Drug Development & Delivery

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Prefilled Syringes & Parenteral Contract Manufacturing

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

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The Second Quadrant

"I realize we may not be able to improve the return on R&D investment and the success rate for APIs for the whole industry, but it's certainly worth our while to focus on tackling bioavailability issues. Agere has done an analysis of the potential impact of collaborating to overcome the challenges we currently face, and we believe there is a significant and as-to-date unrealized market opportunity."

p.20

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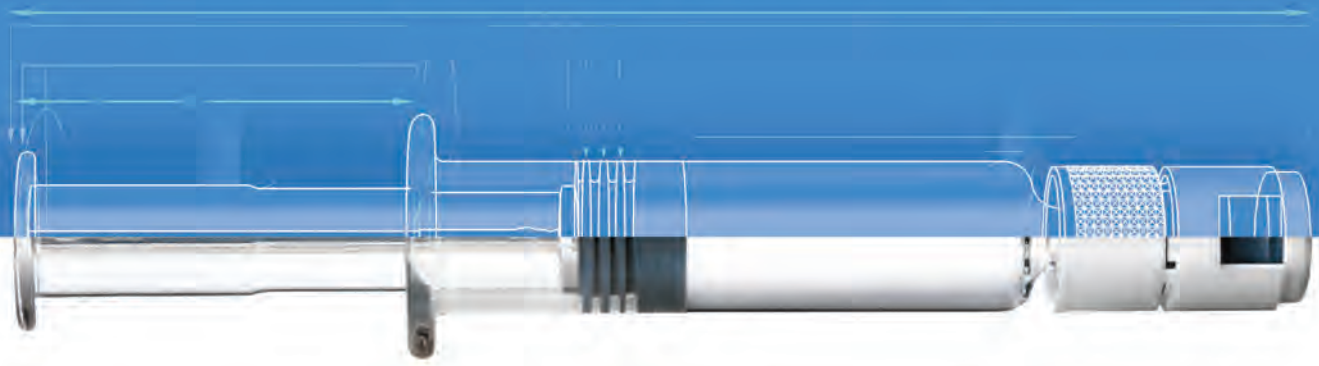

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Flexibility & Customization

"A rise in biologics and complex compounds, specifically in the transition of clinical pipelines in large-molecule drugs that require innovative injection methods, is driving the prefilled syringe market. The erosion of the blockbuster model, expiring patents, and growing competition have also increased the need for differentiation in drug delivery, while changes in demographics, particularly in the growing homecare sector, increase the need for convenient and safe administration forms that are user friendly, reliable, and cost conscious."

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Unilife Signs Long-Term Customization & Commercial Supply Agreement; $110-Million Potential

Unilife Corporation recently announced the signing of a Customization and Commercial Supply Agreement with a US pharmaceutical company for the EZMix™ dual-chamber syringe.

Unilife will supply the customer with a customized device from its EZMix platform of dual-chamber delivery systems for use with a lyophilized drug that requires mixing at the time of injection. The drug, which is a proprietary version of an approved therapy, is entering late-stage clinical development with the customer planning an accelerated pathway to US regulatory approval.

Unilife expects to generate up to $110 million in revenue during the 15-year agreement based upon a customization and production scale-up program, commercial device sales, and a royalty of net drug sales. Unilife will immediately begin to generate revenues under the program.

The customer will pay Unilife approximately $3 million over a 12- to 24-month period for the customization and supply of prefilled EZMix devices for scheduled activities, including human clinical drug trials and compatibility testing. Unilife will receive an additional $3 million from the customer to fund the production scale-up of high-volume assembly equipment to manufacture the customized device at commercial volumes.

In exchange for the customer securing worldwide exclusivity to EZMix for its target drug, Unilife will receive royalty payments on net annual commercial revenue of the drug. These royalty payments are expected to represent approximately a third of the $110 million in cumulative revenues generated by Unilife during the contract period. The agreement includes a guaranteed minimum annual royalty payment that the customer must provide to Unilife in order to maintain EZMix exclusivity for the target drug.

For commercial purposes and due to confidentiality provisions in the agreement, additional terms of the contract and the identity of the customer are to remain confidential at this time.

Aragen Bioscience & Innovent Biologics Announce Collaboration for Biotherapeutic Product Development

Aragen Bioscience, Inc. and Innovent Biologics, Inc. have initiated a collaboration for the development of manufacturing cell lines for biotherapeutic product development. Under the terms of the agreement, Aragen Bioscience is developing robust CHO cell lines and assessing critical product quality attributes for various antibodies and protein therapeutics.

"Aragen Bioscience has demonstrated expertise in cell line development and protein product characterization. We recently completed the first technology transfer of the collaboration and are continuing with multiple additional products," said Michael Yu, CEO of Innovent.

A contract research organization that offers a complete range of high-quality services, Aragen Bioscience focuses on customer service and technical leadership to enable clients to cost-effectively accelerate their research efforts. Aragen Bioscience offers cell line development, protein expression and purification, molecular biology, cell biology immunology and diverse in vivo services to the biotech and pharmaceutical industries.

"Innovent is a great partner for the clinical development of biologic products expressed by the cell lines we have generated. We look forward to the expansion of the collaboration," added Oren Beske, PhD, Vice President of Aragen Bioscience.

Foster Expands Nano-Reinforced Polymer Product Range for Medical Devices

Foster Corporation now offers nano-reinforced composites for minimally invasive devices, such as catheters, with reinforcement loadings up to 30% by weight. Nano-reinforced compounds with high filler loadings provide substantial increase in physical properties of the base resin while maintaining processability in thin wall components.

Nano-reinforced compounds incorporate ultra-fine nano platelets that interact directly with the polymer structure to increase flexural properties and improve rigidity of components. Previously polymers, such as polyamides (nylons) and thermoplastic elastomers (TPEs) were often limited to 15% nano-reinforcement filler loading by weight to ensure dispersion of the ultra-fine platelets in the polymer matrix. Foster has developed proprietary compounding screw designs and processing methods that are now capable of achieving loadings up to 30% by weight resulting in flexural modulus increases up to 300% in common medical catheter materials such as TPEs.

Foster's range of nano-reinforced compounds for thin-wall medical device applications include nylons, TPEs, and thermoplastic polyurethanes (TPUs) with nano-platelet reinforcement loadings from 1% to as high as 30%.

Nano-reinforcement technology allows engineers to tailor the properties of a medical device without changing the base polymer, which may be necessary to for co-extrusion or bonding applications. For example, the flexural modulus of a 72 durometer of a TPE polymer can be adjusted from 100,000 to 400,000 psi (690 to 2758 MPa) using nano-reinforcements up to 30% by weight.

Metrics Offers New Proprietary Technology to Improve Taste, Stability & Deliver SR Characteristics

Metrics Inc. now offers proprietary technology to mask the taste of tablets. The company's innovative Cleantaste technology enables polymer coating of individual drug crystals to produce fine, non-gritty particles sized 25 to 125 micrometers. This technology can improve the taste and mouth-feel of drugs and can be used to support stability or deliver sustained-release characteristics.

"Cleantaste technology is suitable for orally dispersible tablets and encapsulated products," said Dr. Brad Gold, Vice President of Pharmaceutical Development. "If patients don't take their medications because they taste bad - or they're difficult to swallow - then that obviously can have serious detrimental effects on treatment plans and health outcomes. We want to help patients comply with prescription regimens by improving the palatability of medications and making them easier to swallow. Cleantaste technology allows us to do that."

Metrics Inc. is a full-service global pharmaceutical development and manufacturing organization serving clients worldwide. The addition of Cleantaste technology to Metrics' portfolio of formulation and manufacturing capabilities is the result of its recent acquisition by Mayne Pharma Group Limited. Together, Metrics and Mayne offer an impressive proprietary portfolio of advanced drug delivery technologies for controlled release, bioavailability enhancement, and taste-masking.

Management Insight

Rook to D7: Game Theory in the Pharma Industry

By: Derek Hennecke,
CEO & President, Xcelience

Part 4 of a 6-part series offering an overview of this year's six best business books with insights into what they can teach the Pharma industry.

Chess is an allegory for business. Plot several steps ahead of your current move. Anticipate your opponent. Compensate for your weaknesses. Take inventory of your resources, and use them all for maximum advantage before going on the attack.

