidomide was prescribed as an anti-nausea medicine but its side effects on the unborn fetus weren't clear for a few years.

He takes these anecdotal stories as fodder for his theory that medicine is only justified if it's efficacy has been proven for thousands of years, or if the benefit is so great that any possible side effect is justified (ie, an oncology product that might save your life). Taleb started in the financial world, and he seems to view medication through the same lens as one might view a financial option. Does the upside outweigh the downside? Then he generalizes based on a few anecdotes that for every known side effect there are potentially countless horrific and quite possibly deadly unknown side effects that simply haven't come to light yet. When he puts this huge potential negative on the scale beside the known side effects, giving it in effect more weight and value than the known side effects, it is a small wonder that his scale never balances. The result from this logic is that you would never take a pill unless you are certain it will save your life.

Somewhere between a minor blood pressure anomaly and a potentially terminal cancer lies the true balance. His accusation that physicians overprescribe may be true in some fields, particularly the use of psychotropic drugs in children, but most of his discussion of iatrogenics is anecdotal and relies heavily on outdated practices, including the practice of bleeding out patients - the death of George Washington in 1799, and a study of children in 1930. Apparently, because of these mistakes, we should throw out the vast majority of modern medical science.

Given Taleb's very biased approach to medical research, it comes as no surprise that he completely bypasses any discussion of the benefits of modern medicine. The Green Agricultural Revolution, for example, fed billions of people who would have starved if only natural agricultural techniques were used.

But the most glaring of all omissions is the complete or near eradication of smallpox, polio, TB, cholera, and the bubonic plague from our lives. These vaccines do not meet his criteria. Because it cannot be shown that a single vaccine

will save your life, and because we cannot predict whether or not it will save you (not until we have a thousand years of evidence), vaccines should, by his logic, be avoided. It's precisely this type of thinking that spurs anti-vaccination campaigns and has now caused the reintroduction of some of these mid-century diseases.

Epidemics themselves are in fact non-linear, and it is this fact that has taught us how to eradicate them. Take malaria, for example. It is ridiculous to think that we could get rid of this disease by eliminating all mosquitoes. There are simply too many. But because epidemics are non-linear, they have thresholds. We don't need to get rid of all mosquitoes to stop the disease; we only need to reduce their population to below the epidemic threshold. This logic has led to the elimination of many diseases, and it is this logic that will save millions of lives going forward.

AN EDGY ARGUMENT GOES OVER THE EDGE

Somewhere along the way, Taleb takes a well-reasoned argument and pushes it off a cliff. Nothing can be trusted if it hasn't been tried through the millennia. Not even papayas. Taleb avoids all fruits without a Greek or Hebrew name because his ancestors would not have eaten them. Not even fruits that other cultures have eaten for thousands of years pass his threshold for reliability. He drinks only beverages that are at least a thousand years old. By his logic, most of our industry might just as well close up shop right now, because unless your molecule will save a life from a very imminent death, it's just not worth the risk.

I hesitate to recommend this book. I'm not sure it has made me a better person. While Taleb provides a good model for understanding the world around me and the decisions I've already made (don't go into debt; have something set aside for disaster), it hasn't led me to change my behavior. That the past is a bad predictor of the future is a point well made in his previous book. That the world is non-linear - well, anyone who lives in hurricane country, tornado country, earthquake country, or who lived through the 2008 crash - knows that very well. Anyone who has ever dropped a UPS package knows it too. Of course it is good to be antifragile; it is also good to be fit, healthy, young, and strong. Good luck with that.

If I can pay the book one great compliment, it is that it made me clarify my own thoughts. His maddening tendency to overstate and take things to extremes made me stop and justify my disagreements. Taleb makes you think. If that appeals to you, then you should read this book. ◆

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BIOGRAPHY

Derek G. Hennecke is President and CEO of Xcelience, a CDMO in formulation development and clinical packaging located in Tampa, FL. Mr. Hennecke launched Xcelience as a management buyout in 2006, and the company has more than doubled in size. Prior to starting Xcelience, Mr. Hennecke worked for DSM as a turn-around manager in the global drug development community, managing an anti-infectives plant in Egypt, technical and commercial operations in a JV in Mexico, and a biologics facility in Montreal. He developed the formulation and business strategy of several drug compound introductions such as clavulanic acid, erythromycin derivatives and Tiamulin. A Canadian, he covets the Florida sun, but can't be kept away from the rink for long. He is an avid fan of the Tampa Bay Lightning.

Elution of Dexamethasone Acetate Into Buffered Saline Solution Through a Silicone Elastomer Using Excipients

By: Brian Reilly, Mustafa Al-Azzam, and Robert Kivlin

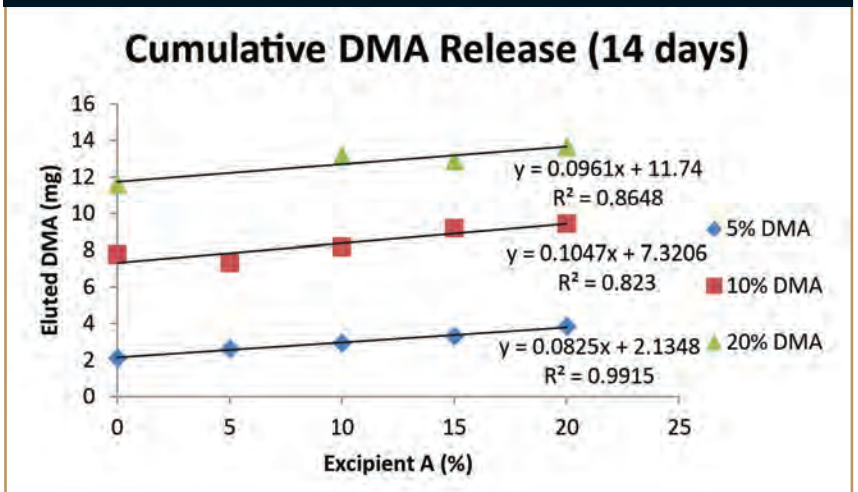
ABSTRACT

A study was conducted to measure the elution rate of the steroidal anti-inflammatory drug dexamethasone acetate (DMA) from a cured silicone matrix into a physiological environment. The goal of the study is to understand the influence of load level and the use of excipients in DMA delivery through a cured silicone matrix. Silicone samples were prepared using various concentrations of DMA and various concentrations of either Excipient A or Excipient B. Elution into a simulated physiological solution was quantitatively monitored over 14 days via daily high-performance liquid chromatography (HPLC) analysis. The resulting data allows for a prediction of physiologically available drug content based on concentrations of DMA and Excipient A or Excipient B in a cured silicone matrix.

INTRODUCTION

Silicone elastomers are extensively used in medical implants and drug delivery systems because of their physiological inertness and high permeability.[1] Silicone materials are hydrophobic in nature, making them particularly suitable for the delivery of lipophilic drugs, such as steroids. In this study, DMA was cured into a silicone matrix at 5%, 10%, and 15% concentrations (m/m) along with varying concentrations of Excipient A (0-20%) or Excipient B (0-12%). The silicone sample was placed in a

FIGURE 1



Cumulative DMA Release With 0-20% Excipient A

simulated physiological environment, and HPLC analysis was conducted daily on the eluent, allowing quantification of drug release into the physiological solution on a daily basis over 14 days.

METHODS

Sample Preparation

NuSil Technology's MED-4840, a liquid silicone elastomer with a durometer of 40 A, was chosen as the silicone substrate. The silicone was blended with various concentrations of DMA, Excipient A, and Excipient B (Table 1, percentages are in m/m).

The samples were then cured into 0.075-inch slabs per NuSil Technology's design specifications for MED-4840. Upon completion of curing, three disks were cut out of each slab for a DMA assay. An assay was performed by carrying out an aggressive extraction on a sample disk and analyzing the extract for DMA via HPLC analysis. The purpose of the assay was to verify that the calculated amount of DMA loaded into a sample correlated to the actual amount of DMA in a sample. An Additional three disks were cut out of each sample slab for elution testing over 14 days.

TABLE 1

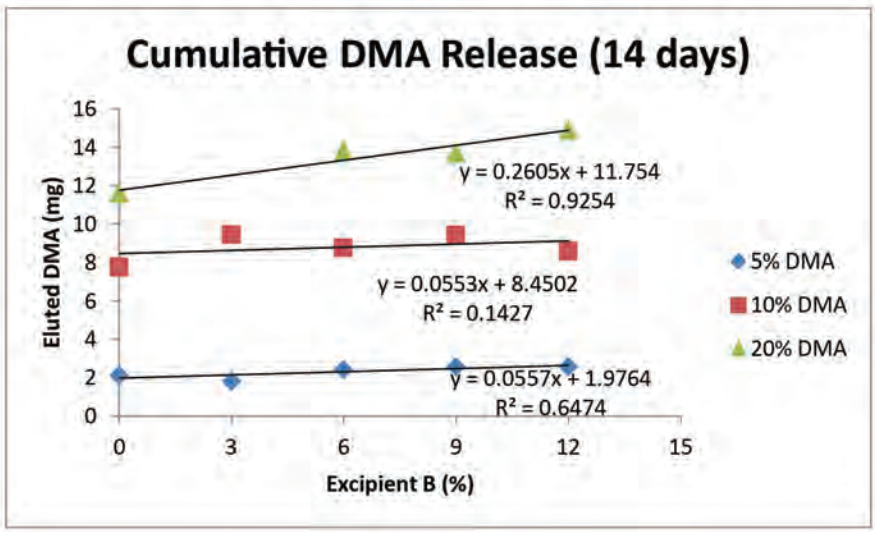
Slab #	%DMA	%Excipient A	%Excipient B	Slab #	%DMA	%Excipient A	%Excipient B
1	5	0	0	16	5	0	3
2	5	5	0	17	5	0	6
3	5	10	0	18	5	0	9
4	5	15	0	19	5	0	12
5	5	20	0	20	10	0	3
6	10	0	0	21	10	0	6
7	10	5	0	22	10	0	9
8	10	10	0	23	10	0	12
9	10	15	0	24	20	0	3
10	10	20	0	25	20	0	6
11	20	0	0	26	20	0	9
12	20	5	0	27	20	0	12
13	20	10	0				
14	20	15	0				
15	20	20	0				

Sample Composition

Assay of DMA Compounded Materials Via Extraction & HPLC Analysis

1. HPLC grade tetrahydrofuran (THF) was chosen as the extraction solution.
2. The mass of each disk was recorded as M_1 to the nearest 0.0001 grams.
3. 20 mL of the extraction solution were transferred to each extraction vessel containing a disk.
4. Extraction vessels were placed into a temperature-controlled oscillating water bath at 37°C and 120 oscillations per minute for 1±0.1 hours.
5. The aforementioned steps were repeated three more times, giving a total volume of 80 mL of extraction solution.
6. An additional 20 mL of extraction solution were added to each

FIGURE 2



Cumulative DMA Release With 0-12% Excipient B

TABLE 2

Parameter	Specification
Column	C18ODS2, 150 x 4.6 x 5 micron
Mobile Phase	Acetonitrile:USP Water Mix @ 4.5:5.5 ratio
Column Temp.	30° C
Flow Rate	1.0 mL / min
Run Time	10.0 min
Injection Volume	10 µL
Detection	254 nm

Parameters for HPLC Analysis

extraction vessel for a final rinse, and the extracts were combined.

7. Extracts were analyzed via HPLC.
8. The disks were allowed to dry at ambient conditions for a minimum of 24 hours. Each disk was weighed and the mass was recorded as M_2 to the nearest 0.0001 grams.
9. Results were averaged across the three samples.

Elution of DMA-Loaded Disks

1. The mass of each disk was recorded as M_1 to the nearest 0.0001 grams.
2. A sodium phosphate saline buffer solution at 6.0 pH was chosen as the eluent.
3. 40 mL of the eluent were transferred to a suitable vessel containing a sample disk.
4. The vessels were placed into a temperature-controlled oscillating water bath at 37°C and 120 oscillations per minute for 24±2 hours.
5. The vessels were removed, and the liquid from each vessel was decanted into an appropriate container labeled with sample ID, day number, and replicate number.
6. The aforementioned steps were repeated daily for 14 consecutive days.
7. Each sample was submitted for HPLC assay of DMA.
8. Results were averaged across the three samples.

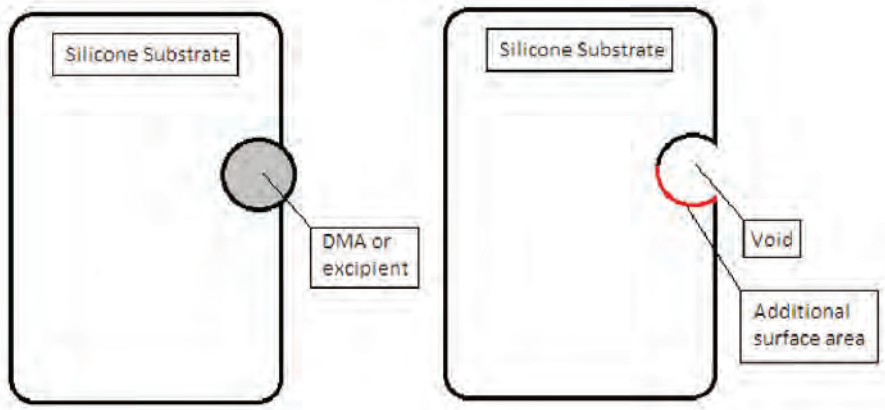
HPLC Analysis of DMA

1. HPLC analysis was carried out under the following parameters (Table 2).
2. Calibration:

   -Six DMA standards were prepared at 1 ppm, 10 ppm, 100 ppm, 250 ppm, 500 ppm, and 1,000 ppm in THF.

   -Each standard was analyzed via HPLC, and the method was calibrated using those standards as the calibration levels. The calibration curve was linear with a

FIGURE 3



R2 value of 1.00000.

-A Calibration verification was performed, and it was verified that the standard response result was accurate to ± 5%.

RESULTS

Assay

An assay was performed on each sample slab to determine the maximum amount of DMA available in each sample. An aggressive extraction was performed in triplicate on each sample material, and the extracts were analyzed via HPLC. Tables 3 and 4 show the averaged assay results across three replicates.

Cumulative Release

Plotting excipient concentration (%) vs. cumulative release of DMA (mg) for these samples allows the prediction of how much cumulative DMA will be delivered after 14 days to a physiological environment for a given percent composition of DMA and Excipient A or Excipient B cured into MED-4840 (Figures 1 & 2).

DISCUSSION

The release of the drug DMA from a silicone matrix into a sodium phosphate saline buffer solution at 6.0 pH is dependant on several factors. Some of these factors are DMA quantity, excipient type, excipient quantity, physical properties of the silicone matrix, surface area, and temperature. While this experiment was designed to limit these variables (using a constant temperature

TABLE 3

Calculated %DMA	%Excipient A	Average %DMA from Assay
5	0	4.74
5	5	4.72
5	10	4.68
5	15	4.72
5	20	4.51
10	0	9.32
10	5	9.46
10	10	9.48
10	15	9.31
10	20	9.03
20	0	18.46
20	5	18.1
20	10	18.32
20	15	18.72
20	20	18.66

DMA With Excipient A Assay Results

TABLE 4

Calculated %DMA	%Excipient B	Average %DMA from Assay
5	0	4.74
5	3	4.43
5	6	4.59
5	9	4.80
5	12	4.51
10	0	9.32
10	3	9.15
10	6	9.06
10	9	9.21
10	12	9.23
20	0	18.46
20	3	18.68
20	6	18.32
20	9	18.89
20	12	18.41

DMA With Excipient B Assay Results

water bath, etc), it is hypothesised that one dynamic factor is surface area. As DMA and excipients are released from the silicone matrix, voids may be left in their place (Figure 3).