People believe chess is a test of intelligence. This may be true at the beginning stages, but not in advanced play. No matter how clever you are, you can't win against an experienced player unless you, too, have studied the tactics. At a C or 1500 level - not an easy level to achieve - 90% of what players do is still just identifying common tactics to be able to avoid traps. Business is not much different.

Chess has a defined playing field and a set number of possible moves, allowing us to calculate its complexity. The number of legal positions in chess is between 10^43 and 10^50, with a game-tree complexity of approximately 10^123. In business, the number of legal positions is infinite, rendering the complexity incalculable. Still, just as in chess, there are basic strategies that are frequently followed, and if you don't recognize the moves and deploy them to your advantage, you will be quickly outmaneuvered, no matter how clever you are.

Len Fisher's book, *Rock, Paper, Scissors*, is a lively study that illustrates many of the basic tactics in game theory; plays that are of infinite value both in business and in life. Developed in the 1940s, game theory looks at the decisions people make when confronted with competitive situations, especially when they have limited information about the other players' choices.

Such games typically have a Nash equilibrium, which (roughly speaking) is the result when players behave selfishly. Many times, there are also cooperative strategies on the table that would make everyone better off, creating a social optimum.

Knowledge of these and other basic strategies of the game are essential reading in today's business world. In the world of chess, you need to know a Caro-kann opening from a Sicilian opening so you can anticipate and react preemptively. In business, you should be aware of a couple of approaches to achieve cooperation in the face of temptations to cheat. Fisher brings us abreast of several basic and advanced tactics, including the Tragedy of the Commons; Free Rider; Chicken; Volunteer's Dilemma; the Prisoner's Dilemna; the Battle of the Sexes; and the Stag Hunt.

PATHEON & BANNER: A FRESH CHESS BOARD

The game was pretty much over in the soft-gel market before Patheon bought Banner. There were only two players in the market: Catalent, a company with a broad range of offerings producing a high-end product with an excellent reputation, and Banner, a one-trick pony producing only soft gels and not really considered a credible vendor. Catalent held a near monopoly.

Customers, predictably, didn't like it. "Numerous existing Patheon customers have been specifically requesting soft-gel manufacturing alternatives to their current suppliers," says Patheon President Geoff Glass to Outsourcing-pharma.com. Adding Patheon's breadth of offerings to Banner's patent-pending drug delivery platforms was like sweeping the pieces off the board and starting the game fresh. Assuming Patheon now offers a credible product of equal value to Catalent's, there is now the potential for some serious competition.

At a glance, it might seem that Patheon should take market share. Not necessarily. Just having the right product in the right market isn't enough. The outcome will depend on how Patheon plays the game. Soft-gel customers can also influence the outcome based on how they play the two major manufacturers against each other. This is the point at which business becomes more about game theory than about product offerings.

GAME THEORY & THE HOLLAND SWEETENER COMPANY (HSC)

To understand the game Patheon and Catalent are playing, it's helpful to recall a classic case study in game theory. This is one that was impressed upon me not just by my MBA professors

many years ago, but later when I spent more than 10 years working for DSM, the parent company that owned Holland Sweetener Company and primary problem owner in this Harvard Business Review case study on game theory.

HSC was a joint venture between DSM and a Japanese company. It was formed with only one purpose: to create a competitor to NutraSweet (remember the little swirl on your Coke or Pepsi can?). NutraSweet was a brand name for aspartame, and a 100% monopoly owned by the Monsanto Corporation. It was a sweet market, enjoying 8% returns in 1986, and the market was projecting 75% growth in the following year.

The product HSC produced was essentially identical to NutraSweet. Shipping costs were so low as to be insignificant, so it didn't really matter where it was produced. The only real basis for competition was price.

HSC was well positioned to withstand a price war. It had the financial strength behind it to take a beating, as did NutraSweet. But the fledgling company also brought with it the Tosoh patented process for manufacturing aspartame, which was less costly and more flexible. In addition, HSC had better knowledge of the European market, and access to raw material supply. Monsanto had good reason to take this new threat very seriously. For its own reckoning, the Monsanto plant had the capacity to produce 7000 tons, compared to HSC's 500-ton plant. Monsanto had economies of scale.

Neither side would want a price war - a game that produces two losers before it produces a winner. A price war, following Fisher's thinking, is just another form of a game of Chicken. How low can you go? The price can go so low that both sides end up subsidizing sales by borrowing from the larger company's reserves, until finally one player is forced to exit the market. If the players take the game too far, it's possible to bring both companies down.

This is the point at which game theory entered the equation. HSC had to put itself in the shoes of its competitor and anticipate what Monsanto would do to minimize the impact of HSC on its own bottom line. HSC determined that Monsanto would not choose a price war. The pie was big enough for both of them, and Monsanto would accept the inevitability of competition, rather than risk ruin for both.

That proved to be a fatal miscalculation, and it was made worse by the fact that HSC made no preparations whatsoever for what they perceived as the slim possibility that Monsanto would indeed launch a price war. HSC was completely vulnerable when Monsanto began aggressively slashing prices. Monsanto, it turned out, had a safety net. With multi-year contracts locking up Coca cola and Pepsi as clients, Monsanto was guaranteed volume, and by extension, something of a profit cushion. HSC had no cushion whatsoever, so the losses came hard and fast. For years a bitter price war ensued, but HSC never filled its 500-ton plant enough to make even the slimmest profit. In 2008, HSC's parent company finally closed the financial spigot, the plant closed, and 100 employees were laid off.

It didn't have to play out that way. If HSC had at least recognized the possibility of a price war, it would have strengthened its opening position with what game theorists call a Pay-to-Play strategy. Before entering the market, HSC should have gone to some of the largest consumers of aspartame and offered them a price substantially lower than what they were currently paying Monsanto in exchange for guaranteed volume. By doing so, they would ensure that they had enough volume to pay salaries and costs and to stay in the game, before entering the market. If Monsanto found out about these deals, all the better. Just demonstrating this staying power might have been enough to dissuade Monsanto from beginning a price war in the first place.

THE PAY-TO-PLAY MANEUVER IN ACTION: THE RANBAXY TEVA DEAL

Here is an example of the Pay-to-Play Theory used effectively. Last year, Ranbaxy was confronted with a major quality complaint from the FDA. Having just secured a 180-day exclusivity period to produce the first generic competitor to Lipitor as it came off patent, this potentially mega-lucrative deal was suddenly threatened.

Ranbaxy chose to create a back-up plan. If the FDA halted production in their own plant, they would have another plant in the wings pre-approved and ready to produce for them. Ranbaxy turned to Teva.

This was undoubtedly a solid strategy on Ranbaxy's part, but Teva is also clever. Teva might have sat meekly on the sidelines waiting and hoping that the understudy would be needed, but instead, it made a deal. Teva gave Ranbaxy its word that it would be Ranbaxy's back-up, in return for promise of payment either way. If Ranbaxy didn't need Teva, Teva would still receive a payment just for its willingness to be ready in the wings. Ranbaxy apparently considered this a worthwhile investment because it accepted the deal, and in the end, Teva collected the payment without ever having to produce a single tablet.

It's risky to do business without some form of guarantees. Wherever possible, you should look for ways to be paid to play. If the market sees value in what you have to offer, there is usually someone who will be willing to pay for your involvement.

PAY TO PLAY: THE SOFT GEL MARKET

According to Patheon, soft-gel capsule customers are demanding competition in this market. That seems likely because Catalent has been operating in a near monopoly - Banner did not make a serious competitor to many buyers. Patheon is changing that by incorporating Banner's soft-gels as part of Patheon's broader array of offerings. But just being there as a viable competitor is not a guarantee of success.

What happens now depends on how Catalent and Patheon play the game. Much as in the HSC case, there is the potential for a price war here. Catalent customers could be waiting quietly for Patheon to offer up lower prices, so that they can take those back to Catalent and force Catalent to lower its prices. If they then stay with Catalent - playing it safe, arguably - Patheon could find itself in HSC's situation. Without a basic level of business - without being paid to play - Patheon could be forced to exit the market. Then Catalent can crank the prices back up, and customers will be back in the same position they were before.

Similarly, if Catalent locks up the major customers with long-term multi-year contracts, Patheon may never gain a foothold.

As is often the case in business, both companies have a quality product to offer in a lucrative market that wants competition. But the outcome won't necessarily be determined by the quality of the offering. It will be determined by the way the game is played. ◆

BIOGRAPHY

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

The Second Quadrant

A Call for Collaboration to Meet the Bioavailability Challenge

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

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

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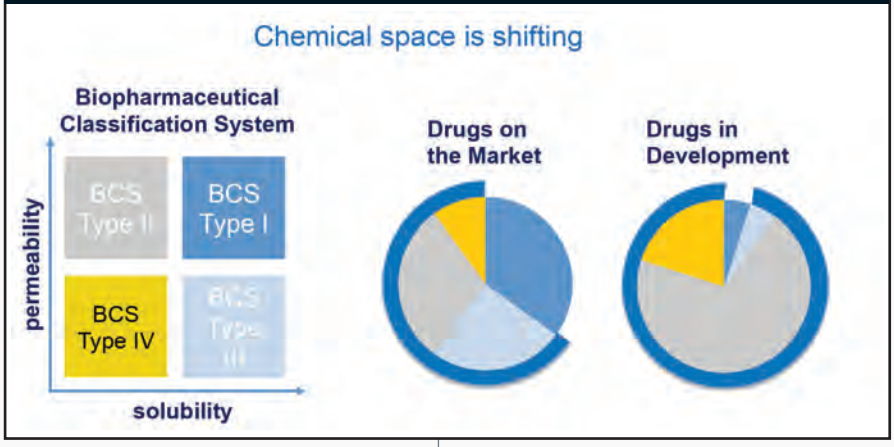
When asked to deliver a column on solubility enhancement, I gladly accepted. I am passionate about this area in particular, and at a higher level, with the common goal of advancing compounds to the clinic and marketplace. A column with this focus has the potential to give all of us who deal with bioavailability challenges an opportunity to share ideas on where we stand, and then brainstorm how we might pull together to overcome the barriers we face. As a first step, I thought I would identify a few of the key issues, and then follow this in subsequent columns with thoughts and ideas from different perspectives about what can be done to advance the science, technologies, and methodologies beyond "challenges" or "concerns" to real implementation. An issue of considerable interest to me is the standardization of approaches for solubilization based on rigorous science.

I want this column to become a forum for discussion among and between pharmaceutical companies, the CROs and CMOs that serve them, the excipient providers that are an essential piece of the puzzle, equipment and lab instrumentation manufacturers, and universities that contribute to advancing the science and technologies we leverage. I personally believe collaboration will lead to breakthroughs to advance our segment of the pharmaceutical industry to the benefit of all.

No inaugural article in this space would be complete without the motivation of why solubilization is emerging as a concern now shared by an increasing number of us. I believe we all know this, so I'll try to be brief and provide an overview that justifies the importance of this topic for our industry and the patients we serve. After this first column, and based on input you provide, I hope to increasingly incorporate thoughts, ideas, and diverse frames of reference in order to better inform us all. So I'll paint the picture as I see it today, and look forward to getting your input so we can gain new insights with the goal of developing a richer understanding of where we are, how we got here, and how we can progress.

FIGURE 1



COMPOUNDING PROBLEMS

It's estimated that more than 40% of APIs today have solubility challenges in early development. Looking at drugs previously brought to market compared with drugs under development, there is a shrinking number of APIs that fall into the range of being both highly permeable and highly soluble. Based on estimates done by Benet, Leslie Z. and Wu, Chi-Yuan in late 2006, and using the Biopharmaceutical Classification System (BCS), the most soluble and permeable compound type (BCS Type I) accounts for approximately 35% of marketed drugs, but for only 5% of drugs in the development pipeline. With such a large percentage of APIs requiring bioavailability enhancement - and the most challenging compounds (BCS Type IV) accounting for more than 20% of these, we're all faced with a significantly changing drug delivery landscape.

Due to the increased complexity of the diseases we are addressing today, it appears that solubility challenges are not a fad but rather firmly rooted in physical chemistry and biology. And as discussed in the interview published in the April issue of this publication, "Solubilization: Accessing Broader Chemistries by Integrating Fundamental Science With Automation for Greater Predictability", there's growing consensus that achieving the required potency and selectivity mandates carefully engineered hydrophobicity. This requirement gives rise to an increasing number of compounds with low intrinsic bioavailability.

R&D INVESTMENT VS. SUCCESS

For the industry as a whole, R&D investment is increasing, and yet FDA approvals are in decline. According to the European Federation of Pharmaceutical

Industries (EFPIA), the global R&D spend in 2010 climbed to more than $120 billion from under $70 billion in 2002. This increase is highly correlated to the cost to develop a new drug, which in 2011 was $1.38 billion, a ten-fold increase in less than 40 years based on estimates from EvaluatePharma. But according to FDA reporting, the number of FDA approvals of new drugs and NMEs throughout that same period has only grown by 50% and 40%, respectively.

We might take solace in the fact there's a higher success rate today in terms of NDA applications vs. approvals, growing to a ratio of just over 5:1 in 1975 to 3:1 in 2011, but with a capitalized R&D cost increasing by 900% in the same period, it's hardly comforting.

LACK OF PREDICTABILITY

The attrition of promising APIs as they progress from discovery into preclinical and then through clinical trials remains high. Recent estimates reported in PhRMA's 2012 Profile of the Pharmaceutical Industry show a continuing trend of the difficulty faced when trying to accurately predict how drugs will perform as they move toward the clinic. Even after extensive investment of money and time before entering Phase I trials, evidence shows that the lack of predictability for efficacy and toxicity is clearly the most pressing challenge of all.

FIGURE 2

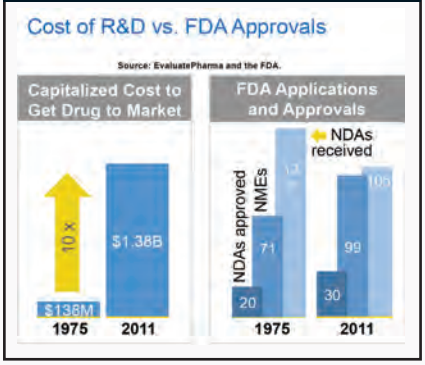
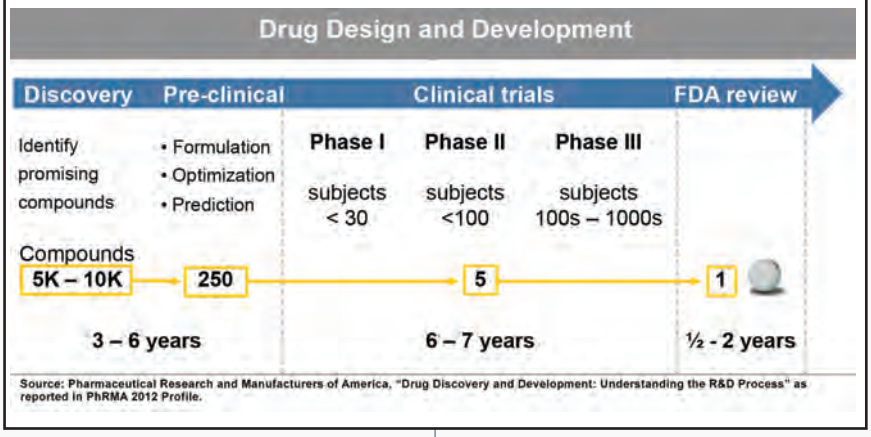


FIGURE 3



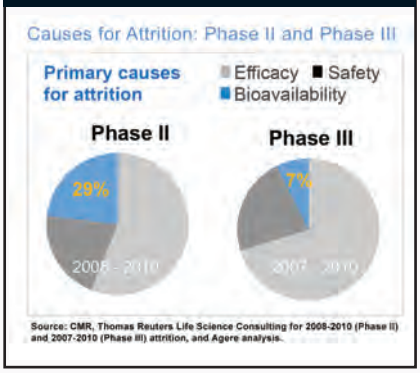
However, the attrition of drug candidates isn't solely due to lack of efficacy or unforeseen toxicity. We estimate that almost 30% of APIs have been historically lost during Phase I & II clinical trials due to bioavailability, and a remaining 7% in Phase III.

The poor bioavailability of these drugs should be predicted and rectified with robust formulation approaches as early as possible. Clearly, this is the goal for every company, and our industry's pursuit of better prediction is partly evidenced by the significant R&D investments that continue to chase what may appear to be elusive solutions. In fact, it may be time for us to audit our current approaches, as in many cases, there may be significant improvements that can be found.