The presence of these voids would effectively increase the surface area of the loaded silicone sample, which in turn would expedite the release of the remaining DMA and excipients. This is an example of just one of the dynamic variables that affect the release rate of a soluble substance embedded in a silicone matrix. Other unknown factors affecting DMA release are sample homogeneity, and the size of DMA aglomerates present in the silicone matrix.

CONCLUSION

This experiment has revealed several trends that are useful for predicting the availability of DMA from a cured silicone matrix into a sodium phosphate saline buffer solution at 6.0 pH over 14 days. As expected, the more DMA that is present in the silicone, the more DMA that will be eluted into the solution. Also, increased excipient concentrations in silicone samples lead to increased DMA elution into a sodium phosphate saline buffer solution at 6.0 pH. However, two expections to this trend were observed in this experiment. Both exceptions occurred at the lowest levels of loading: 5% Excipient A and 3% Excipient B. In these instances, silicone samples with 10% DMA eluted more DMA into a sodium phosphate saline buffer solution at 6.0 pH than silicone samples with 20% DMA. ◆

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BIOGRAPHIES

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Robert Kivlin has worked in Quality Assurance at NuSil Technology since 2001. He is an ASQ-certified Quality Engineer and earned his Bachelor of Science in Biochemistry from the University of California, Santa Barbara.

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The Second Quadrant

Diffusion of Innovation & the Adoption of Solubilization Technologies: Observations of Trends & Catalysts

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

Diffusion processes of new and innovative products and services have been studied extensively for nearly 45 years, although most of the research has focused on consumer markets. It seems reasonable that we might learn from others' experiences and observations, and the frameworks they've developed to model diffusion of solubilization technologies. Guiding drugs with poor bioavailability through the labyrinth of discovery, development, and clinical trials into the market is challenging enough, so borrowing any insights that might help us navigate, interpret, or even predict change might simplify our task, or at least give us a glimpse of what to expect moving forward.

The last article in this series on innovation diffusion (Drug Development & Delivery, April 2014) discussed some of the barriers to change, including the concept of "lock-in" developed by Arthur in the late 1980s.[1] The famed economist observed that in spite of cost or performance advantages of superior technological solutions, decision-makers can be strongly influenced by the dominance of a technology or methodology. However, other influencers (market shifts, regulatory bodies, and incremental or disruptive innovations) can come into play to overcome the momentum of the status quo, and can have significant impact over the rate of change.

Taking an example from the automobile industry, some of us remember when seatbelts were optional (or non-existent), and for many, "buckling up for safety" was even annoying. From the 1930s founding of the Automobile Safety League of America, and the creation of the National Transportation Safety Board 37 years later, regulatory bodies guided by lobbyists and the public imposed rules and regulations that have redirected the trajectory of automobile and road design. Since the early 1960s, regulations have significantly impacted safety features of cars and how highways are built, in spite of the predominant opinion in the 1970s that auto accidents were primarily attributable to "crazy drivers." Difficult as it may be to objectively assess or quantify driver behavior and its contribution to accidents, throughout the past 40 years, automobile-related fatalities (rate per vehicles registered and vehicle distance travelled) have steadily declined.[2]

THE RATE OF INNOVATION ADOPTION

In addition to today's preponderance of insoluble molecules, other ecosystem interactions and dynamics can serve as catalysts to alter the path of the acceptance and utilization of solubilization technologies. In Everett M. Rogers book, Diffusion of Innovations, he proposes categories of variables that determine the rate of adoption of an innovation.[3] Borrowing from his work, I'd like to propose an abbreviated version in terms of variable categories (three vs. his five), and alter them to apply more directly to our industry and more specifically to adoption of solubilization

FIGURE 1

Variables influencing solubilization innovation adoption.

technology. The three main variable categories: 1) types of decision-making entities; 2) perceived attributes of innovation; and 3) communication channels (Figure 1). While these categories are highly interdependent, it's useful to note them in isolation and then explore the momentum they have created collectively that is driving progress in solubilization of challenging molecules.

DECISION-INFLUENCERS

The first category is of course an essential and extremely influential one in our industry, consisting of the FDA and other federal and state agencies that regulate pharmaceutical companies along with numerous industry associations, key industry players, the public, and lobbyists. These key influencers of course include the American Association of Pharmaceutical Scientists (AAPS), the International Society for Pharmaceutical Engineering (ISPE), and the Pharmaceutical Researchers and Manufacturers of America (PhRMA). The boundary conditions these entities create (rules, guidelines, and recommendations) have significant impact on the success from formulation development through manufacturing of all drug products. A specific example of this type of influence in the solubilization of drugs is the adoption of the Biopharmaceutics Classification System (BCS). This framework and subsequent waivers for in vivo bioequivalence (BE) testing that reference it are providing access to cost efficiencies in utilizing various solubilization technologies and excipients to address insoluble and impermeable molecules.[4] Quality by Design (QbD), while not specifically addressing solubilization, is another example of boundary conditions that add discipline to achieve right-first-time results and can be leveraged for bioavailability efforts.

PERCEIVED ATTRIBUTES

The second category, perceived attributes, can contain benefits or advantages that accrue based on the entities that influence the desirability, economic barriers, or acceptance, as previously noted. The main variables considered in this category are: advantages (time, cost, efficacy); familiarity (or compatibility with existing processes); accessibility or doability; and the ability to test and validate.

With respect to familiarity and doability, some of today's solubilization techniques have been in existence for over a century. For example, micronization has its earliest roots as manual mortar and pestle, dating back to 35,000 BC, and finding early use in drug processing with the Wedgwood system in 1779. Micronization as we view it today for improving bioavailability started appearing as a pharmaceutical manufacturing process in the late 1960s.[5] Spray-drying first emerged as an industrial process in the late 19th century, and the concept of solid dispersion as a method to increase the dissolution and oral absorption of poorly water-soluble drugs was proposed in 1961.[6] By 1983, the two technologies were merged, and first detailed accounts of spray-drying amorphous solid dispersions for solubilization enhancement were published.[7]

I hypothesize that the fact that these techniques were familiar and in use by other industries has contributed to the perception of achievability. In addition, the fact that the technologies could be readily tested and validated with observable improvements was critical to the early success. But perhaps the strongest driver in considering and then adopting solubilization platforms - and the perceived attribute of the potential benefits that they can accrue - has been the information that has been proliferated through the industry's communication channels.

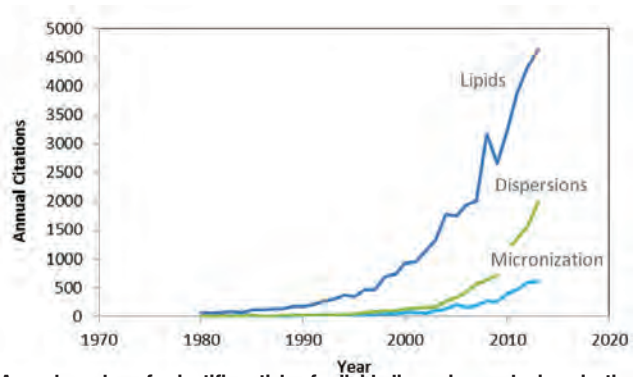
COMMUNICATION CHANNELS

The importance of peer-to-peer conversations in the spread and adoption of innovation may be one of the most crucial in scientific endeavors, and from our data analysis, it appears to apply solubilization technology adoption as well.[9] The dispersion of knowledge itself serves as a form of infrastructure required to build a network supporting the acceptance of emerging platforms. To analyze and perhaps even predict the proliferation of solubilization technologies, we have conducted a study of the literature (articles and citations) for lipid, micronization, and solid dispersion platforms. We acknowledge that other technologies exist to address poorly soluble molecules, but for this study and the sake of expediency, we limited our analysis to these three.

Our analysis indicates that solubilization technologies, in particular lipid and dispersion platforms, are in a rapid growth stage (Figure 2, a plot of the literature and citations for three technologies).[10] Another study Agere performed and presented on the number of approved solubilized drugs (*Drug Development & Delivery*, March 2014) reflected a similar trend, with lipids and solid dispersion technologies combined accounting for nearly 80% of all such drugs since 1980.

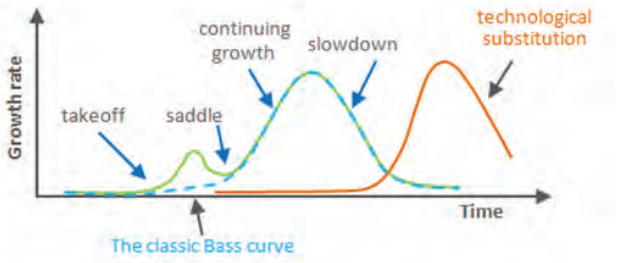
Both analyses reveal noticeable interruptions to a smooth curve when plotting the data. To begin to interpret these "bumps," we again borrow from theories of diffusion of technology and new product growth models that have typically been used to describe, interpret, and predict behavior in consumer markets and industries other than pharmaceuticals.

FIGURE 2



Annual number of scientific articles for lipid, dispersion, and micronization bioavailability-enhancing delivery technologies.

FIGURE 3



Turning points in adoption of solubilization technologies.

THE BUMPY ROAD OF INNOVATION DIFFUSION

In April's column, the classic Bass framework developed in 1969 was presented, along with the types of change agents responsible for the path of diffusion of innovation developed by Rogers in 2003.[11,12] The catalysts influencing those who drive the acceptance and adoption of new methods of behavior (the entities, perceived advantages of change, and methods by which information is propagated) have been proposed in this article. When researching data on literature, patents, and finally adoption of solubilization technologies as evidenced by FDA-approved drugs enhanced for improved bioavailability, smooth curves indicating a trend toward a symmetric bell curve of a Gaussian distribution are not at first obvious. And this isn't surprising, especially given that our segment of the industry (relatively speaking) is still at the pioneering stage with only around 6% of all NMEs approved since 1970 utilizing solubilization technology.[13-18] Borrowing from the experience and extensive analyses that have been undertaken in other industries, we can expect a somewhat bumpy path toward maturity of today's technologies, along with an emergence of new innovations offering viable and competitive alternatives.

TAKE-OFFS & SADDLES

The classic smooth innovation adoption curve doesn't capture what researchers in the field of marketing have referred to as "take-offs" or points at which a steep climb in utilization is observed and "saddles," where there may be a significant and brief drop-off before innovation diffusion resumes its climb. Figure 3 borrows from work done between the late 1990s through 2002 that defined, described, and analyzed turning points in product lifecycles.[19,20] We believe it could be useful to borrow this framework to explain turning points in the diffusion and adoption of solubilization technologies.

With respect to literature related to lipid technology, the take-off stage appears to have occurred lipid in the mid-1990s, with a saddle around 2010; during those same periods, FDA approvals of drugs using lipid technologies also climbed between the mid-1990s through the mid-2000s, with a leveling since 2010. Solid dispersions' literature experienced a take-off in the early 2000s, and hasn't experienced a saddle. FDA approvals is yet tracking with an apparent take-off around 2005 and continuing through 2013, based on available data.

Simple correlations can be thought-provoking. But much more analysis to understand better what the key catalysts are is underway. In the solid dispersions space, for example, the groundbreaking work of Chiou and Riegelman in 1971 surely was a foundation for the take-off in literature that was in this field nearly 30 years later.[21] Can we quantify the impact (if any) the introduction of BCS classification system and biowaivers of BE studies had on the rate of adoption of solubilization technologies? And will the fast-tracking of promising drugs that qualify under The Orphan Drug Act (1983), while not addressing insoluble molecules directly, be a contributor to the diffusion rate of solubilizing platforms?

At a more global level, understanding the role regulatory bodies have had in other markets and industries could enable us to weigh more heavily or to discount lessons learned from the research conducted throughout the past half century on technology adoption. Given the large ecosystem and complexity of the pharmaceutical industry as reflected in the effort and time required to move drugs from development through FDA approval, I welcome any insights you might have as we try to understand the dynamics at play with respect to the diffusion of solubilization innovations. ◆

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Incorporating Patient-Centric Design Into a Novel Anti-Needlestick Safety Device

By: Sarah Baer, MBA

Historically, safety devices have been primarily added to prefilled syringes to meet anti-needlestick legislation around the globe. Today, we see a growing number of biotechnology drugs in pharmaceutical company pipelines that require devices to meet both healthcare practitioner and self-injecting patient needs. For example, patients with chronic diseases often suffer from impaired dexterity, making it difficult to perform an injection. And, many biologics have more complex properties, which make them harder to inject subcutaneously. Therefore, the design of a safety device to support biotechnology drugs must be able to address these requirements.

FIGURE 1

The BD UltraSafe Passive™ Needle Guard

NEEDLESTICK SAFETY TODAY

The exposure of healthcare practitioners to bloodborne pathogens as a result of injuries caused by needlesticks are of a significant public health concern. The US Centers for Disease Control and Prevention (CDC) has estimated the number of sharps injuries in healthcare to be approximately 600,000 each year, with about half of those injuries occurring in US hospitals.[1,2]

Given the high incidence of needlestick injuries, we have seen an increase in legislation on a global scale. In 2000, the US enacted the Needlestick Safety and Prevention Act; in 2008, the Province of Ontario passed 474/07; Brazil passed rule Norma Regulamentadora NR32 in 2005; and Portaria MTE N.° 939 in November 2008 with a deadline to implement in October 2010.[3-5] The EU passed a mandate 2010/32/EU that requires all EU member countries to address the danger of accidental sharps injuries (including needlesticks) by enforcing this legislation beginning May 13, 2013, and as a result, many member countries have passed new legislation.[6] For example, Austria, Belgium, Finland, Germany, Hungary, The Netherlands, Norway, Poland, Slovenia, Spain, Sweden, and the UK have all subsequently finalized and passed needlestick safety legislation to support the May 2013 deadline. It is also anticipated that this increase in legislation will impact the

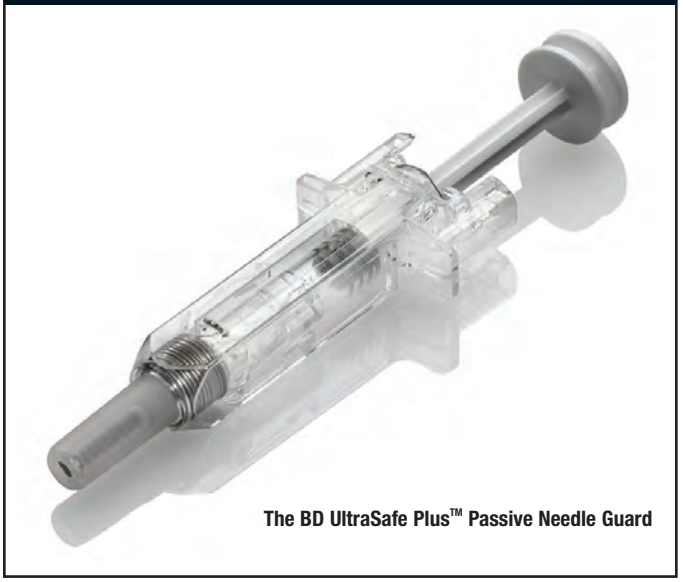
presentation of injectables, especially those in prefilled syringes as although it does not specifically target the pharmaceutical manufacturer, many pharmaceutical companies are using this as an opportunity for brand differentiation as they are seeing value in offering safer injection presentations for end-users.

During a recent onsite seminar at the headquarters for BD Medical-Pharmaceutical Systems in Le Pont de Claix, France, Mrs. Stephanie McCarthy, a registered nurse from the Derby Hospitals NHS Foundation Trust in the UK emphasized the importance of hospital worker safety legislation to protect both healthcare workers and patients. Mrs. McCarthy also spoke regarding the costs for implementation of needlestick safety in the workplace and how they far outweigh the monetary and psychological costs of not introducing safety-engineered medical devices in the hospital.