SOLUBILIZATION APPROACHES

Throughout the past 50 years, numerous approaches have been developed to improve the solubility of intrinsically insoluble compounds. By far, the most common approaches are salt forms. However, many other methods have been successfully applied. Other platforms include: co-crystals, co-solvents, complexing agents, lipid-based vehicles, particle size reduction, solid dispersions, and surfactants. Each approach has its own set of advantages, and the selection process to identify the optimal platform for any particular compound can be daunting. While it is in principle possible to screen each of these approaches for viability using a brute force method, it is often not practical from a cost, time, and API availability perspective. Nor should it be necessary. More fundamental understanding is needed industry-wide to relate the properties of a given compound to the preferred formulation platforms. Further, we should never be satisfied with "this formulation worked best" without analyzing "why." Our past successful experiences and assumptions about "why," and what can and cannot work may themselves be barriers to our progress as they often preclude us from taking a more scientific and objective approach.

FIGURE 4



THE OPPORTUNITY

I realize we may not be able to improve the return on R&D investment and the success rate for APIs for the whole industry, but it's certainly worth our while to focus on tackling bioavailability issues. Agere has done an analysis of the potential impact of collaborating to overcome the challenges we currently face, and we believe there is a significant and as-to-date unrealized market opportunity. As reported in the aforementioned April interview, we've performed an analysis on a database containing data on more than 1,300 marketed drugs. We explored what the impact might be if we could shift the distribution slightly, to a lower solubility and higher water-octanol partition coefficient, and then assume similar numbers of compounds compared with historical records. This can be accomplished leveraging today's more modern solubilization technologies and approaches, and by our estimates, would enable approximately 450 new and yet-to-be-discovered compounds to enter the market.

We estimate this represents an expansion of the market by 35%, which translates into an opportunity of $135 billion in today's dollars.

WHAT WILL IT TAKE?

To start things off, I thought I'd summarize my thoughts about what could have significant impact on advancing solubilization technologies. This is not an exhaustive list, but I hope that this will stimulate thought and conversation toward our shared goal for improved solubility prediction, which promises to reduce R&D spend and time to market.

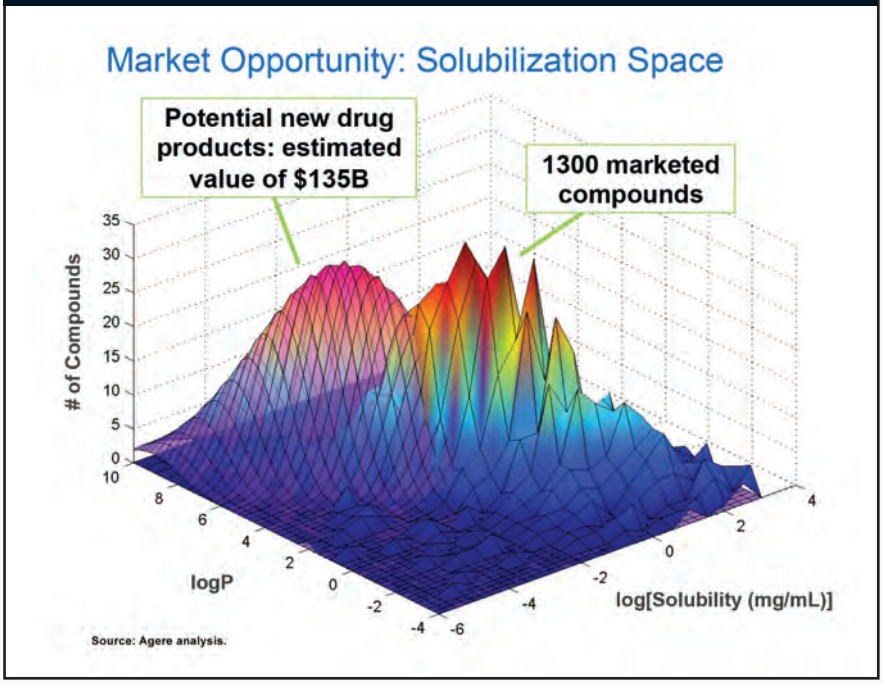
Innovation

We need to innovate at every stage, but with consideration for the ultimate goal: that is, local optimization in a global context. Progress is possible if we tackle problems that are both critical and solvable, and simplify them using fundamental science and robust approaches. Our success at innovation will strongly correlate with the level of discipline and structure we can impose on the problem and solution space, and integrating an awareness of the impact an isolated change will have on subsequent stages in the development process. Shared understanding of the APIs, excipients, and solubilization technologies at a fundamental level will be essential. Part of this will involve more distributed knowledge about of the variables and complexities being faced by those in our ecosystem and those whose work comes before and after ours. In other words, we need to apply what we have learned in the past to today's problems. In general, I believe that we as an industry spend far too much time re-hashing the same issues that have been solved by great science and scientists in previous decades. You may have had a similar impression at a recent conference.

Specification

Detailed specifications at the beginning of the formulation development process would increase the probability of satisfying solubility requirements. While it is almost never possible to completely

FIGURE 5



define the requirements for bioavailability improvement, dose, etc., it is essential that every effort be made to define our goal. In addition, such specifications should include information regarding the company's best practices and preferences. This information will serve to constrain and guide formulation design and optimization. How detailed and under what context this information is provided is for another discussion, but a more formalized approach to using specifications to constrain and put discipline into the flow from drug substance to drug product in the clinic will help us all efficiently identify which formulation approaches have a greater chance for success, and which have a higher risk profile.

Standardization

Given the interdependence of the players in our industry, standards on many levels could have great impact. Detailed descriptions of the chemical properties of excipients that enable apples-to-apples comparisons would enable formulators to do rigorous modeling and testing to seek the best excipient candidates for a given API. Empowered in this way, formulators can rationally explore excipients based on specifications for the drug performance and commercial image.

Exploration

Specifications and standardized information about APIs and excipients will facilitate a broader and more agnostic explorations of platforms and excipients that fall into the "most likely to succeed" category for every compound. Each compound is chemically unique, and armed with the same level of information about the drug requirements and a broader set of platforms and excipient candidates will enable a more comprehensive and unbiased exploration for the best solution.

Design Automation

Today's complexity of bringing modern medicines to the clinic exceeds the abilities of any one person or team to apply an empirical approach, based on what's worked in the past. This method alone clearly isn't delivering the innovations and efficiencies demanded in 2013 and beyond to achieve a successful drug product. With specifications and standardization, formulation design automation could be enabled to facilitate fast, rigorous, and accurate in silico exploration of combinations unimagined today. This will be the underpinning that delivers greater predictability, translating into a higher-proportion of drug candidates that successfully navigate through the clinic.

Going Forward

In subsequent columns, I plan to present other ideas and opinions on what it will take to tackle the challenges we face, and any other bioavailability-related subject matter of interest to the DDD readers. To initiate this interactive and collaborative process, please send me your reactions, thoughts, and suggestions so we can a start the dialogue. I look forward to hearing from you (see my bio for contact information), and together moving our part of the industry toward a new era. Toward solubility success! ◆

BIOGRAPHY

Dr. Marshall Crew is President and Founder of Agere, a leading CRO/CMO focused on improving the oral bioavailability of insoluble APIs. The company supports clients from formulation design and development through cGMP manufacturing for Phase I through Phase IIb clinical trials. Agere is expert in spray drying and amorphous technologies, and at in vivo study design and interpretation. Dr. Crew has devoted his career to improving oral bioavailability, developing innovative technologies and approaches for the delivery of poorly soluble drugs and then managing their application to achieve client success. Prior to Agere, he was VP of Chemical and Biological Sciences at Bend Research. Dr. Crew's scientific expertise includes formulation design and development, solid state characterization of drug substance and product, and computational modeling (predicting shelf-life and pharmacokinetic and bioavailability for oral, devices, and parenteral delivery). He is a world expert in the design of API physical properties to optimize efficacy and overcome PK and delivery constraints. Over 27 patents and patent applications have been issued or filed under his name on various drug delivery platforms, including controlled release, nanotechnology, and solid dispersions. Dr. Crew earned his PhD in Physical Chemistry from Oregon State University, and is a member of Agere's Board of Directors. He can be reached at crew@agerepharma.com or LinkedIn: https://www.linkedin.com/profile/view?id=17815140.

Delivering Gastric-Resistant Functionality Via a Colorless Top Coat

By: Philip J. Butler and Thorsten Cech

Several formulation development challenges exist in the field of gastric-resistant film-coating. The functional polymer, poly(methacrylic acid-co-ethyl acrylate) (MAE), can react with some pharmaceutical actives (eg, omeprazole), and also with excipients (such as pigments or colourants) commonly used in enteric coating formulation development. Additionally, the selection of the correct plasticizer is important with respect to the optimization of film properties and process conditions. Plasticizer selection can also be further complicated by regional regulatory acceptance limits and maximum daily intake allowances.[1,2]

Film-coating ingredient incompatibilities with MAE can be eliminated by formulating a coating with just a plasticizer.[3] This makes choosing the right plasticizer even more important. For these simplified, two-component formulations, characteristics, such as moisture up-take (eg, pellet or tablet) during the first 2 hours of dissolution testing, can be significantly influenced by the hydrophilic or lipophilic characteristics of the plasticizer selected.

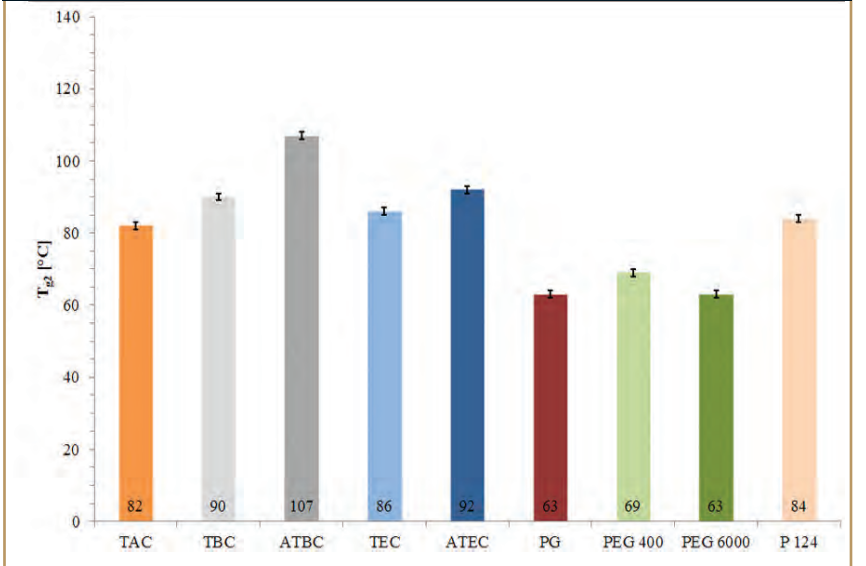
This work was initiated to investigate the gastric-resistant functionality obtained by applying a clear, two-component MAE coating formulation onto a tablet sub-coated with a pigmented instant-release coating. The impact of hydrophilic and lipophilic plasticizers on the film characteristics of MAE-based coating formulations was also evaluated. Specifically, glass transition temperature, isolated film elasticity, and the water up-take of films and tablet cores were tested along with tablet dissolution.

MATERIAL & METHODS

Pigmented sub-coat trials were conducted on seven individual batches using a different Kollicoat® IR Coating Systems base coating color for each trial. Tablet cores were coated to a theoretical 3% weight gain. An equal number of tablets from each sub-coat trial were combined to form one batch for the enteric coating top-coat.

An aqueous dispersion of methacrylic acid - ethyl acrylate copolymer (non-proprietary names: BP: Methacrylic Acid–Ethyl Acrylate Copolymer (1:1) Dispersion 30

FIGURE 1



T_g of isolated MAE films plasticized to 15% with various plasticizers (mean ± s, n=2).

A lot alike? Completely different.

Like the patients they will someday help, no two APIs are identical. Agere's drug delivery platform leverages experience, fundamental science and design automation to enable personalized formulation and development solutions for every compound.

A global leader in designing and implementing advanced solubilization technology, Agere delivers fast, effective and efficient formulation solutions.

Realize the value potential of your compounds with a modern and customized approach.

Solubility Solutions™

› cGMP analytical and manufacturing
› Formulation design and development
› All services customized
› Offered on a fee-for-service basis

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per cent; PhEur: Methacrylic Acid–Methyl Methacrylate Copolymer (1:1); USP-NF: Ethyl Acrylate and Methyl Methacrylate Copolymer; synonym: dispersion Kollicoat® MAE 30 DP, BASF) was chosen for this study. Triacetin (TAC) – Kollisolv® GTA (BASF), propylene glycol (PG) – Kollisolv® PG (BASF), polyethylene glycol (PEG) 400 – Kollisolv® PEG 400 (BASF) and PEG 6000 – Lutrol® E 6000 (BASF), poloxamer 124 (P124) - Kollisolv® P 124 (BASF), triethyl citrate (TEC) – (Jungbunzlauer) and acetyl triethyl citrate (ATEC) – (Jungbunzlauer) were chosen as hydrophilic plasticizers. Acetyl tributyl citrate (ATBC) – (Jungbunzlauer) and tributyl citrate (TBC) – (Merck) were used as lipophilic plasticizers.

Round-shaped 9-mm tablet cores were coated with various coating levels from 3 to 12 mg/cm². Tablet cores were formulated with the following excipients: 15.5% Caffeine (gran. 0.2-0.5), 74.0% Ludipress® LCE, 5.0% Kollidon® CL-F, 5.0% Kollidon® VA64, and 0.5% magnesium stearate.

A Manesty XL Lab 01 side vented pan coater assembled with a 480-mm diameter drum insert and filled to a 3.5 kg batch size was used for all coating trials. Drum speed was varied between 12 and 22 rpm. An OptiCoat spray gun with a 0.8 mm orifice diameter was used at atomizing and pattern air pressures of 1.8 bar. All coating runs were conducted at a 55°C inlet air temperature with a 450-m³/h inlet air quantity and fluid delivery rate of 13 g/min.

Preparation of Isolated Films

Isolated films were prepared by spraying the dispersion onto a rotating Teflon roll while continuously drying to approximately 33°C with warm air (fan heater). The samples were made with an approximate film thickness of 100-150 micrometers.

Differential Scanning Calorimetry (DSC)

A DSC Q2000 V24.4 Build 116 (TA Instruments) was used with a sample weight of 8 to 9 mg. After fast cooling from 150°C, the glass transition temperature (T_g) was determined with a heating rate of 20 K/min (n=2).

Elongation at Break (EaB)

A texture analyzer (TA-XT2i HR, Stable Micro Systems) was used to determine the mechanical properties of the film. The test was performed under controlled climatic conditions of 23°C and 54% rh.[4]

Dynamic Vapor Sorption (DVS)

A SPS11-1µ (PMT Analytical) was used for determining the water uptake of isolated films at conditions of: 25°C/60% rh, 30°C/70% rh, and 40°C/75% rh. At each temperature, the samples were dried at 0% relative humidity before altering the relevant humidity (n=3).

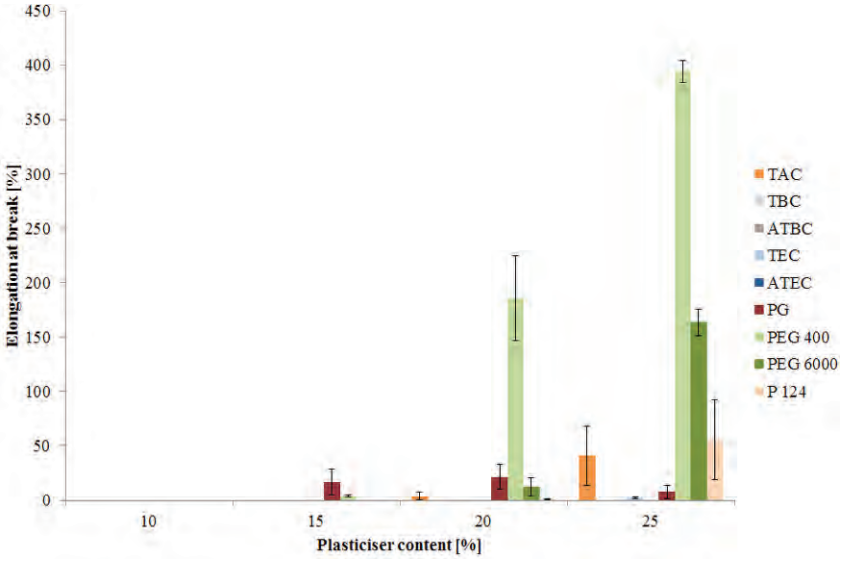
Dissolution Testing

Dissolution testing (n=3) was conducted in a USP dissolution apparatus 2 for 2 hours at pH 1.1 (HCl, 0.08 mol/L; volume 880 mL) and 37°C (± 0.5 K) with a paddle speed of 50 rpm. The pH was then adjusted to pH 6.8 by adding 20 mL of a concentrated potassium phosphate buffer system and testing continued for additional 60 minutes. The drug release was determined photometrically via on-line measuring.