INTUITIVE SAFETY DEVICE DESIGN

Several studies have confirmed that the safety aspect of an injection device is highly valued with nurses and self-injecting patients, and preferred over a bare prefilled syringe.[7] However, it is very important that the correct device is selected. A passive safety technology has been shown to be the most effective as demonstrated by the Tosini study, a 2010 study conducted by GERES (Groupe d'Etude sur le Risque d'Exposition des Soignants), which confirmed that passive, fully automatic safety devices offer better protection against accidental needlestick injuries.[8] The BD UltraSafe Passive™ Needle Guard (Figure 1) uses an innovative passive safety technology. The superiority of the passive safety technology arises because most needlestick injuries happen in the few moments after needle withdrawal.[9] Because of this, it is critical that the needle is shielded right after the injection. Any extra steps required by the user may result in no activation of the safety mechanism, resulting in an unshielded and potentially infectious needle until disposal.

FIGURE 2



The BD UltraSafe Plus™ Passive Needle Guard

SUPPORTING BIOLOGICS

The growth in the biologic segment, estimated at $176.4 billion in sales for 2012, is driving the need for novel delivery systems.[10] The majority of the over 550 biologics in development are monoclonal antibody therapies targeting chronic and auto-immune diseases, such as rheumatoid arthritis (RA), psoriasis, or multiple sclerosis (MS).[11] These biologics are typically administered by a subcutaneous injection by the patient or caregiver at home rather than at a clinic or doctor office. This provides convenience for the patient while also reducing healthcare costs.

Many self-injecting patients suffering from chronic diseases may also suffer from reduced dexterity, making self-administration especially difficult. Self-injecting patients are trained when they receive treatment for the first time; however, intuitiveness and ease-of-use are essential factors in overall injection device design. To address this, many devices are provided in a variety of designs and different activation mechanisms to suit patient requirements.

In addition, biotech drugs, specifically monoclonal antibodies, can be quite viscous, which can then make them even more difficult to inject. This is especially true for patients who suffer from debilitating disease, such as RA.

FIGURE 3

The BD UltraSafe Plus™ Passive Needle Guard is Intuitive & Easy to Use

Furthermore, biologics often are administered in varying doses and volumes, requiring that the injection device design be able to support a range of fill volumes.

BD ULTRASAFE PLUS™ PASSIVE NEEDLE GUARD

BD Medical-Pharmaceutical Systems, Safety has developed a novel injection device, BD UltraSafe Plus™, based on the clinically proven BD UltraSafe Passive™ Needle Guard platform. The BD UltraSafe Passive™ Needle Guard, designed primarily for use in a clinical setting, has been marketed for over 12 years and successfully commercialized with over 30 different drugs.

The design of the BD UltraSafe Plus™ Passive Needle Guard (Figures 2 & 3) is to specifically support biotechnology drugs and provide improved handling, especially for those patients who prefer manual injection control. Specific features include the following:

- Extended built-in finger flanges and ergonomic plunger head provide a better feel for manual injection by the self-injecting patient (Figure 4).
- Robust plunger rod supports injection of viscous drugs.
- Larger drug inspection window improves drug visibility.

PATIENT-CENTRIC DESIGN

Many patients have different requirements depending on their technique, injection site, and dexterity impairment. Therefore, there is not always a single device that meets all end-user requirements. BD offers many options for self-injecting patients, including the BD Physioject™ Autoinjector for patients who prefer automatic injection as well as the new BD UltraSafe Plus™ Passive Needle Guard for patients who may prefer more manual control over their injection. BD incorporates a rigorous human factors and patient-centric design approach to meet the needs of healthcare providers, patients, payers, and pharmaceutical companies.

The overall design of the BD UltraSafe Plus™ Passive Needle Guard was validated by performing handling studies with both nurses and self-injecting patients. In June 2012, a large clinical focus group was performed, which included 500 injections by self-injecting patients and nurses. Patients in this study suffered from RA, MS, cancer, Crohn's, and asthma. These diseases can have very different effects on dexterity, thus it was important to test the design with a broad range of patients.

Results from the user study confirmed that the BD UltraSafe Plus™ Passive Needle Guard was intuitive and easy to use with a 100% activation success rate for all 500 injections.[12] In addition, the added design features, such as the wider finger flanges and ergonomic plunger rod, were positively received by all users in providing additional

injection support.

The results of the user study not only supported the added design features, but also the ability of BD UltraSafe Plus™ Passive Needle Guard to provide additional support in injecting drugs of higher viscosity. All users preferred to inject viscous solutions using BD UltraSafe Plus™ Passive Needle Guard than a standard prefilled syringe.[13]

ADD-ON FINGER FLANGES FOR INJECTION SUPPORT

The BD UltraSafe Plus™ Passive Needle Guard was designed with extended finger flanges to accommodate one full finger on each side of the device. There are, however, some patients who may prefer even wider finger flanges to support their injection. Given this requirement, BD Medical-Pharmaceutical Systems will offer specific add-on finger flanges to support the BD UltraSafe Plus™ device. Moreover, the design of this add-on finger flange will take into consideration particular shapes and textures that are perceived differently across various patient populations allowing for more disease-specific designs.

SUPPORTING MANUFACTURING CAPABILITIES

After the design of the BD UltraSafe Plus™ Passive Needle Guard was confirmed, we consulted with leading automation machine builders to ensure assembly of the BD UltraSafe Plus™ Passive Needle Guard was compatible with minimal modifications to existing or planned secondary packaging lines for the BD UltraSafe Passive™ Needle Guard device. The BD UltraSafe Plus™ Passive Needle Guard is designed to be used in conjunction with 1.0-mL long prefilled syringes with staked needles, such as the BD Hypak™ or BD Neopak™ Glass Prefillable Syringe.

The BD UltraSafe Plus™ Passive Needle Guard received 510(k) clearance as an anti-needlestick safety device in April 2013 and was commercially launched by a pharmaceutical company in 2013.

FIGURE 4

The Ergonomic Features of the BD UltraSafe Plus™ Passive Needle Guard Provide Injection Support

SUMMARY

The market for biotechnology drugs continues to grow, and there is a need for pharmaceutical companies to offer injection devices that support both the complex properties of the biologic as well as the needs of the end-user who will be performing the injection. Patients, especially those with limited dexterity, have very specific needs and requirements for the injection device. Providing a prefilled syringe with a safety device specifically designed for patients who prefer manual injection control and for drugs with higher viscosity provides pharmaceutical companies with a viable option that supports both of these requirements. ◆

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BIOGRAPHY

Sarah Baer is currently the Marketing Product Manager at BD Medical – Pharmaceutical Systems, Safety (formerly SafetySyringes, Inc.) with over 10 years of experience in the Biotechnology and Pharmaceutical industries. Before joining BD, Ms. Baer was a Senior Product Manager at Teva Pharmaceuticals in Irvine, California. Ms. Baer earned her MBA at San Diego State University and her BSc Biochemistry at McMaster University in Hamilton, Ontario, Canada.

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COLON-SPECIFIC DELIVERY

Toward Reliable Colon-Specific Drug Delivery

By: Wilfried Andrä, PhD, Pieter Saupe, and Matthias E. Bellemann, PhD

INTRODUCTION

Targeted drug delivery in the digestive tract had long been a desired goal. To date, drug release triggered by pH value, time, enzymes, or intestinal pressure is standard practice. Unfortunately, such physiological triggering suffers from ill-defined parameters, which may vary considerably from individual to individual, and also depends on a patient's state of health.[1]

There is, however, an alternative approach: remote controlled drug release (RCDR). More than 30 types of capsules that might be suitable for RCDR can be found in the literature.[2] However, only the Enterion™ capsule has been used in practice.[3] Although the capsule has been widely applied in numerous Phase I clinical studies, to date, one important problem has yet to be solved: the accurate localization of the capsule to find the correct position for drug release. To localize the Enterion capsule, the time-consuming procedure of scintigraphy has to be utilized. This technique, however, is costly and its application restricted to healthy volunteers.

Recently, a novel capsule, the IntelliCap, was developed and tested.[4] It is claimed that the IntelliCap can determine its own local position by measuring the pH value of the environmental intestinal fluid. For this purpose, two instants of time are recorded. The first one takes place when the pH value significantly rises at the transition from stomach to duodenum. The other one shows the less-significant change at the transition from small intestine to colon. The accurate capsule position in the small intestine is determined by interpolating between these two points. In the colon, however, the capsule position cannot be determined at all. It is precisely at that location, however, that RCDR is particularly interesting. Therefore, a suitable localization method for the RCDR capsule remains an urgent requirement.

MAGNETIC LOCALIZATION OF CAPSULES IN THE GASTROINTESTNAL TRACT

In gastroenterology, magnetic capsule tracking has been used since about 1990, particularly to observe the motility in the digestive tract. For that purpose, the magnetic field of a small magnet (marker) incorporated in a capsule is measured. Usually, the marker is magnetized parallel to a fixed direction with respect to the capsule. The magnetic field (H_D) of the marker penetrates the human tissue and can be measured outside the body, for example, by a three-axis magnetometer. Conversely, the strength and direction of the measured field can be used to calculate the capsule position. Because those values depend not only on the position but also on the orientation of the capsule, the mathematical procedure calls for measuring H_D at more than one point. For this purpose, up to 300 sensors have been used in earlier investigations.

Even more troublesome is the fact that in addition to H_D, there is a background field. It is normally stronger than H_D and may considerably vary as function of space and time. Already, it has been shown that the displacement of an office chair or even the traffic on a nearby road may cause serious disturbances.[5]

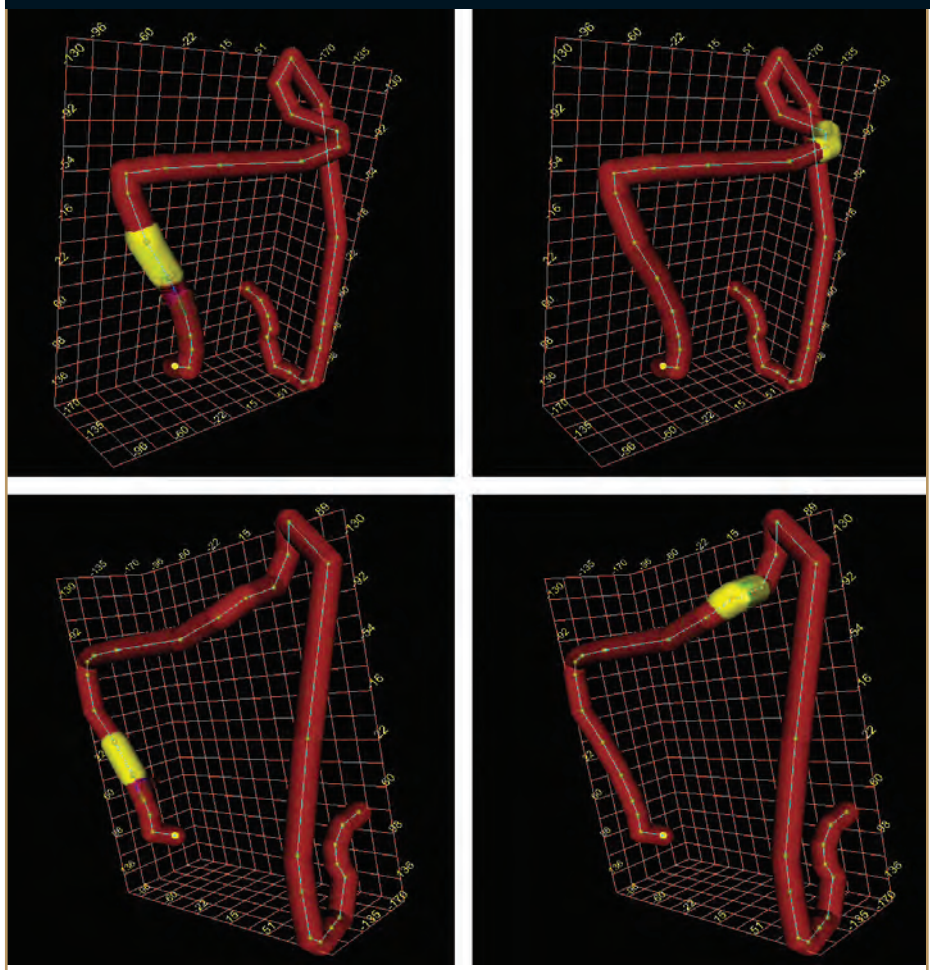
Nevertheless, the mentioned difficulties can be overcome. One of the first successful studies was performed by Weitschies et al who used 37 sensors.[6] The background field was almost

completely excluded by measuring in an extremely well- shielded room. This technique is very expensive and cannot be applied to routine investigations in normal medical laboratories.

Recently, the aforementioned problems were circumvented by a novel monitoring principle. It uses a small spherical marker that can freely rotate in a liquid bearing integrated in the capsule. This marker consists of permanent magnetic material (NdFeB) and can be aligned like a compass by an externally applied field H_p of known direction and moderate strength. Hence, the marker orientation is known, and its position can be found by a straightforward calculation.[7] An initial preclinical study was performed with a stationary installation and confirmed the proper operation of this novel monitoring principle.[8] Recently, the technique has been improved and can now be applied with a small unit carried on the belt of the examined person. This technique was tested with a natural-size phantom of the large intestine.

Figure 1 shows the capsule position in 3D representation for two different situations. The viewing line is directed from the top left (upper row) and from the top right (lower row), respectively, and can be changed during the examination. The yellow segments show the actual capsule position in the Colon Ascendens (left hand side) and near the Flexura Sinistra (right hand side), respectively.

FIGURE 1



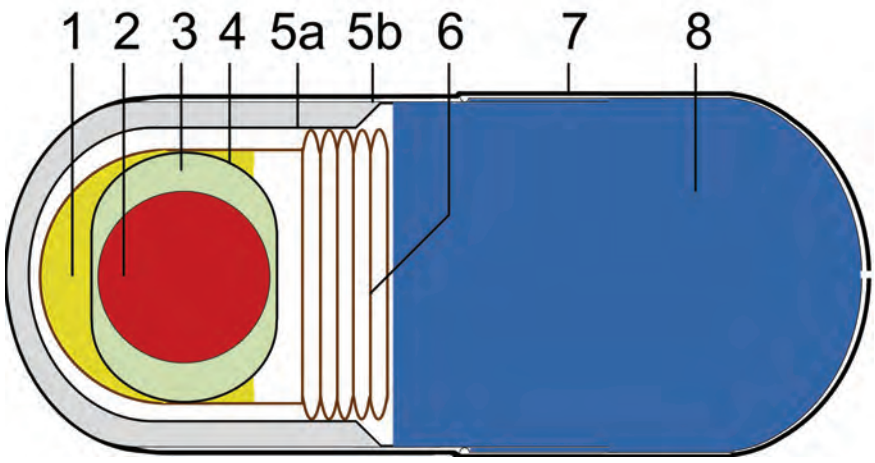
Traces of the capsule passage through an adult-sized phantom of the large intestine (front view).

MAGNETICALLY INITIATED DRUG RELEASE

The spherical magnetic marker additionally offers a particular advantage. It not only can be used for capsule monitoring, but can also be applied to trigger the drug release. For this purpose, the pulsed field (H_p) of the localization procedure is switched off as soon as the capsule has reached the predetermined delivery position. Then a rotating magnetic field is switched on. This field continuously turns the marker sphere and causes ejection of an agent from the capsule, for example, by means of the generated heat of friction. The rotating field can be generated by a small cylindrical magnet that is turned by a small-sized electric motor (power < 50 W; rotational frequency < 400 Hz).

Figure 2 shows schematically an example of the experimental capsule. Capsule parts are denoted with numbers in round brackets. The marker (2) can freely rotate in a liquid bearing (3, 4) and is turned by a rotating magnetic field of moderate strength (not shown in the Figure). A low-boiling liquid (1) is heated above boiling temperature by the friction of the rotating marker. The evaporating liquid expands a swelling bag (6) and expels the agent (8), which in this case must be an anhydrous liquid, out of the container. A

FIGURE 2



Scheme of a capsule designed for remote controlled drug release.