Determining the Water Uptake of Cores

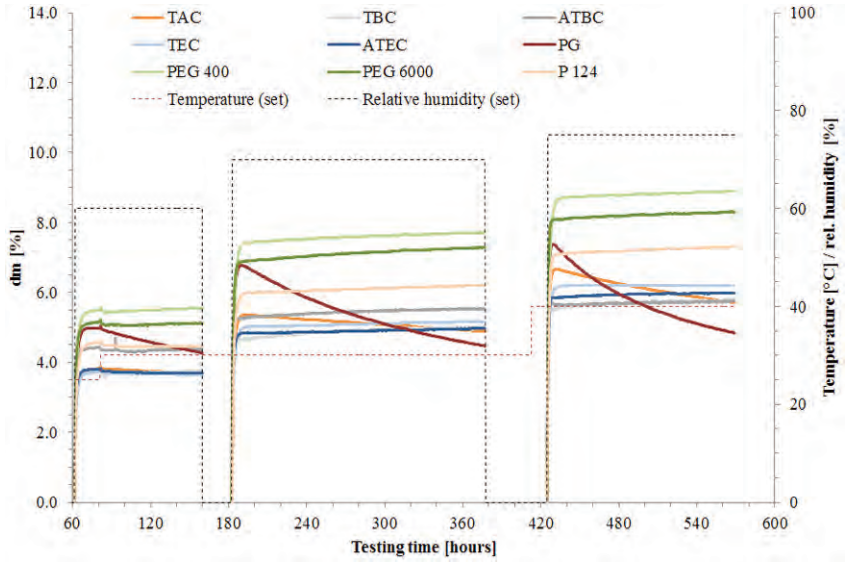
Ten coated tablets were weighed and put into a filter bag. The filter bag was then placed into a beaker of hydrochloric acid (HCl, 0.08 mol/L) and removed after 1 and 2 hours in exposure. The tablet surfaces were dried carefully and weighed again for determining moisture uptake.

FIGURE 2



Elongation at break of isolated MAE films plasticized with different plasticizers at increasing concentrations (mean ± s, n=5).

FIGURE 3



Humidity uptake of isolated films plasticized to 15% concentration with various plasticizers stored at different climatic conditions.

RESULTS & DISCUSSION

MAE inherently forms a very brittle, non-tacky film in a dry state due to its relatively high T_g of 113°C (± 2 K). Therefore, a plasticizer is needed to apply the polymer using standard pharmaceutical film-coating applications and conditions. The physical properties of the plasticized MAE films markedly depend on the character of the plasticizer. Hydrophilic plasticizers are preferred due to their more efficient incorporation within the MAE hydrophilic film matrix.[5] It was found that the more hydrophilic the plasticizer added the lower the resulting T_g will be (Figure 1). However, even at a plasticizer content of 15%, the T_g remains above 60°C, resulting in non-tacky films at ambient temperatures.[3]

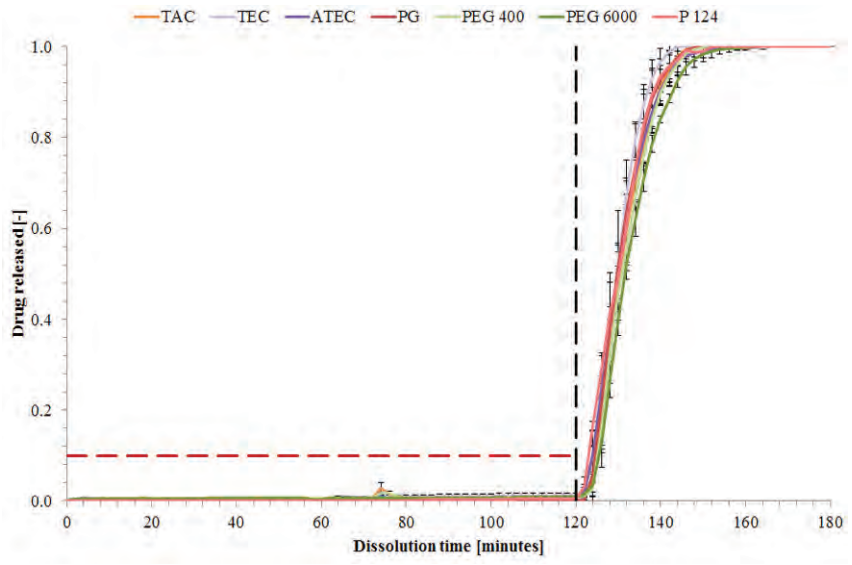
The hydrophilic properties of MAE allow water to act as a plasticizer, which is important to the film-forming process. As a result, minimum film-forming temperatures (MFFT) of < 0°C were measured in formulations containing only 10% TEC or TAC.[5] Only a plasticizer concentration of 10% resulted in a brittle, cracked film immediately evident after the coating process. Plasticizer concentrations of 15%, 20%, and 25% were found to lead to suitably plasticized films. Interestingly, it was found that even a relatively high 25% plasticizer level resulted in a non-tacky film.[3]

EaB as a measure of film elasticity can be used to appraise the risk of film cracking. It was found that both the type and concentration of plasticizer affect EaB values (Figure 2). Comparing the EaB results with those derived from DVS measurement (Figure 3) revealed a correlation of water uptake and elasticity, which provided further support for the plasticizing effect of water. Furthermore, losses in weight indicate certain volatility of PG and at elevated temperatures for TAC.[2,6]

All films tested containing plasticizer concentrations of 15%, 20%, and 25% provided full enteric functionality. No drug release was found during the first 2 hours of dissolution testing. After altering the pH-value to 6.8, immediate drug release with negligible lag-phase was observed. More importantly, drug release was found to be independent of the MAE coating level. Even the highest coating thickness of 12 mg/cm² resulted in the immediate release of caffeine.

The color appearance of Kollicoat® IR Coating Systems sub-coat was minimally affected by the application of the MAE top-coat, with Kollicoat® IR Sunset Yellow

FIGURE 4



Dissolution profiles of MAE coated caffeine tablets (coating level: 3 mg/cm²) holding 15% of different hydrophilic plasticizers (mean ± s, n=3).

exhibiting the most noticeable change. The change in color appearance was found to be independent of coating level and plasticizer content. Gloss values also remained relatively unchanged with increasing MAE top-coating levels.[3]

In regard to the use of PEG 6000 as a plasticizer, earlier studies with polyvinyl acetate based Kollicoat® SR 30 D have revealed that the complete incorporation of PEG 6000 into the polymer depends greatly on product temperature (T_P) during the coating process. Highly variable dissolution profiles were observed for tablets coated at different T_P with formulated Kollicoat® SR 30 D.[5]

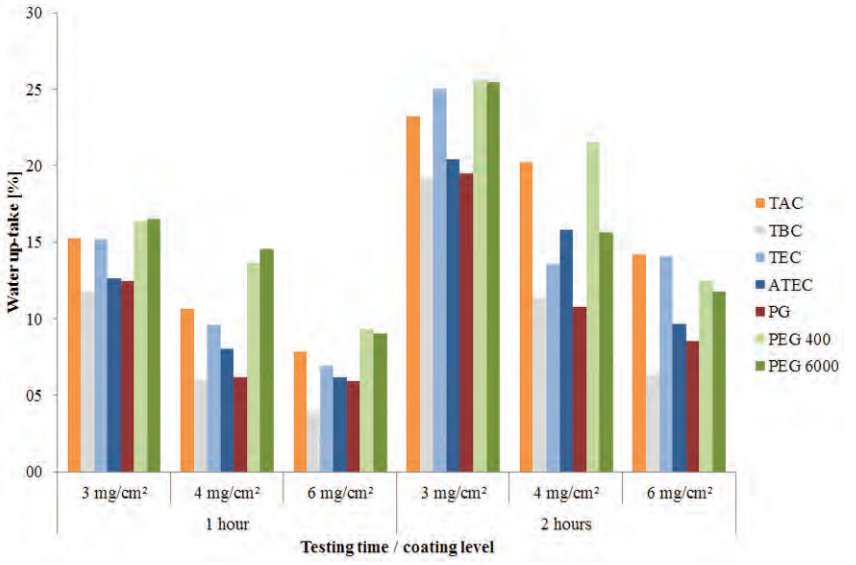
A similar phenomenon also occurred with Kollicoat® MAE 30 DP. White coating defects evident on the surface of MAE coated tablets at a T_P of 33°C are indicative of precipitated PEG 6000. However, this effect had no impact on the dissolution properties of these coated tablets. This is exhibited by the stable dissolution results seen with tablets stored for 12 months under climatic conditions (ICH). From these results, it is ascertained that PEG 6000 can be used as a plasticizer. The described effects that high concentrations of PEG (eg, in laxative applications) interfere with the gastric-resistant properties of MAE were found to be not relevant for this application.[7]

Eventually, all hydrophilic plasticizers tested led to the same dissolution profiles (Figure 4). Negligible drug release is seen in the first 2 hours of the testing in simulated gastric fluid across all coating levels, including the lowest value of 3 mg/cm². However, a fast drug release is observed over all enteric coating levels after altering the pH value to 6.8.