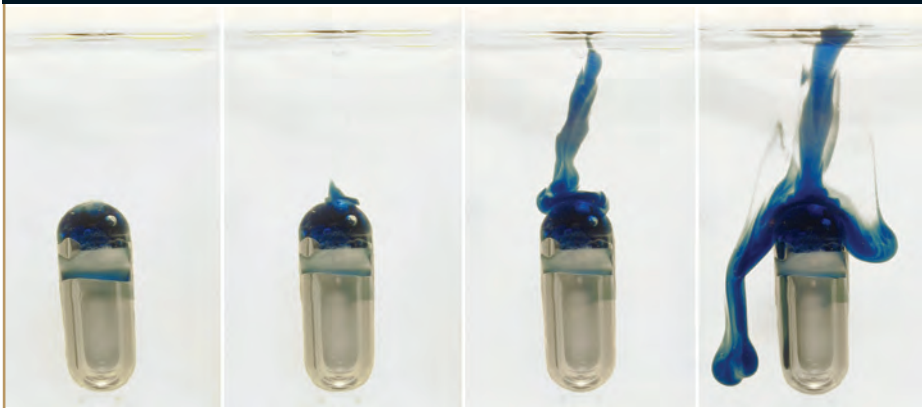
double wall structure (5a, 5b) serves as thermal insulation that prevents heat from dissipating. The outer capsule shell (5b) consists of hard gelatin. Its outer surface is protected by a film (7), for example, made of ethyl cellulose, against the aqueous environment. The external dimensions correspond to those of the standard capsule size 000 (length = 28 mm; diameter = 9.9 mm).

It should be pointed out that all capsule parts, except the sphere, are biocompatible. The property of the sphere material (NdFeB) is unknown in this respect. However, it is well protected by a multi-film coating consisting of Ni-Cu-Ni-Au and additionally encased in the bearing capsule (4) and the bag (6).

The size of the capsule is similar to those used for capsule endoscopy. Therefore, the risk of capsule retention must be taken into consideration.[9] In order to overcome this hazardous feature, the outermost capsule wall is made of hard gelatin and is protected against the aqueous intestinal fluid with a suitable film on its outer surface. In cases in which retention may be feared, drug delivery is initiated. Then, after ejection of the drug, the aqueous intestinal fluid is pulled into the agent container and dissolves the wall from the inside. Afterward, the capsule collapses, and the passage through the digestive tract remains problem-free.

The functioning of this capsule type was tested many times in vitro and published in 2009.[10] Figure 3 shows a typical picture sequence taken during the release of a model drug (edible oil colored with Sudan Blue). The left-most picture of the sequence shows the capsule before the rotating field was started. In this state, the model drug is only partially visible. The main part is hidden by the previously described double wall structure. The other pictures were taken at intervals of about 30 seconds. The total drug release took about 2 minutes. More than 70% of the agent was expelled within a period of about 20 seconds.

FIGURE 3



Magnetically triggered release of a model drug.

CONCLUSIONS

The greatest obstacle on the road to targeted drug delivery in the GI tract was, until now, the lack of a practicable method to localize the capsule. Reliable capsule localization is indispensable in order to find the correct administering site. This barrier could be overcome by applying a novel method of magnetic monitoring conceived and developed by our group at the University of Applied Sciences, Jena, Germany. This method has reached the state of preclinical studies.[8]

Furthermore, we developed novel capsules that are suitable for remote controlled drug release. During the

corresponding investigations, it was found that the spherical marker used for localizing can additionally be utilized to trigger the release of agents at a predetermined site. This fact enabled a radical simplification of RCDR capsule construction. Numerous laboratory experiments confirmed the operational reliability of the novel capsule type.[10]

The next step has to be taken by a company able to produce prototypes or demonstration models for trade fairs and exhibitions. Our knowledge gained in recent years ensures that prototyping requires a small amount of effort and only moderate technical means. Prototypes have to be produced to demonstrate the operational reliability of the novel system and thus to win over investors or companies suited to carry out the process of clinically testing and putting the system onto the market.

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BIOGRAPHIES

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Pieter Saupe is a Diploma Engineer at the Ernst-Abbe University of Applied Sciences in Jena, Germany. He has nearly 15 years of experience in monitoring of magnetic markers.

Prof. Dr. Matthias Erich Bellemann has been a full Professor in the Department of Medical Engineering and Biotechnology at the University of Applied Sciences in Jena, Germany, for more than 15 years. He earned his PhD from the Max-Planck-Institute of Experimental Medicine in Heidelberg, Germany. His main research field is the development and application of functional and molecular imaging techniques.

INJECTABLE MICROEMULSIONS

Prolonged-Release Injectable Microemulsions: Opportunities for Pain Treatment

By: Rajesh Dubey, PhD, and Luigi G. Martini, FRPharmS, MBA

ABSTRACT

Recurrent pain in several conditions demands repeated oral or parenteral dosing. However, available therapies do not provide palliative care without limitations. For example, oral treatment efficacy demonstrates significant dose-response variability leading to non-response in several cases. Injectable formulations have their own challenges. Novel formulations that can provide prolonged release promise to bring significant benefits for both-modes of drug delivery as well as treatment of pain. However, available technologies do not support development of such formulations due to challenges associated with complex development and manufacturing procedures, limited excipient and process options, as well as high cost for the finished product. Microemulsions with their unique features can provide a viable alternative to develop such formulations.

INTRODUCTION

The International Association for the study of pain (IASP) defines pain as an unpleasant sensory or emotional experience associated with actual or potential damage. While pain has been classified into acute or chronic pain (lasting for more than 12 weeks), both may be equally debilitating in nature, especially when they persist beyond 24 hours. As per the American Academy of Pain Medicine, 26% of Americans aged 20 years or older, and 30% of those between 45 to 64 years, reported pain that lasted for more than 24 hours.[1] Hence, while chronic pain patients need long-term medication, even acute pain patients often need medication for more than 1 day. Various approved analgesic medications are used based on the type of pain, as well as other factors, which include severity of pain, pathological condition associated with pain (eg, malignant or non-malignant pain, postoperative pain, headache), and the age of the patient (eg, patients older or younger than 65 years). For example, the WHO 3-step analgesic ladder for treating cancer pain suggests initiating treatment with oral non-opioids administered every 3 to 6 hours (ie, by the clock rather than on demand).[2] However, opioids are the first-line treatment for acute postoperative pain, and are very often used in the form of patient-controlled analgesia (PCA).[3]

These different requirements have led to the development of a variety of formulations other than conventional immediate-release solid oral and injectable formulations for various analgesic agents, eg, orally disintegrating tablets, transmucosal lozenges, extended-release tablets/capsules, prefilled syringes, and so on. Each of these specialized formulations has unique features in terms of dosing convenience, speed and extent of absorption, onset, and duration of action. However, there are still significant unmet needs as evident by the continuous effort to develop better products. For example, a single dose of Exparel®, a liposomal formulation of bupivacaine, was approved in 2011. The formulation administered locally into the soft tissues at the surgical site provides effective analgesia for up to 72 hours in contrast to the non-liposomal formulations, which need to be injected every 3 hours. However, the employment of the complex technology platforms makes new product development and manufacturing challenging, or adds to the product cost significantly, or fails to meet

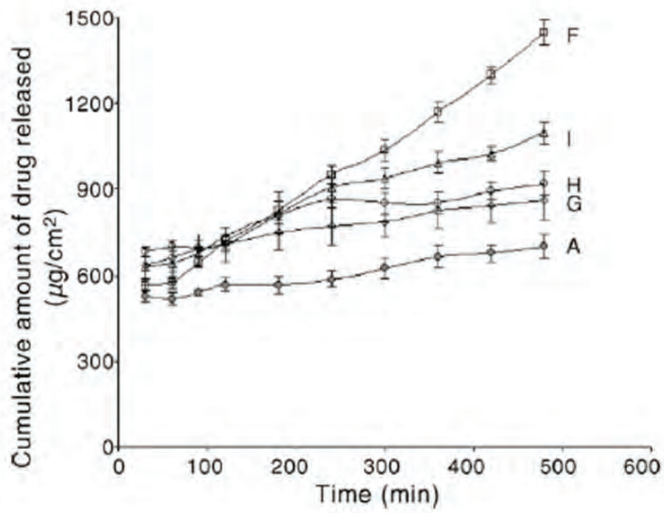
desired safety/efficacy norms. In the case of Exparel, its cost may be viewed as significantly high ($285 per 20-ml vial) compared to non-liposomal formulations ($10 to $15 per 20-ml vial). Depodur®, an intramuscular (IM) injectable formulation of extended-release liposomal morphine sulphate, was withdrawn due to incidence of adverse events and higher cost ($327 to $491 per dose compared to morphine sulphate injection at $1 per dose). Thus, while new improvised formulations are required for delivering effective pain treatment, it is also important to use a technology that is technically as well as commercially viable.

Microemulsions, comprising an oil phase, aqueous phase, and surfactant/cosurfactant phase, are spontaneously forming isotropic monophasic systems. Their unique features combined with the ability to maneuver their functional performance makes them a promising technology to design prolonged- release injectable formulations.[4] While injectable microemulsions have been evaluated primarily for the intravenous (IV) route, the subcutaneous (SC) and IM routes will enable prolonging in vivo drug release beyond 24 hours, and potentially for multiple days similar to Depodur or Exparel.[5-7]

INJECTABLE THERAPIES FOR MODERATE-TO-SEVERE PAIN: PREVAILING TREATMENT MODALITIES & CHALLENGES

The majority of moderate-to-severe pain conditions are treated with non-steroidal anti-inflammatory agents (NSAIDs), opioid agents, or anaesthetic agents. Use of injectable formulations is often preferred in severe pain conditions due to fast onset and a more consistent response compared to oral formulations.[3] Table 1 shows the top injectable analgesic drugs as per the total units sold in the year 2012. The table also shows elimination half-life and dosage regimen for the drugs in respective formulations. As can be seen in the table, most of these drugs have elimination half-lives in the ranges of 2 to 3 hours, indicating their analgesic effect would vanish rapidly after injection. This short half-life necessitates repeated dosing (which may be as much as 3 to 4 times a day as evident by the dosing regimens shown in the table) or infusion to realize adequate analgesia. Injectable drugs are often considered as first-line treatment for moderate-to-severe pain conditions.[3] However, the burden associated with their frequent administration, patients' needle-phobia, clinical visits, need of getting treatment in in-patient set-up, and consequences of missed dose often discourage patients' preference for injectable formulations. Fosnocht et al have reported that even patients suffering with severe pain prefer oral medication over injectables.[8] However, the proportion of patients opting for injectable formulations increases significantly as the severity of pain increases, indicating that patients are aware that injectable formulations would provide faster pain relief compared to oral formulations. Todd et al reported that in an emergency room setting, the majority of long bone fracture patients suffering with moderate-to-severe pain preferred the parenteral route over oral medication.[9] While patients prefer faster onset of analgesia, they also prefer treatment that results into lower adverse events and hence are often willing to trade off pain relief for less severe side effects.[10] Conventional injectable formulations

FIGURE 1



Dissolution profile of DDA from the investigated microemulsion vehicles containing various concentrations of water: 10% (A), 25% (G), 32.50% (H), 35% (I), and 60% (F). (Source: Reference 20).

TABLE 1

Generic Drug Name	$T_{1/2}$ (hrs)*	Dosage Regimen*	Units Sold in 2012
Hydromorphone	2.3	IM 1 to 2 mg every 4 to 6 hrs0 as needed.	7,101,803
Morphine	2-3	SC/IM 5 to 20 mg/70 kg every 4 hrs as needed.	6,993,204
Fentanyl	3.5	IM 50 to 100 mcg. May repeat in 1 to 2 hrs as needed.	6,588,108
Ketorolac	2.5	30 mg every 6 hrs.	5,039,824
Ropivacaine	5-6	Initial epidural block of 5 to 7 mL. Maintain analgesia with an infusion of 2 mg/mL (0.2%). Use epidural infusions up to 72 hrs.	3,710,443
Bupovacaine	2.7	(Epidural) 25-150 mg repeated every 3 hrs with total 400 mg/24 hrs.	3,342,023
Meperidine	8	IM/SC/PO 50 to 150 mg every 3 to 4 hrs as needed.	3,282,253
Sumatriptan	2.5	6 mg initially, repeat once after 1 hr max 12 mg/day.	2,483,245
Buprenorphine	2.2	IM/IV 0.3 mg deep IM or slow IV (over at least 2 mins) injection at up to 6-hr intervals, as needed. May repeat once (up to 0.3 mg) 30 to 60 mins after initial dosage, if required.	1,315,378
Acetaminophen	2.4	650-1000 mg repeated 4-6 hrs with total daily dose not more than 4000 mg.	804,469
Nalbuphine	5	10 mg repeated every 3-6 hrs with a maximum total daily dose of 160 mg	749,784

***For intravenous(IV), intramuscular (IM), or epidural injectable formulations.**

Elimination half-life, dosage regimen, and unit sales (US) of best-selling analgesic injectable formulations.

as those approved result in dose dumping, resulting into higher initial exposure and higher peak-trough fluctuation due to faster elimination. This increases the adverse events associated with injectable formulations. For example, 42% of subjects receiving Imitrex® injection (sumatriptan 6 mg) reported atypical sensation against 6% of those treated with oral Imitrex tablet (sumatriptan 100 mg). Different classes of analgesics have their own set of problems that strongly influences their choice which, in some cases, results in under-treatment, also known as oligoanalgesia. For example, opoiophobia (due to concerns related to opioid abuse as well as severe adverse events like respiratory depression) drives physicians to be over-selective while prescribing opioids, while concerns related to adverse effects, like bleeding from NSAIDs, limits their duration of use.[11] Both of these events result in oligoanalgesia.

Treatment of patients discharged from emergency rooms is also important. Patients often report similar pain intensity (ie, moderate to severe) post-discharge as that during their hospital stay, and a significant proportion of them continue the same medication they were administered in the hospital.[12] However, in many cases, patients fail to take their medications, resulting in oiligoanalgesia.

Analysis of these facts vis-à-vis pharmacokinetic (PK) and pharmacodynamic (PD) attributes of products highlight the following key points:

- Patient suffering with moderate-to-severe pain needs multiple doses for more than a day. For example, post-surgical patients may need medication up to 96 hours for adequate pain relief. While oral medications are preferred due to convenience, variable response resulting in unsatisfactory pain relief leads to discontinuation and hospital visits in several cases.

- Patients are aware that injectable formulations provide rapid pain relief. While patients prefer oral medications in general, more of them tend to use injectable formulations as the pain intensity increases. However, concerns related to the injectable route (as previously highlighted) would still limit the actual number of use.

Injectable formulations that release the drug for more than 24 hours, more preferably for 72 to 96 hours, would result in reduction of dosing frequency, higher use of injectables, and better pain relief. Recent efforts to develop products like Exparel and Depodur that serve similar objectives is the evidence of the acute need of such formulations.

POTENTIAL TO DEVELOP PROLONGED-RELEASE INJECTABLE FORMULATIONS

Microemulsions for Parenteral Delivery: Advantages

Microemulsions have several unique features. Microemulsions are thermodynamically stable systems. In simple terms, dispersed phase in microemulsion does not undergo coalescence or flocculation. This stability is achieved due to emulsifier film (comprising surfactant and cosurfactant) as well as small globule size that result in very high Brownian motion, which neutralizes the effect of gravitational force.[13] The emulsifier film is disordered and fluid due to voids created by cosurfactant molecules penetrating surfactant film.[14,15] This film has higher surface pressure compared to the surface tension between the immiscible phases in absence of surfactant.[13,16] Thus, mixing of the immiscible phases with surfactant/cosurfactant mixture, and consequent net negative interfacial tension created at the interphase leads to a spontaneous breakdown of dispersed phase (ie, phase with smaller volume fraction) into small droplets, which remain stable for its entire shelf-life. Propofol microemulsion product's mean globule size of 69.3 nm (t=0) remained stable up to 6 months at (20°C/65%RH) with the mean globule size 66.4nm at the end of 6 months.[17]

The technically simple preparation method of microemulsions is a major advantage. Emulsions or nanoemulsions often need multiple cycles of mixing, homogenization, or sonication to reduce globule size to the desired range, achieve uniform size distribution, and ensure absence of larger droplets so as to meet pharmacopoeial requirement (USP chapter <729>), which specifies that the mean globule size for injectable emulsions should be below 500 nm, while percentage of globules with size >5 microns should not be more than 0.05% of dispersed phase. Such processes are strongly influenced by the composition of the formulation.[18] In the case of microemulsions, the spontaneous (or a little external energy mediated) breakdown of inner phase to globules, which are usually below 140 nm with narrow size distribution, significantly simplifies the manufacturing procedure.

Filter-sterilizability of microemulsions is another major advantage, as other technologies, including liposomes, often need complex and costly aseptic manufacturing conditions due to large globule/particle size or higher viscosity.[19]

Prolonged-Release Microemulsions: Factors Influencing Drug Release

The typical structure of microemulsions, comprising dispersed droplets surrounded by emulsifier film in a continuous phase provides a significant barrier to drug dissolved in inner phase against its rapid diffusion to external phase. The rate of drug release from microemulsions is influenced by the factors related to the drug molecule (eg, logP, pKa, solubility, etc), type of microemulsion (o/w, w/o, or bicontinous), and proportion of the constituents. Thus, a careful selection of constituents (ie, oil, surfactant, cosurfactant), and formulation characteristics (eg, pH) vis-à-vis drug characteristics would help to modulate drug release for microemulsions. Djordjevic et al prepared w/o microemulsion containing an amphiphilic drug, diclofenac diethylamine (DDA), and adjusted the formulation pH to >7.2. At this pH, the completely ionized drug (pKa 4.87) in w/o system remained mostly entrapped in inner aqueous phase and released very slowly. However, for the same system, o/w emulsions (ie, systems containing higher proportion of aqueous phase) would release the drug at a faster rate due to the drug being in external phase (Figure 1). As most of the drugs are weak acid or base form, formulation pH often governs the release rate by influencing lipo/hydrophilicity of the drug dissolved in microemulsion.

The surfactant layer surrounding the droplets would also have a major impact on the extent of release as the film often plays a crucial role in migration of drug from the inner droplets to aqueous phase. This was demonstrated by modulating release of capric and caprylic acid using different surfactants with different hydrophilicity.[21] The nature and volume of internal phase should also be an important consideration. For example, increase in oil phase component of an o/w microemulsion containing doxorubicin resulted in significant decrease in release rate due to formation of more organized, and hence rigid, lamellar structure, which resulted in lower mobility of the drug dissolved in the internal oil phase.[22]

Selection of drug candidate also plays a very critical role, especially when solubility of the different forms of drug differ significantly. For example, an oil- soluble drug with very

high LogP and hence high oil solubility formulated as an o/w microemulsion can be expected to provide a slow and prolonged release of the drug. Salem and Hope demonstrated that using o/w formulations with a morphine base and higher lipophilicity resulted in a more prolonged and consistent exposure compared to morphine hydrochloride salt, which released faster.[23]

Advances in Development of Prolonged-Release Microemulsions

Controlled-release potential of microemulsions has been explored so far primarily for prolong residence time of drugs administered intravenously as well as to prepare formulations of highly lipophilic drugs, which can be administered as bolus. Such formulations with slow and prolonged exposure also decrease toxicity and improve efficacy. This improvement in PK leading to prolonged exposure has been ascribed to longer circulation time of drug molecules entrapped in oil droplets, which undergo slower uptake and phagocytosis by the reticuloendothelial system (RES).[24] These long-circulating oil droplets release the entrapped drug load slowly, resulting in prolonged and higher drug exposure. The consequant improvement in PK and PD can bring significant benefit in cases like post-operative pain in which patients often need to be treated with a PCA morphine pump and are prone to serious adverse events, such as respiratory depression in case of overdosing. Nalbuphine, a morphine-like kappa agonist/partial mu antagonist analgesic, is often used for treating moderate-to-severe pain. It is currently approved as a solution for injection, which can be administered by the IV, IM, or SC route. The short plasma half-life (5 hours) necessitates frequent administration (every 3 to 6 hours). A submicron formulation of nalbuphine and its prodrugs were prepared and subjected to a tail-flick test to evaluate antinociceptive activity after IV administration in tail vein in rats at equimolar dose.[24] The formulation doubled the duration of analgesia to 3 hours compared to 1.5 hours from the nalbuphine solution.

OPPORTUNITIES

Recurrent pain in several conditions demands repeated oral or parenteral dosing. However, available therapies do not provide the palliative care in the most acceptable fashion. Oral treatment efficacy demonstrates significant dose-response variability leading to non-response in several cases. For example, proportion of patients who experienced >50% pain relief after 2-week treatment with Ibuprofen and celecoxib were 29% and 30%, respectively, and the number needed to treat were 6.5 and 5.6, respectively.[25] While such high variability can be attributed to differences in pain threshold, disease severity, etc, poor and variable oral absorption resulting from difference in drug disposition during gastro-intestinal dissolution, absorption, gut wall metabolism, and hepatic clearance also play a significant role. This is evident from the fact that the lower bioavailability (22% to 40%) and 10-fold inter-subject variability in the exposure of celecoxib, the most widely used Cox-2 selective agent.[26,27] Such variability often fails to result in satisfactory pain relief in moderate-to-severe pain incidences, prompting use of injectable formulations which result in fast onset and more predictable treatment outcome. However, injectables have their own set of problems. Frequent injectable treatment inflicts pain, results in frequent clinical visits, or worse, demands in-patient treatment. Injectable formulations that provide prolonged release promise to bring significant benefit in such conditions. However, available technologies do not support development of such formulations due to challenges associated with complex development and manufacturing procedures, limited excipient and process options, as well as high cost of finished product. Microemulsions offer significant opportunities in this area. With several drugs being highly lipophilic, and hence difficult to formulate as injectables, microemulsions can be used to successfully develop injectable formulations by dissolving such drug in the oil phase. While such simple-to-develop formulations can be used similar to fast-acting IV injectable formulations (eg, Microfol) without using toxic co-solvents, by careful designing of formulation as previously described, in vitro and in vivo release of entrapped drug can be modulated to increase duration of analgesia. An SC or IM formulation would further prolong the duration of drug exposure, and can potentially sustain the drug release beyond 24 hours.

CONCLUSION

Improved, prolonged-release formulations for palliative care of patients in in-patient and out-patient care are a widely acknowledged need that has not been met. As per an IASP report, even after major advancements, 50% of patients have severe or intolerable pain after surgery, which increases risk of persistent pain after surgery.[28] Currently approved products often lack consistent efficacy and/or result in severe side effects or add a significant dosing burden. Due to these reasons, patients often discontinue the treatment or are undertreated, which results in significant social, clinical, and economic burdens.[29,30] While there is general consensus on the need of better drug delivery, available technologies often fail to support the development. Microemulsion technology needs more investigation for developing such formulations. With its various features, it is very likely to facilitate development of prolonged-release injectable analgesic formulations. ◆

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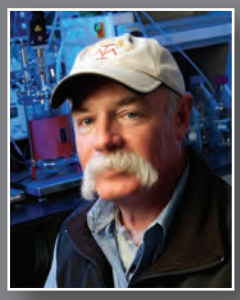
BIOGRAPHIES

Dr. Rajesh Dubey is presently working with Dr. Reddy's Laboratories Ltd (Associate Director, Business Development), where he is involved in the conceptualization and development of proprietary formulations. He is also a visiting lecturer at King's College London from where he completed his post-doctoral studies in pharmacy.

Dr. Luigi G. Martini is the CEO of Rainbow Medical Engineering Ltd, a specialist ultrasonic welding and medical device fabrication company and appointed Professor of Pharmaceutical Innovation at King's College London, where he is the UK's first and only Industrial Pharmacist teaching practitioner providing an important link between Industry and Academia. His research interests include personalized medicine, drug delivery systems, and medical device engineering. He consults for global companies and regulatory agencies in Europe and the Middle East, recently being invited to participate in European Parliament debates and appointed to the REF2014 sub-panel for Pharmacy, Dentistry, Nursing, and Allied Healthcare professionals in 2011.

DRUG DEVELOPMENT Executive

Bend Research: The Integration of Bend Research With Capsugel Dosage Form Solutions (DFS)



Rod Ray, PhD, PE
Member, Scientific & Business Advisory Board
Capsugel

"The technology range, intellectual property estate, collaborative product development approach, and internal product development pipeline differentiates Capsugel DFS from typical CRO/CDMO players. Customers can now come to one partner to develop, optimize, and manufacture robust drug or nutritional products."

Small molecules have properties that pose increasing challenges for drug formulators. These include physical properties that lead to low bioavailability, high-potency/low-dosing requirements, and the need for modifying dissolution profiles. Market drivers, such as pediatric dosing and FDA 505(b)2 filings, also require innovative solutions. These dynamics are combined with an ongoing emphasis on speed to market, minimized development costs and risk, and enhanced patent protection. Bend Research, now integrated with Capsugel's Dosage Form Solutions (DFS) business unit, has a broad spectrum of technologies for bioavailability enhancement and other key formulation challenges facing its clients, and provides integrated design, formulation, and commercial manufacture of products. Rod Ray, former Bend Research CEO and now a member of Capsugel's Scientific and Business Advisory Board, speaks to *Drug Development & Delivery* about the enhanced capabilities of Capsugel DFS and the advantages offered to companies developing new and/or enhanced medicines.

Q: How did the acquisition of Bend Research enhance the capabilities of Capsugel DFS, and how do these capabilities differ from other CROs/CMOs?

A: Bend Research is well known in the industry for its technologies, including spray-dried dispersions (SDDs) for solubility enhancement. Additionally, Bend Research has a reputation for its depth of scientific and engineering expertise, including a long history of developing new drug delivery technologies. Capsugel is the world leader in hard capsule technology and supply, with a reputation for quality and innovation in capsule product range, materials, and manufacturing technologies. In addition, formulation and commercial manufacture of liquid-fill hard capsule and soft-gel capsule products have historically been among Capsugel's core capabilities and formed the basis of the Capsugel DFS business unit, which was further augmented by the acquisition of Encap Drug Delivery in March 2013.

The subsequent acquisition of Bend Research in October 2013 has created a powerful combination with substantial synergies to the Capsugel DFS technology offering, especially in the areas of bioavailability enhancement, modified

and targeted release, and other design and formulation services. The technology range, intellectual property estate, collaborative product development approach, and internal product development pipeline differentiates Capsugel DFS from typical CRO/CDMO players. Customers can now come to one partner to develop, optimize, and manufacture robust drug or nutritional products.

Another differentiator, and shared value between Bend Research and Capsugel, is working collaboratively with the customer for the best solution to a drug delivery problem. The customer knows its drug best and often has market-driven preferences on the type of technology and final dosage form most appropriate for the target patient population. Capsugel DFS respects these preferences, and our multi-disciplinary teams work with clients to identify the best platform, based on meeting the target product profiles within the commercial parameters.

Q: Bioavailability continues as a key formulation challenge - and has always been core with Bend Research. How has this capability been enhanced with the integration?

A: The breadth of technologies, technology selection processes, and overall formulation know-how has been enhanced.

Bend Research has extensive experience, expertise, and capitalization in amorphous bioavailability-enhancement technologies. Most broadly applicable is the SDD technology, which has been used to advance numerous compounds through feasibility screening, with many advancing to Phase III and moving toward commercialization. Bend Research also has deep capabilities and understanding of hot-melt extrusion (HME) technology, as well as of attrition milled and assembled nanocrystals.

Lipid/liquid-based formulations (LBF) have long been a core technology platform and capability of Capsugel and Encap Drug Delivery, and hundreds of compounds have been advanced and commercialized. This formulation expertise is further evidenced with the development of lipid multiparticulate (LMP) technology and an expert system for accelerating LBF development.

The end result is that regardless of the compound's properties Capsugel DFS has the technology platform and experience to advance compounds rapidly to market, while also incorporating a range of modified-release profiles and finished dosage formats.

Q: Spray-Dried Dispersion Technology has always been core to Bend Research. What are the plans and capabilities now and in the future in this area?

A: For more than 20 years, Bend Research has been focused on designing and developing SDD formulations through the clinical supply stage, which can typically be accomplished in 6 months or less.

Our process experience, mathematical engineering models for process development and scale-up, capitalized scale-up train, and above all else, skillful Bend Research engineering staff, have led to a rapid, robust process-development effort. Years of engineering work devoted to understanding the SDD process have resulted in efficient scale-up efforts today, as well as efficient transfer to the GMP Phase III and commercial processes. Our deep process understanding has also resulted in a natural Quality-by-Design (QbD)-ready process. This gives our clients the option of filing a QbD regulatory document and also results in such thorough process understanding that post-approval improvements and/or troubleshooting are facile.

With the newly combined resources and expertise of Bend Research and Capsugel, we are now ready to take SDD and our other technologies to the next level. Extensive capital is being invested in the late-stage development and commercial capabilities at Bend Research. Central to this investment is the addition of a commercial "wing" in the Bend Research GMP facility, equipped with a large spray dryer capable of commercial production of multiple compounds. This addition is being designed and constructed with a high-containment capability that will be unique in the industry. We have been awarded multiple commercial contracts to date.

Q: How will Bend Research's technologies in modified release be utilized in Capsugel DFS?

A: Modified release is another exciting growth area for us - one in which our collective technology and know-how is very complementary in both established and IP-protected technologies. The integrated Capsugel DFS has a full array of technologies with which to modulate dissolution profiles - delayed release/enteric protection, first- and zero-order controlled-release profiles, combination drugs and/or pulsatile release, and specific GI tract targeting, such as colonic delivery.

Optimal technology selection has been developed for determining the right type of coating and the right process for applying the coating for modified-release applications. This protocol gives the customer a coating formulation with the best performance and a coating process that is scalable and transferrable - key issues in the industry.

Additionally, our capsule technologies - intrinsically enteric capsules, capsule-in-capsule formats, and specialized capsule coating approaches - provide additional and proprietary formulation options to our clients. It is also worth noting the complementary nature of our technology platforms. Our modified-release approaches are often used in conjunction with bioavailability-enhancing technologies to meet pharmacokinetic profiles and optimize finished dosage forms, which can be supplied as osmotic or matrix tablets, multiparticulates in capsules or sachets, liquid fill hard capsules, or soft gels.

Q: Multiparticulate formulations continue to grow in application - can you speak to the Capsugel DFS offering?

A: Multiparticulate formulations are quite versatile and increasingly utilized in meeting our client formulation challenges. Once it has been determined that multiparticulates are appropriate, the choice of type of multiparticulate follows our rational technology-selection process.

Layered multiparticulates are routinely developed using fluid-bed coating technology, a core capability of Bend Research, when there is a need for modified release or "triggered" release of either solubilized or non-solubilized drug. A range of mechanisms are utilized, eg, pH trigger, time trigger, or diffusion controlled to modulate release and/or provide taste-masking.

Bend Research also has fundamental capabilities in matrix multiparticulates, including mini-tablet formulations and melt-spray-congeal (MSC) processing for lipid multiparticulates (LMP) manufacture. Our LMP technology can provide a combination of bioavailability enhancement, controlled-release, and taste-masking functionality, and are manufactured by hot-melt extrudate being introduced to a spinning disc that generates particles with a very narrow size range. The resultant particles can be formulated into capsules, tablets, or sachets, and have market precedence - the Pfizer Zmax® commercial product utilizes this technology. Commercial-scale LMP production is being installed currently at one of Capsugel's commercial manufacturing sites to fully integrate this offering.