However, unlike hydrophilic plasticizers, different results were found with the lipophilic plasticizers TBC and ATBC. These lipophilic plasticizers were not incorporated into the MAE films as homogenously, and lead to a more porous coat. The increased porosity provides a conduit for active drug release during the first 2 hours of the dissolution testing. Improvement can be achieved by using a high shear mixer to prepare an aqueous micro emulsion of the plasticizer, which can then be added to the coating dispersion. To assure reliable gastric resistant functionality, a higher coating level of approximately 4 mg/cm² is recommended.[2]

Incorporation of lipophilic plasticizers into aqueous dispersions can be difficult, but their lipophilic properties improve water barrier functionality. It was shown that the quantity of water that permeates through the coating layer during the first 2 hours of acid testing clearly depends upon the properties of the plasticizer. Less water permeated the lipophilic plasticized coatings than the hydrophilic plasticized coatings during the first 2 hours of acid testing (Figure 5).

FIGURE 5



Water uptake of MAE-coated caffeine tablets (different coating levels) holding 15% of different plasticizers (mean, n=10).

CONCLUSION

In a dry state, MAE inherently forms very brittle, non-tacky films due to its T_g of 113°C. As a result, plasticizers are required for successful coating applications. The hydrophilic and lipophilic plasticizers evaluated in this study reduced the T_g to only about 65-85°C, which is out of the range of acceptable film-coating applications. Therefore, as fully functional MAE-based gastric-resistant film-coatings are routinely formulated and coated at product temperatures of less than 30°C, it's safe to assume that water acts as a plasticizer during the coating process as well.

A similar conclusion is derived when correlating the results of dynamic vapor sorption and elongation at break measurement: plasticizers that lead to a higher humidity up-take yield more elastic films.

Hydrophilic plasticizers, however, led to a higher water uptake during the first 2 hours of dissolution testing. If minimum

water uptake is crucial to overall tablet integrity, lipophilic plasticizers should be selected. For instance, the use of tributyl citrate as a plasticizer in lieu of polyethylene glycol 400 can reduce water permeation during gastric-resistance testing by 50%.

The application of a pigmented sub-coat and a colorless, functional top-coat is an easy method for preventing potential interactions between the API and the functional film-forming polymer. By formulating the functional coating by adding only a plasticizer to the polymer, the benefits of the pigmented coating systems (such as color matching) can be utilized as well.[8]

Applying MAE as a colorless top-coat not only provides an easy and efficient coating process, but also results in reliable drug-release functionality. By choosing the right plasticizer, the coating can be tailored for a particular dosage form. ◆

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BIOGRAPHIES

Philip Butler is the North America Technical Sales Manager for Coatings in the Pharmaceutical Ingredients & Services business unit, Care Chemicals Division at BASF. He graduated from Albright College with a BS in Biology, and started his career in the pharmaceutical industry at Teva Pharmaceuticals, where he worked in QA and Formulation Development for 4 years. Prior to joining BASF, he worked at Colorcon for 16 years in varying positions in the Technical Service and Sales departments. Mr. Butler joined BASF in 2008 as a Business Development Manager for Pharmaceutical Excipients applications and technologies in the areas of drug solubilization, controlled release, tablet compression, and coating.

Thorsten Cech joined the pharmaceutical industry as a lab assistant in 1990. After gaining some years of experience in different departments of Knoll AG (BASF Pharma), he moved to the galenical development group of Soliqs in 1995. In this position, he was responsible for the development of solid oral dosage forms, with particular focus on pilot and production scale hot-melt-extrusion technology. In 2000, Thorsten accepted a job opportunity at Boehringer Ingelheim Pharma GmbH & Co. KG. Being responsible for the formulation of OTC products, he supported the development of several solid dosage forms, nasal sprays, and syrups. After 7 years in galenical development, he started a work-study program in the field of process technology (with focus on pharmaceutical technology) at the University of Applied Sciences Bingen, receiving his Bachelors degree in 2007. Since 2005, he has been working for BASF SE in Ludwigshafen. As engineer, he is in charge of the European Pharma Application Lab. In his current position, he supports customers in Europe, West Asia, and Africa in regard to product application, formulation development, and process optimization. Further responsibilities are trainings and workshops.

Important Considerations in the Delivery of Large-Volume & Viscous Drugs

By: Kevin Cancelliere, MS

For more than 20 years, biotechnology-derived medicines have aided those suffering from chronic conditions, including cancer, diabetes, and multiple sclerosis. Biologic drugs, which are derived from living cells, are typically genetically engineered proteins, such as monoclonal antibodies (mAbs), that can be formulated to target specific components of a disease pathway. For example, biologics designed to treat rheumatoid arthritis may target components of the immune system involved in inflammation.

Biologics may offer patients better long-term outcomes than traditional, chemical-based therapies, along with the promise of fewer potential side effects. Throughout the past several years, there has been an increase in approved biological drugs and, in 2011, more than 900 biotechnology medicines were in development.[1] Protein-based therapies will most likely continue to require administration to patients in an injectable format for the most part, leading to an increase in the need for such formats.

Unlike traditional, chemical-based drug products, biologic molecules can be sensitive to products commonly found in prefillable syringe systems. These substances, which include metal ions and silicone oil, may impact drug efficacy and a delivery system's performance. Additionally, biologic molecules are typically very large and may require a higher concentration of the drug product for efficacy. The result is a drug product whose viscosity is significantly higher than currently approved self-injected products. In a traditional drug delivery system, such high viscosity may require clinical administration, multiple dosing, or more frequent injections, which can be less convenient for the patient.

Many biologics in use today are administered via intravenous (IV) infusion in an acute-care setting. However, trends toward self-injection and home care have increased demand for products that are easily injected by patients or caregivers in a home setting. At present, there are several approved biologic products intended for self-injection by patients, including Johnson and Johnson's Simponi®, Amgen's Enbrel®, and AbbVie's Humira®. These injections are typically designed for delivery into the subcutaneous space, require a relatively low dose (< 100 mg) for efficacy,

FIGURE 1

The West SmartDose® electronic patch injector technology platform, which uses a Daikyo Crystal Zenith® cyclic olefin polymer cartridge, was designed to meet the pharmaceutical industry's growing need for drug delivery devices that can deliver higher volumes of drugs subcutaneously.

and have a reduced risk of life-threatening adverse reactions. Both Simponi and Humira are packaged in 1-mL long prefilled syringes and dosed on weekly, semi-monthly, or monthly basis, depending on the patient's particular indication.

As biotechnology companies continue to create and test therapeutic proteins for new therapeutics that may require larger doses given over a longer period of time, packaging and delivery challenges may arise. As the trend toward self-administration continues, the need for careful consideration of primary container design, interaction with the drug product, method of administration, and end-user needs becomes more critical.

Novel materials, unique devices, and enhanced administration systems may improve the overall effectiveness of biologic therapy and, ultimately, the health, safety, and comfort of the patient. Even the most innovative drug product can only provide the appropriate therapeutic benefits to the patient if it can be delivered effectively, and the patient adheres to the necessary treatment regimen. As such, a successful integrated delivery system should consider the following four key elements:

1. The needs of the patient, caregiver, and healthcare professional: A drug delivery system should take into consideration the clinical benefit, ease-of-use, and the ability to adhere to a treatment schedule.