Q: How does Capsugel DFS approach technology selection and project de-risking?

A: Technology selection is a core capability of the integrated Capsugel DFS that differentiates our product development process and results in optimized dosage forms, rapid first-in-human trials, and reduced costs in terms of client time, API usage, and scale-up activities. Our breadth of technologies especially in bioavailability enhancement, fundamental science and engineering, and extensive formulation experience are the foundation of our technology selection processes. With the integrated Capsugel DFS, a customer can now bring its molecule(s) to a single partner for integrated development with rapid technology selection, instead of evaluating various specialized technologies with multiple contract vendors. Avoiding the management of multiple programs decreases risk, cost, and overall complexity of product development. We can develop enabling formulations for evaluation in as little as 2 to 3 weeks with minimal API, and reach clinical in 6 months or less independent of technology utilized.

We typically begin with consideration of the drug's physicochemical properties and biological factors that can drive technology selection: solubility, dose, potency, and other properties that are relevant, based on our extensive investigation and experience.

Biomodels have been developed that accurately predict the performance of the

API based on its properties and the characteristics of the formulation technology. This type of modeling has proven highly useful in choosing the best bioavailability-enhancement technology and/or controlled-release technology, as well as key process parameters.

Additionally, after formulating literally thousands of drug compounds, we have formulation guidance "maps" centered on key drug properties. These maps can help immensely in combining knowledge of drug properties, dose, and solubility over many compounds to choose the right technology for a given situation without parallel empirical testing that would otherwise unnecessarily consume valuable time and API.

Q: How do the Capsugel DFS offerings benefit 505(b)2 and product-enhancement trends in the industry?

A: Our offering is especially suited to the growing 505(b)2 category and continued trends in re-positioning established drug compounds (ie, technologies to improve bioavailability, modify or target drug release for improved therapeutic effect or reduced pill burden, and develop pediatric or geriatric applications leveraging multiparticulate or other finished dosage forms). Our integrated product development and technology selection processes provide optimal speed to market, critical for the 505(b)2 product concepts.

Proprietary technology plays a key role, and a few specific examples are worth mentioning in addition to the aforementioned LMP technology. Our new intrinsically enteric capsule technology provides unique enteric protection and delivery profiles without coating. Specialized approaches for abuse deterrence and colonic delivery are also increasingly utilized in developing products.

Capsugel DFS is also utilizing its technologies to develop enhanced "in-house" nutritional and pharmaceutical products for eventual licensing to commercial partners.

Q: What does the future hold for Capsugel DFS?

A: We are very excited about our future and will continue to invest to drive growth and innovation. Three key areas of investment for Capsugel DFS will be infrastructure, new technologies, and the optimal use of data.

We will continue to scale our premier bioavailability-enhancement, as well as modified- and targeted-release technology platforms. As previously mentioned, our infrastructure is being expanded with commercial production investments ongoing for both SDD and LMP technologies. We are also adding additional non-GMP SDD capability to enhance and speed our development work. High-potency suites, already in place at our co-located product development and manufacturing sites, also continue to be enhanced.

Additionally, we are leveraging core capabilities and synergies in two key growth areas: inhalation and abuse-deterrent formulation technologies.

Our inhalation formulation offering for pulmonary and nasal delivery benefits from Bend Research's particle engineering expertise, based on spray drying, and Capsugel's specialized dry powder inhaler (DPI) capsules. We have a number of client projects underway with both pharmaceutical and delivery device clients.

Our abuse-deterrent formulation technologies, offering formulation options tailored to the likely route of abuse for a particular API, are increasingly utilized and driven by regulatory requirements. We have a number of client projects underway, several of which also utilize our modified-release technologies.

Finally, we are investing in the broad area of "getting the most from our data" or "big data." It is well known in many industries, with Pharma being no exception, that more valuable information can be created from existing data sets. Bend Research is a "center of excellence" in this area, given its extensive work in developing science of scale, process understanding, and QbD approaches for Pharma companies for various small molecule and large molecule applications. This capability, combined with breadth and depth of technology offerings, is a key differentiator for Capsugel DFS, and should reduce the number of direct experiments and studies that must be performed and paid for, while extracting more information. ◆

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OUTSOURCING EARLY-STAGE CLINICAL TRIALS: HOW TO MITIGATE COSTS AND RISK

By: Cindy H. Dubin, Contributor

The most comprehensive survey of clinical success rates across the drug industry to date shows productivity may be even lower than previous estimates. According to a report from Nature Publishing Group, Hay and colleagues conducted a detailed analysis of phase transitions of 4,451 drugs with 7,372 independent clinical development paths from 2003 to 2011.[1] On average, the likelihood of successful transition from Phase I to Phase II was 64% and the probability of success from Phase III to NDA/BLA was 60%. Only 32% of the drug successfully made the transition from Phase II to Phase III. On average, the likelihood of reaching FDA approval (LOA) from Phase I was about 10%.

The successful transition rate from Phase I to Phase II was 60% in the period of 1991–2000. Insufficient or lack of clinical efficacy is the principal cause of program termination during development.[2,3] Thus, strategies for risk mitigation have to focus on Phase II as that is where most failures occur. Achieving proof of mechanism in Phase II is one of the most important attributes of success. Drugs that achieved proof of mechanism (an integrated understanding of the fundamental pharmacokinetic/pharmacodynamic principles of exposure at the site of action, target binding and expression of functional pharmacological activity) in Phase II have the highest likelihood to be transitioned to Phase III and LOA.[4]

Thus, the Contract Research Organizations (CROs) outsourcing services market has witnessed significant growth in the past decade. This growth has been attributed to the rising costs involved in conducting various phases of clinical trials ranging from drug discovery up to post-marketing approvals. Pharmaceutical companies opt to outsource clinical trial activities to vendors capable of providing bundled services such as regulatory services, clinical data management, medical writing, site management, pharmacovigilance, risk-based monitoring, biostatistics, and protocol development. As a large number of molecules fail during the drug discovery process, outsourcing helps mitigate financial risks.[5]

Drug Development & Delivery magazine recently asked some leading CROs to describe the benefits of outsourcing early-stage clinical trials, the best way to recruit and retain trial participants, and how they help offset costs and minimize risk. Change to Participating companies include Covance, PAREXEL International, Sofpromed Investigación Clinica, SLU, and Theorem Clinical Research.

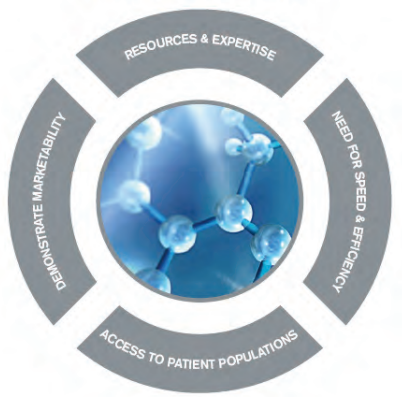
Q: Please describe your company's service offerings as they related to early-stage clinical trials.

Dr. Potthoff: Theorem Clinical Research is a midsized provider of comprehensive clinical research and development services. We consistently plan and execute successful medical device, combination, and complex trials across all major therapeutic areas and have offices spanning the Americas, Europe, and Asia. Our team includes renowned scientists and global regulatory affairs experts, and we also provide staffing partnership solutions (including full-service, augmentation and FSP models) and world-class clinical bioinformatics and analytics capabilities. Overall, when it comes to Phase I-III development, we can work to any capacity our clients' needs.

Mr. Ledesma: Sofpromed is a technology-based CRO offering a range of services for early-stage clinical trials, including regulatory affairs, site activation, enrollment support, monitoring, data management, pharmacovigilance, pharmacodynamics and pharmacokinetics study logistics, statistical analysis, medical writing, and project management. We also provide a suite of electronic Case Report Form (e-CRF), patient database, medical imaging, and biological sample management web tools to increase the efficiency of key Phase I processes.

Dr. Pretorius: PAREXEL offers a full spectrum of services, ranging from first in human (FiH) through proof of concept (PoC). Within this segment, we provide our customers a variety of early-stage development services and niche capabilities through an integrated early phase network, which consists of five Clinical Pharmacology units located in hospitals across the United States, United Kingdom, Germany, and South Africa, as well as a large number of partner/alliance units around the globe. Our full-service, in-house service offerings include protocol design and consulting, global and local project management and regulatory support, monitoring, and clinical conduct. Our offers also include bioanalytical services, data management, biostatistics, clinical pharmacokinetic/pharmacodyamic (PK/PD) and pharmacometrics, and medical writing services.

Mr. DiMatteo: Covance focuses on two critical aspects of studies: Scientific integrity and human subject safety. Covance Early Clinical Services draws upon a comprehensive continuum of services to drive more go/no-go decisions than ever before based on our FIH/SAD/MAD experience and human AME capabilities. Our end-to-end early clinical focus can save time for some clients, as we can begin scientific discussions to transition from healthy volunteers to patients. As early clinical research continues to demand more complex studies, we have additional groups dedicated to client solutions in early-stage clinical trials, such as clinical pharmacology, early clinical development, clinical data analysis and reporting, and molecule development.



Demonstrating a compound's proof-of-concept (PoC) is an important development milestone. If compelling, valid data supporting the safety, efficacy, quality, and commercial potential can be shown at this stage, a compound's market value can be optimized, the ability to reach drug development goals are enhanced, and the demands of regulators, providers, and patients are met (Covance).

Q: Early-stage trials have shown a dramatic rise in per-patient costs as clinical teams look to collect more data earlier in the drug development process. What factors impact clinical trial costs the most and how can companies reduce that impact?

Dr. Potthoff: There is a growing demand for more data earlier, and equally so, there should be a higher demand for more powerful ways to collect and utilize that data earlier. Technologies that can help collect and aggregate data into something useful, both when it's collected and down the road, can play a major role in reducing costs. Along that same line of thought, making it easier for people to digest and communicate early findings is essential, and that goes beyond the technology. Instituting and upholding clear chains of communication lead to more efficiencies in early development.

Dr. Pretorius: The key drivers of cost include (amongst other things) increased Phase I study complexity, higher regulatory hurdles, and increased competition for patients. Companies can mitigate or reduce these increasing costs by:

- Strategically partnering with vendors, and benefiting from learning curve efficiencies and economies of scale that a Strategic Partnership (as opposed to tactical engagements) outsourcing offers.
- Employing a disciplined and targeted approach to early-stage drug development that focuses only on information that is absolutely required. However, this approach may hinder innovation – something that is at the core of exploratory development.
- Leverage innovation and technology (e.g., modeling and simulation, biomarkers, genomic data, risk-based monitoring, etc.).

We have actually reduced our Phase I price per volunteer considerably over the past few years given the unfavorable macro-economic forces at play in our segment.

Dr. Lang: The traditional drug development paradigm that focused efforts on moving drug candidates through the various stages of development has changed. The current focus is on rapidly reaching a proof-of-concept (PoC) with a go/no-go decision. The advantage is that it de-risks later-stage development and costly Phase III failures. Although the individual costs for early phase PoC trials may increase, this has the potential to allow for an overall decrease in the pharmaceutical development costs as more compounds can be evaluated earlier in the development sequence and decisions to progress or not progress these compounds can be made earlier. Good PoC trials require biomarkers, novel designs to determine efficacy, which can cost more, but can be prudent cost-saving investments.

There are also the costs associated with risk-based monitoring (RBM). Monitoring costs are a main component of total clinical trial costs. While not every trial may realize cost savings with the implementation of RBM, the majority of RBM studies would see a reduction in monitoring costs. The reason for this is RBM's movement away from 100% source data verification (SDV) to a more targeted SDV approach, focusing on study risks and mitigating them with proactive management.

Mr. Ledesma: Factors impacting early-stage trial costs are mainly related to infrastructure and in-house specialized staff of dedicated Phase I units, intensive monitoring, demanding recruitment coordination and data management derived from dose ranging and toxicity assessments, the implementation of pharmacological studies with multiple blood extractions, and the need of imaging-based efficacy evaluations in oncology trials. Per-patient costs are dramatically increased when delays take place, so time to completion becomes a crucial financial driver. Expenses are even higher in orphan drug development for rare diseases requiring the activation of several sites in multinational settings. Sponsors can reduce costs by outsourcing with full-service technological CROs to alleviate operational burden through global coverage, local support, and innovative software tools to accelerate workflows. Regional CRO personnel, familiar with local authorities, ensure rapid start-up and close monitoring at lower expense. e-CRFs with effective built-in checks speed up data collection, diminish monitoring efforts, and shorten time to analysis. Cloud platforms should also be in place to save costs through centralized biological sample and medical imaging management.

Q: What are some best practices to boost clinical trial recruitment and retention?

Dr. Potthoff: One is to strive to work with as local of an understanding as possible. Having a physical presence in the places you're doing research helps you better understand regulatory and cultural climates, as well as what patient recruitment methodologies work. As far as retention, there's a lot of value in thinking through retention strategies ahead of the game and how incentives will best appeal to the patients you're targeting. The best recruitment and retention practices for trials are unique to the product at hand and the patients being targeted, and therefore, so should the approach to building the strategies to fulfill enrollment. You need dualistic intelligence — both of the product being developed and the patients you need to reach — and you need to have people who know how to build a plan that will bridge the two.

Mr. Ledesma: Educating investigators and potential participants is the first key to successful trial recruitment. Research teams

must understand the factors influencing patient decisions. For example, although Phase I trials are usually focused on the safety and pharmacology of a drug, patients should know that these studies can be therapeutic, and not necessarily toxic. Good education related to trial-specific procedures and safety aspects encourages participation. Concerning retention, patients appreciate kind visit reminders, accessibility to site staff, avoiding lengthy and uncomfortable procedures, as well as receiving educational information and personal appreciation. Nevertheless, retention plans will also depend on the specifics of each trial, such as study design and regional aspects.

Making it easier for people to digest and communicate early findings is essential. Instituting and upholding clear chains of communication lead to more efficiencies in early development (Theorem Clinical Research).

Ms. Weir-Hauptman: Successful clinical trial recruitment and retention are vital to preventing delays in completing clinical trials and moving forward with drug development. With today's technology, more innovative means to recruit and retain subjects are being implemented to supplement the traditional means still in practice. For recruiting subjects, monetary incentives can attract healthy volunteer subjects. In early trials involving patients, while monetary reimbursement may not be possible, the ability to get free healthcare can be an incentive. Additionally, with both healthy volunteers and patients, providing transportation to and from the clinical site could also encourage participation. Meeting recruitment goals also comes from engagement from the clinical sites. Tools for these sites include advertising material (brochures, radio scripts, flyers,) and funds for such advertising and for reviewing patient charts. Social media has proven to be an effective medium for advertising clinical trials and can greatly aid sites in recruiting patients. Also, conducting a recruitment meeting for all investigators during the trial can boost morale and motivate sites to put forth effort to recruit patients.

For longer studies that require either long stays in-clinic or frequent visits to the clinic, patient retention is imperative. Tools that provide information about the clinical trial's importance, procedures, and appointments can greatly aid in retaining study participants. A great tool for this is a mobile application that can house all this information in one location on the participant's smart phone. The patient can learn about the clinical trial, receive appointment reminders, learn about the procedures that are being conducted at each visit, and learn about the investigated disease. The goal is to engage the study participant as much as possible to keep them committed to participating in the trial.

For studies with a high withdrawal rate, it is important to determine why subjects are leaving the study and create educational material for both the sites and participants to prevent further drop outs.

Dr. Pretorius: In addition to traditional approaches (printed media, radio and television advertising community outreach, etc.), mobile devices and social media offer new and exciting recruitment channels. Digital enrollment in clinical trials is enhancing patient retention rates by creating an easy-to-use platform that not only aids in enrolling and tracking the patient, but also in providing disease-specific information and details about medication and office visits. Additional ways of reaching and retaining patients include online databases that contain information about clinical trials for various studies and open platforms that post trial details for patients interested in finding disease-specific information and enrolling for a trial.

Despite the digital world in which we live, the most successful retention tool continues to be personal contact from site staff directly to volunteers/patients.

Q: Describe a customer project you tackled within the last year related to an early-stage clinical trial: the need of the client and how you handled the project.

Mr. Ledesma: We recently completed the management of a Phase I oncology trial consisting of the combination of an anthracycline antibiotic with a tyrosine kinase inhibitor administered to patients with liposarcoma of the retroperitoneum. The main goal of the study was to establish the recommended treatment dose of the combination for a future Phase II and perform a toxicity assessment based on dose escalations with cohorts of 3-6 patients. A total of 13 subjects were recruited, allowing the inclusion of a different sarcoma subtype without standard treatment available. The trial required the activation of 11 sites in Spain given the rareness of the disease. Our company provided regulatory authority approval, site activation, enrollment support, monitoring, data management, and pharmacovigilance services, along with the management of a pharmacodynamics study assessing expression levels of multi-drug resistance-associated proteins in lymphocytes. The trial required the review of baseline and post-treatment CT scans for each patient in order to evaluate tumor response. As added value, we provided our suite of web-based tools for data collection (e-CRF), blood sample, and radiological imaging management. A suitable combination dose was established after three escalation levels. The experimental treatment was not only safe, but showed encouraging evidence of tumor control.

Dr. Tong: One of our client companies was in early-phase testing of a novel therapy for cardiovascular disease. The regulatory environment was changing in this area in a way that could significantly impact the scope of the development program required. By sharing our experience in developing drugs in this therapy area, we were able to advise our client of elements to incorporate into its Phase II program to get preliminary data. We also used publically available trial data to advise them on timing of their program in light of other large-scale trials related to their drugs mechanism of action, scheduled to report out during their Phase II period. This allowed a staged investment in their drug project to put them in a position to go forward at full speed if these other trials enabled this opportunity, but limited their investment and resource utilization until that risk reduction milestone was achieved. It also allowed them to be in a position to know what to incorporate into their Phase III program based on regulatory guidance and outcome of other ongoing trials.

Dr. Pretorius: Let's consider the early-stage clinical development of a compound to treat cognitive impairment associated with Parkinson's disease and for Major Depressive disorder from first-into-human through to PoC. To reduce the standard projected early clinical development time (from 48 months to 24 months – i.e. 50% faster) as well as cost (making it 40% more cost effective), we could use several innovative strategies to accelerate global development. In order to facilitate the assessment of two therapeutic indications, we would use our functional domain strategy, where the mechanism of action of the molecule has common pathways of benefit, which can be evaluated by functional magnetic resonance imaging (fMRI) and Evoked Potential Biomarkers. When taking this approach, the sample size for these two small parallel PoCs is based on the anticipated neurochemical circuitry changes observed with this molecule and not powered based on the usual behavioral or motor outcomes used in Phase II.

Hypothetically speaking, some of our innovations would include combining the first-into-human, single ascending dose and multiple ascending dose studies into a single combination protocol. Once proof of target engagement and/or CNS penetration was demonstrated in healthy volunteers, the study would include one healthy elderly patient arm to assess tolerability and PK, and additional Parkinson's patient arms to determine the maximum tolerated dose in this target population.

Guided by the above, including the identification of a potentially efficacious dose range, two PoCs should be conducted. One PoC study conducted in mild Parkinson's patients with complaints of cognitive impairment, and the other in patients with Major Depressive Disorder who demonstrated clinically significant symptoms of anhedonia. To meet aggressive recruitment and enrollment timelines, we used a spoke and hub model, in which several outpatient investigators identified, enrolled, evaluated, and managed patients suitable for the study. All outpatient procedures were conducted at the investigator 'spoke' sites, which were geographically close to the hub, PAREXEL's Early Phase Unit. ◆

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REGULATORY INFORMATION MANAGEMENT

Renewed Focus on Reg IM as Commercial Takes Center Stage

By: Joel Finkle

INTRODUCTION

There has been a significant though subtle change in the way pharmaceutical companies think about the management of their regulatory information and, indeed, the regulatory function overall. In the past 18 months to 2 years, larger pharma companies in particular have begun asking important questions about the purpose of the regulatory function within the business in light of the increasingly pressing need to follow the guidelines and meet the mandates of regulators worldwide and to make effective commercial decisions in a competitive climate.

Rather than have regulatory affairs devote time to administrative tasks, that department now plays a more strategic role in helping secure and maintain market access to a company's pipeline of products. And in that context, regulatory information management (Reg IM) has become both the enabler of those intrinsic regulatory functions and is itself forced to change as a consequence. Indeed, Reg IM is no longer seen simply as the application of information management tools and techniques to regulatory matters, but rather is recognized as the management and exploitation of regulatory information as a resource.

ARCHITECTURE RETHINK

For many years, pharma companies have quite haphazardly collated, stored, and managed their regulatory information, maintaining a multitude of databases and spreadsheets that are disconnected from other systems, and often spread around the world at local market companies. But several changes within the industry have caused companies to rethink that approach. To start with, the growth of off-the-shelf solutions and the fact that database searches have become easier, faster, and cheaper (at least for the computer hardware) have made companies more inclined to manage and track large-scale databases of regulatory information.

Furthermore, companies now work extensively with external partners and need to be able to share information during that collaboration. It means that some of the traditional methods of gathering information are no longer productive. For example, some companies have used Lotus Notes-based systems to manage workflows. But that is an inherently platform-dependent solution, meaning that it is difficult to share information between a Lotus Notes organization and an organization that is not one.

As a result, companies are asking whether the tools they are deploying

can be readily accessed by their partners. They are also beginning to understand that if they are to operate in a heterogeneous, distributed environment and enjoy the benefits of the outsourcing of low-value-add commodity services, then investment in huge, bespoke information management solutions to support those activities is not helpful. This is forcing a rethink about architecture components in favor of more-open systems in terms of access and connectivity.

When companies decide to take advantage of the outsourcing of commodity regulatory services, they also begin to realize that not having regulatory function management and regulatory function staff in the same geography means they must communicate changes and progress in a more systematic way. Very quickly then, companies begin to query the adequacy of departmental spreadsheets and to look to more formalized Reg IM systems, such as tracking tools. For example, a biopharma company that had recognized the business benefits of outsourcing its routine regulatory activities - in particular, activity prone to cyclical peaks and troughs - found that in order to outsource, it had to formalize and standardize significant parts of the Reg IM solution and decouple it from individuals' embedded knowledge.

Indeed, the architecture and infrastructure in place play significant parts in ensuring Reg IM delivers value to an organization. Without stable processes and solutions that ensure a clear and formalized flow of data, the Reg IM solution becomes untenable. Once that happens, the quality of the decisions that regulatory, commercial, manufacturing, or other leaders can make from the information quickly degrades.

WHAT HAS CHANGED?

Among the several reasons behind companies adopting broader (and deeper) perspectives on the regulatory function and Reg IM are the demands of regulators with regard to product information and the need to ensure products adhere to those requirements. For example, the Extended EudraVigilance Medicinal Product Dictionary standard (XEVMPD), which became mandatory in July 2012, requires routine communication of data sets not typically held within one system previously, which in turn requires integration of both central regulatory and worldwide market-specific information. The EudraVigilance Medicinal Product Dictionary itself is expected to ultimately be replaced by the Identification of Medicinal Products (IDMP), which was approved in November 2012 as an ISO (International Organization for Standardization) standard. Companies are now awaiting the International Conference on Harmonization's implementation guide on how that ISO standard is going to be used, because potentially, enormous amounts of information will have to be gathered.

But it is the needs of the business that drive a sharper focus on the regulatory function, including Reg IM and regulatory intelligence. Companies are beginning to assess how the regulatory function should operate, and at the same time, they are looking to Reg IM to provide vital market information answers to such questions as: How can we get more revenue from our current drug bases? And: What is the best way to enter new markets?

On one hand, many European companies are using regulatory requirements as a way to release budget to improve commercial decision making. On the other hand, a US-based company is more likely to request funding for a Reg IM Solution that would help create organizational change so as to reduce costs and improve market access. In reality, both the European and the US companies would likely be using Reg IM to fulfill the needs of their businesses.

To plan their market strategies, companies need actionable information that tells them, say, which markets are not currently selling a given product, where can they exploit their strengths, and what specific efforts would get a product licensed in those markets.

One large pharma manufacturer has been looking at ways it could integrate information across the business. To that end, the company has been working to put in place a more sophisticated tracking solution that would enable it to plan both across the portfolio and across markets. For

example, the tracking system would prompt, with reminders such as, "You are 20 days from filing an annual report; You are 5 days from an expected regulatory response; or Your license expires in Country X in 30 days," across all countries in which it markets products.

The company would use its Reg IM solution not only to stay on top of regulatory needs and to plan market options but also to use the gathered regulatory intelligence to gain a greater understanding of additional markets in which the company might consider marketing its products.

One of the business benefits of outsourcing routine regulatory functions, companies have discovered, is that it frees the regulatory function to look at managing the bigger picture of the plans for regulatory activity in their markets, which in turn means that tools that let them see the full picture become prerequisites rather than luxuries.

Another large life sciences company has been using Reg IM for some time as a high-level planning tool for determining how long it takes to get variations approved in different regions and for answering commercial questions about registered products. For example, if a product is registered but not marketed, the company can determine how best to proceed: sell the product, withdraw it, or begin marketing it. Furthermore, being able to answer questions about the company's assets revealed that the company had significantly more products registered worldwide than it originally realized.

REG IM DEFINED

The concept of Reg IM as a distinct discipline is relatively new. Indeed, in the past 5 or 10 years, Reg IM has evolved from companies simply wanting to track what is happening with their products to the integrated, life-cycle management of products and product families.

Until recently, companies' understandings of Reg IM varied widely from one to the other, but today, there is a coalescence around common understandings regarding, say, the functions that certain tools, such as tracking systems, should be performing. Companies generally recognize that Reg IM involves far more than submissions management. As one regulatory leader put it, "We're realizing that when we collect that information, we can make smart decisions that can affect what we do with a product, whether on a global or an individual market basis."

Indeed, a 2012 CSC survey of regulatory affairs, operations, and information technology (IT) managers found that 57% of respondents described Reg IM as a "method of bringing together all of the pieces of information and data that tell the complete stories of all products for the purposes of compliance with regulatory authorities' requirements and improvement of commercial decision-making." Only 15% perceived Reg IM as existing purely to track the data associated with reports for regulatory submission. However, that recognition has, until now, not necessarily resulted in action: the survey found that only 20% of companies had fully implemented a formal strategy, and very few of them could lay claim to a completely centralized repository where all of their global registration information is held.

A further, more recent, trend is the move toward integration of regulatory intelligence, and there is an emerging sense that regulatory intelligence is an important part of Reg IM. The pharma industry (or at least, big pharma) has evolved from the stage where its Reg IM (1) was tactical and based on operational systems, (2) is moving through a phase with tracking systems and in which they need to coalesce all that information and understand the bigger picture, and (3) is just beginning to recognize the importance of understanding the context of that bigger picture, which is where regulatory intelligence comes in.

At this stage, however, regulatory intelligence means different things to different organizations. For one, regulatory intelligence might simply consists of understanding what the regulatory process and the regulatory submission is in a given market, including having a database of worldwide regulators and their current rules. At the other extreme, another company must have information that is more about policies and direction of travel -

in other words, not what the policies state but why they have been put in place. This helps a commercial organization learn, for example, what types of products its scientific committee would be open to and what types it might be more concerned about at any given time.

CXO IN THE SPOTLIGHT

The way companies are beginning to think about the regulatory function and the use of specific tools is now being driven by the business or commercial side rather than the IT side - in particular, the COO or the CEO. This is a very recent change. In fact, only 2 years ago, when an organization talked about changes to Reg IM, the discussion was generally led from the level of the CIO; the IT side of the business drove the initiatives and then brought the business partners along with them.

The current shift to a business-driven initiative is prompting demand from the information side that is having a huge impact on how the regulatory function and Reg IM are perceived and implemented. Rather than technologies enabling the business to consider potential options, the drive of the established business intent is demanding that same technology. After all, once a company embarks on business change, it can no longer rely on informal processes and repositories that exist in functions. The result is a gradual move away from island systems into more-corporate systems, with the ultimate goals of increased communication and interoperability between tracking systems, regulatory intelligence, regulatory submissions, medical information, and safety systems - indeed, between and among all aspects of the regulatory function.

SUMMARY

In the past, pharma companies largely took the view that the focus of the regulatory function was on acting in response to required standards and regulations. But as companies start to shift their thinking toward their commercial needs, they're coming to realize that the regulatory function plays a crucial role in securing and maintaining market access and that Reg IM is more than simply a useful submission tool - that it is essential to managing the big picture. That realization will in turn lead to a more inclusive approach to the management of regulatory information and intelligence.

In recent years, pharma companies have looked at ways they could increase efficiency while lowering costs, and they have achieved those in many parts of the enterprise. Now the focus is on the regulatory function and the role it plays in the commercial organization at large. ◆

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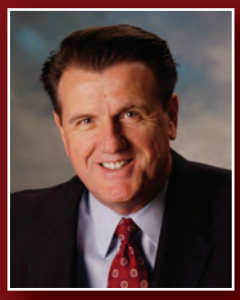
BIOGRAPHY

Joel Finkle is Senior Strategist, Regulatory Informatics within CSC's Regulatory Solutions Group (formerly ISI). He is the architect for two of their Document Creation solutions: ISIRender and ISIWriter. In his nearly 7 years, he has performed business process consulting, provided customizations to our solutions, and developed several software business partnerships. In his current role, he is working to find novel ways to solve regulatory software and service processes for customers, as well as providing the focal point for industry standards and regulatory guidance. Mr. Finkle comes from a background in the Pharmaceutical industry, with 26 years of experience in software development and support of electronic submissions, publishing, and document templates, from custom CANDAs through eCTDs. He is currently a member of the HL7 Regulated Product Submissions (RPS) standard development team, the DIA Electronic Regulatory Submission SIAC Core Team, the DIA Cross-SIAC EDM Reference Model development team, and the OASIS DITA Pharmaceutical development team.

DRUG DEVELOPMENT Executive

4P THERAPEUTICS: DEVELOPING NEW & INNOVATIVE TRANSDERMAL PRODUCTS



Steven Damon
Founder
4P Therapeutics

"Our in-house capabilities allow us to work with proven preclinical models either in vitro or in vivo and have the capability to move quickly to the clinic with a technology and formulation tailored for each specific transdermal product. We believe that the keys to success in the novel transdermal space are having the freedom to choose from multiple technologies and not be burdened with a one-size-fits-all platform technology as well as having world-class experience in transdermal formulation and product development."

In today's market, patent losses and faltering pipelines are causing pharmaceutical companies to reposition currently marketed drugs through reformulation using novel drug delivery technologies. In addition to reformulating products for lifecycle management, pharmaceutical companies are combining drug delivery technologies with their NCEs early in development. 4P Therapeutics is taking advantage of these market trends by providing its partners with novel drug delivery technologies and expertise in product development with fully integrated capabilities. Founded in 2012, 4P Therapeutics is a privately held company based in Atlanta, GA, focused on the development of innovative transdermal products. The company's team of scientists has vast experience in developing drug delivery products ranging from conventional transdermal systems to novel transdermal systems , utilizing technologies such as skin poration and microneedles. The company's team also has experience with developing oral drug delivery technologies, medical devices, diagnostics and vaccines. Drug Development & Delivery recently spoke with Steven Damon, Founder of 4P Therapeutics, to discuss his vision for the company and how 4P intends to create new and innovative transdermal products that meet the needs of patients, physicians, and payers.

Q: Can you provide our readers with some additional background on 4P Therapeutics?

A: We founded 4P Therapeutics to be a company based on taking innovative approaches to developing new transdermal products. 4P is not dependent on a specific platform technology but instead evaluates multiple different transdermal technology and formulation approaches to find the right match for a particular drug or biologic product being developed. Our in-house capabilities allow us to work with proven preclinical models either in vitro or in vivo and have the capability to move quickly to the clinic with a technology and formulation tailored for each specific transdermal product. We believe that the keys to success in the novel transdermal space are having the freedom to choose from multiple technologies and not be burdened with a one-size-fits-all platform technology as well as having world-class experience in transdermal formulation and product development. Current industry dynamics for transdermal product development and commercialization have led us to create a business model for 4P that takes advantage of our

own proprietary technology as well as the freedom to operate with multiple technologies. 4P has built an infrastructure that allows our experienced team to go from concept to proof-of-concept in humans in our Atlanta, GA, facility.

The 4P Therapeutics team is experienced in developing a broad range of drug delivery technologies, particularly novel transdermal technologies for compounds that are currently injected or administered by SC or IV infusion. These compounds consist of biologics, including proteins, peptides, other large molecules and water-soluble small molecule drugs that cannot be delivered using conventional transdermal systems. The team's experience in developing drug delivery products ranges from conventional transdermal systems for drugs such as nicotine, fentanyl, hormones and other small molecules to novel transdermal technologies, such as skin poration and microneedles for water-soluble drugs and macromolecules that are typically injected. The company's team also has experience with developing vaccines, medical devices and diagnostics.

Q: What are the opportunities in the drug delivery arena today?

A: Researchers have estimated that patent expirations will result in many billions of dollars of lost sales of branded products. These patent losses coupled with some faltering pipelines and expensive and risky development plans for NCEs create opportunities for and interest in the benefits of products enhanced by drug delivery through reformulation or a change in the route of administration using novel drug delivery technologies. Products using drug delivery technologies are designed to potentially enhance efficacy, improve safety, and extend patent lives for currently marketed products. This focus on drug delivery technologies provides a significant opportunity for 4P Therapeutics.

Q: What are the market opportunities for 4P Therapeutics?

A: As pharmaceutical companies continue turning to drug delivery technologies to develop new products, we undoubtedly believe novel transdermal products offer an attractive option for many drugs and biologics. Oral products remain simple and easy to use and are preferred by patients and physicians. However, market research has shown a strong preference for transdermal products as well. Transdermal versions of currently marketed oral, nasal and/or inhaled products may have value. Transdermal products that replace injections or infusions should be widely accepted by patients and physicians, and we believe they represent the best opportunities for growth in the transdermal space. The key is to understand the opportunity as it relates to all stakeholders, including patients, physicians, and payers. The goal is to develop products that have real market value while staying within the appropriate development spend and cost of goods necessary for a successful commercial product. 4P Therapeutics is positioned with the experience and capabilities to take advantage of the real opportunities in transdermal product development.

We are seeing a focus by pharmaceutical companies on the use of transdermal drug delivery technology to reposition currently marketed products and bolster their pipelines. We are also seeing an interest in the use of transdermal technology to deliver NCEs early in the clinical development program prior to pivotal safety and efficacy studies. 4P is uniquely suited to support our partners with proof-of-concept work early in the development program to provide direction for further product development.

Q: What makes 4P Therapeutics unique in developing drug delivery products?

A: Many companies in drug delivery consider themselves unique. The challenges we all face in developing drug delivery-enhanced products are often specific to a certain drug and/or therapeutic area. 4P Therapeutics has the expertise in developing various novel transdermal technologies and products. These include

products based on small molecules, proteins, peptides, carbohydrates, that are injected, infused, or otherwise delivered. We believe a key uniqueness is our ability to quickly and efficiently move through the proof-of- concept phases of development with minimal spend and major risk reduction before underwriting the high-cost pivotal studies that are required for regulatory approval.

In our approach to partnering with companies to develop new transdermal products, 4P Therapeutics utilizes our highly efficient "concept" to "proof-of-concept" model to assess the delivery of a drug using a transdermal technology. The model is designed to establish preclinical feasibility followed by proof-of-concept in human clinical trails – both conducted within our Atlanta-based facility. Potential partners interested in developing products with 4P Therapeutics are not required to invest significant capital and resources upfront. This step-wise approach has contributed to 4P Therapeutics' success with our partners.

Q: Can you explain further on your company's "concept" to "proof-of-concept" model?

A: Sure. Our model consists of efficient in vitro and in vivo screening to determine the feasibility of delivering a compound in preclinical and Phase I clinical studies. As an initial step, and based on our experience and knowledge of multiple transdermal technologies, we will determine the feasibility of delivering a compound through the evaluation of the compound's chemical characteristics and delivery requirements such as dose, pharmacokinetic profile and regimen. Additionally, our team has the expertise in selecting the technology that presents the best probability for development success before moving into in vitro testing.

After completing the in vitro testing phase, 4P Therapeutics conducts feasibility testing in our preclinical models. We optimize the formulation to meet the target delivery profile before moving into clinical proof-of-concept studies in human subjects. 4P Therapeutics has in-house capabilities to conduct these feasibility studies, including a vivarium for preclinical work and a Phase I clinical unit. In addition, we have formulation development and bioanalytical/analytical capabilities in-house, allowing us to obtain high-quality data with a rapid turnaround time.

Q: Are you able to discuss an example of one of your current collaborations?

A: 4P Therapeutics has entered into multiple partnerships with companies ranging from a global healthcare conglomerate to small biotech companies and academic institutions. An example would include our partnership with Medicure International, Inc., a specialty pharmaceutical company headquartered in Canada. The partnership with Medicure is initially focused on developing a transdermal patch for Aggrastat® (tirofiban HCl injection for intravenous use), Medicure's lead product currently marketed for the treatment of acute coronary syndrome.

4P Therapeutics initially partnered with Medicure to demonstrate the preclinical feasibility of delivering tirofiban transdermally as an alternative to its current IV delivery. After successfully completing the feasibility studies, 4P Therapeutics and Medicure entered into a product development and commercialization partnership. This approach allowed Medicure to assess the preclinical feasibility of delivering tirofiban transdermally and offered the flexibility to generate valuable data before entering into a broader partnership with 4P Therapeutics and committing additional resources to the project. This development program presents an important lifecycle management strategy for Aggrastat. Drugs in the Glycoprotein IIb/IIIa inhibitor class (GPI), including tirofiban, are currently only available for IV delivery. Transdermal delivery of a GPI promises to offer several benefits over IV delivery, including ease of administration using a transdermal patch that can potentially be self-administered, possible reduction in hospital length-of-stay to lower healthcare costs, and the potential for new indications that could lead to additional market penetration. 4P Therapeutics and Medicure have demonstrated in vivo proof of concept for transdermal tirofiban delivery. The

development program is now focusing on refining the transdermal tirofiban delivery system in preparation for initial human studies.

Q: What is the market potential for Medicure's transdermal tirofiban?

A: The global market for antiplatelet drugs is more than $8 billion per year, of which Aggrastat and the other IV GPIs make up approximately $500 million per year. The largest share of the market is held by oral antiplatelet drugs, such as Plavix® and Aspirin®, which by virtue of their route of administration can be used in a variety of settings in which IV administration is not feasible. While these treatments will continue to serve an important role in cardiovascular therapy, the use of oral antiplatelet drugs for some patients and conditions is limited by a number of drawbacks, including inter-individual variability, drug resistance, drug-drug interactions, and delays in reversal of effect. Transdermal tirofiban has the potential to avoid these problems and to carry the unique benefits of a GPI, including the ability to dissolve and to directly prevent formation of blood clots. For this reason, transdermal tirofiban has the potential to capture a significant share of as well as grow the GPI market.

Q: Does 4P Therapeutics have experience and capabilities for product development beyond proof-of-concept?

A: Yes, in addition to our efficient model to demonstrate preclinical feasibility and proof- of-concept in human subjects, 4P Therapeutics offers a complete solution for product development, ranging from preclinical to commercialization. The company's integrated capabilities include in-house preclinical feasibility, analytical sciences, bioanalysis, CMC development, QA/QC, pilot manufacturing, clinical development, regulatory affairs, and strategies for the development and registration of combination products. As mentioned previously, our Atlanta-based facility is equipped with a vivarium for preclinical testing, an in-house Phase I unit for clinical studies, laboratories for CMC development, and a pilot manufacturing facility for process development and early stage clinical manufacturing. Additionally, our team has experience with supporting late-stage clinical and commercial manufacturing.

Q: What should we expect from 4P in the future?

A: We have begun development of our own proprietary transdermal products. Now that we have established our capabilities and supporting partnerships, we are excited about 4P internal projects that are focused on some of our own ideas for valuable products with clinical and therapeutic benefit. We also recently acquired the rights to a continuous glucose monitoring technology we believe has great potential. In the future, we expect to successfully advance our partnerships and projects with the goals of getting multiple products approved and marketed.

Q: Why should a company partner with 4P Therapeutics?

A: Our team has experience with developing drug delivery products through clinical development with various pharmaceutical partners. These development projects include reformulation of currently marketed products to be delivered transdermally and the application of transdermal technologies for delivering NCEs still early in development. A primary focus is on developing novel transdermal products for compounds that have to be injected or infused and cannot be delivered using conventional transdermal systems. This expertise, coupled with the dynamics of today's pharmaceutical market, make us an ideal partner for companies seeking to develop new products to offset generic competition and to build pipelines. 4P Therapeutics can leverage its experience in drug delivery to successfully develop products designed to meet the needs of patients, physicians and payers. ◆

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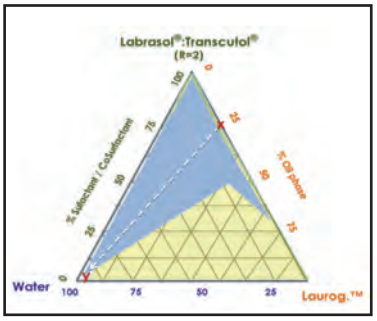

Ternary diagramming is an indispensable tool for developing microemulsions and SMEDDS for topical or oral delivery of poorly soluble drugs. In this example, the blue zone represents unlimited number of formulations possible by simply varying combinations of three excipients. Point "X" for instance is SMEDDS containing 25% Lauroglycol™ +75% mixture of Labrasol®: Transcutol® (2:1). Continuously adding water to formulation "X", we would be following the dilution path along the white arrow. In other words, the formulation "X" may be diluted with no risk of phase separation as it will remain a nano-dispersion even at a very diluted state. Designing SMEDDS and Microemulsions binary and ternary diagramming is a Gattefossé expertise. For more information, please contact **jmusakhanian@gattefossecorp.com**

Technology & Services Showcase

Insulin Management Systems

Development & Manufacturing

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Successful Succession Planning

By: John A. Bermingham

In a recent discussion I had with our Executive Director of this publication, Dan Marino, he suggested an article on succession planning. Why would anyone want to do succession planning? Why would you want to develop a person or persons below you in the company organizational chart who could take your job? What, are you crazy? Well, not so fast.

First, I believe every company should have succession planning as part of its management philosophy. This must be ensured and led from the most senior level. Unfortunately, my guess is that 75% or more of the companies in the United States do not have any succession planning.

From a management perspective, whether you have a formalized succession planning activity or not, it is still your obligation to develop the "bench strength" your company requires, not just below you, but throughout the organization if you are at a senior enough level. But if you only have one direct report, you should be grooming that person to be your successor.

So let's begin with my most basic management philosophy. That is, "to make the people with whom I work, successful." Part of that philosophy is to make certain people who I work with achieve their career goals and are prepared in their current positions to achieve the next step. There are many avenues to take when it comes to succession planning.

Some managers, and the Japanese are famous for this, like to move people around laterally to increase their exposure to others parts of the company and for their personal exposure to others within the company. I'm not a big fan of this because it can create its own problems for the employee as well as others. I believe there are more effective ways to increase a person's exposure.

You can assign this person to special projects in which they will be working with others they do not normally work with. You can make them a team leader on a project and let them lead a diverse group of people. You can also send them to outside education to broaden their working knowledge.

One of the benefits you will quickly notice from the aforementioned succession planning strategy is that really outstanding employees will have high morale and will want to stay with the company because they realize and appreciate the time and attention you are investing in them. That also builds loyalty from that person directly to you.

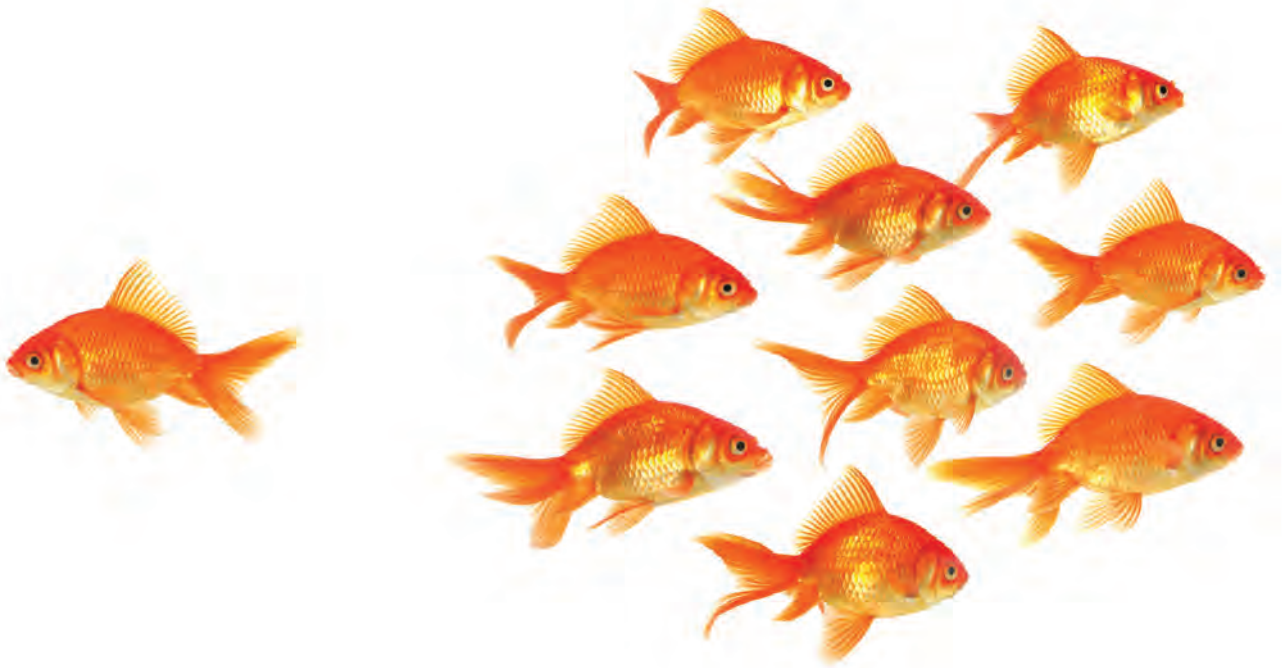
Here's the other thing you should think about when it comes to succession planning. I have seen it several times when a person who is in a critical position with his/her company is being considered for a promotion. As managements' discussion continues, inevitably the question will come up as to who will replace the person being considered for the promotion.

When the answer comes back that there is no one internally that can replace the person being considered for the promotion, management has the option of going outside on a search or just hold off on the promotion for the time being. More times than not, management just temporarily tables the promotion. You don't want that to happen to you! ◆

BIOGRAPHY

John A. Bermingham
Executive VP & COO
1st Light Energy & Conservation Lighting, Inc.

John A. Bermingham is currently the Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. He was previously Co-President and COO of AgraTech, a biotech enterprise. Previous to that, he was President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. More previously, he was President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turn around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the US Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and graduated from the Harvard University Graduate School of Business Advanced Management Program.



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