2. The drug: A drug product must provide effective treatment in an appropriate form that enables effective delivery with an optimum delivery rate and frequency.

3. A primary containment system: The drug must be held in a container that maintains effectiveness, safety, and optimum quality over a period of time.

4. A delivery device or system: The drug should be compatible with the containment system and designed to enhance the drug delivery experience for the patient or caregiver.

Understanding the key elements of a drug delivery system provides the cornerstone for biotechnology manufacturers to deliver a unique system that meets the needs of the drug and the patient while mitigating product and development risks and encouraging patient compliance. In addition, drug manufacturers should seek a partner who can offer innovative technology, manufacturing excellence, and ensure patient needs for safety and efficacy are built into drug product packaging from early stage development. Such partnerships will help drug marketers offer successful, integrated solutions, benefitting manufacturers, clinicians, and patients alike.

HUMAN FACTORS CONSIDERATIONS

To make an effective product, the patient must be at the forefront of the design of the delivery system. Human factors testing enables manufacturers to support delivery system development from a range of critical perspectives and makes it easy to predict (and design out) user-based risks or failures.

Recent FDA guidance on human factors and the mitigation of user-based risk in the development of medical devices has spurred biotechnology manufacturers toward understanding the scope, depth, and nuance of human factors engineering and design for usability. Human factors experts, those experienced in both the science and art of understanding human capabilities and limitations, have developed a thorough understanding of design options and how they affect human interaction.

For any product on the market, a measure of success is the consumer's ability to use that product effectively. In the healthcare arena, a successful delivery system must be easy-to-use, intuitive, efficient, and effective. In addition, any system must be safe for the patient or caregiver to use in the environment for which the product was intended, which could include the home setting. Biotechnology and packaging manufacturers must work together to ensure ease of use and mitigate risk, which may help to improve patient dosing compliance through the use of a device or system that considers the needs of the patient as well as the drug.

To design a delivery system that will resonate with patients, it's important to first understand the behaviors and motivations of the intended user groups. Insight into the unique experiences and situations of those users can be best achieved by conducting research that will drive innovation in design and development processes to create a solution that works for end users in a variety of situations throughout the course of treatment.

FLEXIBLE CONTAINERS FOR LARGE-VOLUME & VISCOUS DRUGS

New designs are evolving around the needs of today's growing biotechnology markets. Many of these technologies may increase the price of the drug product, and biotechnology companies are challenged to justify those additional costs, particularly in reference to the delivery system or device. Integrated systems that encourage ease of use may aid in increased sales, higher revenues, customer loyalty, and retention of market share. However, to justify the cost, it may help to go further back in the manufacturing process.

Material selection can make a difference in the quality of the product. Moldable cyclic olefin polymers (COPs) can be used throughout a drug product's lifecycle, which can diminish the many rounds of testing required to ensure the drug product is stable in different containment systems. Other quality issues, such as rejection rates and breakage, can be mitigated through the use of high-quality polymers. Often, the extra cost associated with these materials can be justified through quality improvement and increased sales as well as a faster move to market.

Glass prefilled syringe barrels still dominate the market despite several limitations, including quality and performance issues that may directly affect patients and caregivers. Switching from a glass to a COP-molded prefillable syringe can reduce variability and breakage issues associated with glass, as well as reduce the need for silicone oil, another potential source of drug product contamination.

With the development of novel materials, including COPs, manufacturers can now select a high-quality, transparent, break-resistant material that is more inert than glass, is scratch resistant, and can reduce potential for particulate contamination from the syringe barrel. These components also can be stored and shipped at low temperature, which is a common requirement of many biologics. With a prefilled syringe system using a plunger coated with a fluoropolymer barrier film, superior and consistent break loose and extrusion forces can be achieved without the use of silicone oil as a lubricant. The film is molded to the surface of the plunger and provides a barrier against constituents from the elastomer leaching into the drug product. Another benefit of a silicone-oil-free system is the reduced risk of silicone-induced protein aggregation.

In addition, because COP barrels are manufactured using injection molding technology, dimensional tolerances can be very tight, which helps to ensure consistent functionality (eg, break loose and extrusion) and minimize the risk of incompatibility with secondary devices, such as auto-injectors.

Cyclic olefin polymer syringe systems, which have been used in the market for many years in Japan, Europe, and the US, continue to gain strong acceptance from biotech drug makers. COP syringes offer the following clear advantages over traditional glass syringes:

- Flexibility: COPs allow for customized sizes based on the attributes of the drug, such as large volumes and viscosity.
- Durability: COP offers high break-resistance and consistent break loose and extrusion, as well as excellent low-temperature characteristics.
- Low Risk of Reactivity: COP offers low exposure to extractables and leachables as well as low particulate levels, minimum levels of adsorption and absorption, and improved drainability.
- Visibility: COP has high transparency.

Recent trends in auto-injectors include the increasing use of electronics for reusable systems, continuing growth in disposable devices and ergonomic enhancements designed to improve an impaired patient's ability to deliver an effective injection. However, current systems based on glass primary containers have had problems with issues such as breakage, incomplete injection, and variability of functional performance. Many are also limited with regard to dose size, which can detract from the patient experience either by requiring more frequent injections or intravenous administration due to the high volume of drug needed.

With the increasing trend toward self-injection and home administration of drugs, there is a growing need for drug delivery devices that can deliver higher volumes of drugs subcutaneously. Innovations in this area include novel devices that are attached to the body, such as a patch injector, or delivery systems that meet the requirements of biologics.

Whether seeking to create a custom integrated delivery solution or to package a drug product in an existing delivery option, such as an auto-injector, biotechnology companies should seek out a partner with expertise and experience in providing packaging solutions. Packaging manufacturers who are focused on providing quality solutions will have the knowledge and partnerships in place to ensure that all four key elements of an integrated design are met. New and innovative drug delivery systems can optimize the quality of life for patients by effectively managing the interrelationship of the four primary components: the drug, the end user, the primary container, and the delivery system. Together, packaging and biotechnology manufacturers can work seamlessly as partners to provide innovative solutions that help mitigate risk, encourage patient adherence, and enhance value through unique integrated delivery combinations. ◆

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BIOGRAPHY

Kevin Cancelliere joined West Pharmaceutical Services, Inc. in January 2013 as Director of Marketing, Pharmaceutical Delivery Systems. Mr. Cancelliere brings almost 30 years of broad operational and strategic marketing and sales experience to this position. He came to West from Vicept Therapeutics, where he was Senior Director of Project Management for an investigational drug for the treatment of Rosacea. Prior to Vicept, Mr. Cancelliere was the Senior Director, Marketing at Wyeth Laboratories. Mr. Cancelliere earned his BS in Biology from De Sales University and his MS in Biochemistry from Thomas Jefferson University.

New Frontiers in Transdermal Drug Delivery

By: Kenneth B. Kirby and Chandan A.S. Alam, BSc, MD

INTRODUCTION

When it comes to assessing the future of the pharmaceutical industry, one cannot overlook the rising importance and opportunities in the field of transdermal drug delivery. The advantages of a non-invasive method of drug delivery that offers both convenience and efficiency already outweigh the more traditional methods of oral delivery and hypodermic needles as the process eliminates gastrointestinal toxicity and first-pass metabolism associated with the more conventional techniques. In addition, the field has progressed well beyond the first generation of patches and gels to now include various devices and modalities, such as microneedles, phonophoresis, and iontophoresis; however, the transdermal drug delivery process has yet to reach its full potential.

To date, the number of drugs that have successfully breached the skin at therapeutically useful levels have been severely limited due to difficulties moving larger, and chemically non-compatible molecules across the skin's biologically active barrier. The outermost layer of the skin, the stratum corneum, acts as a natural barrier against the entry of hydrophyllic drugs and macromolecules that have higher melting points and molecular weights. As of April 2013, only a handful of low-dose hormones, nicotine, Fentanyl, 2 Anti-parkinson drugs, a bladder incontinence drug, and nitroglycerin transdermal solutions have been approved by the FDA.

As industry experts continue to focus on optimizing the existing modes of delivery to account for the limitations imposed by the stratum corneum, the team at Transdermal Delivery Solutions Corp. (TDSC) has been leveraging its patented technology to develop a unique patchless, metered pump, spray-on drug delivery system and products.

TDSC DEVELOPMENT

In 1997, the team at TDSC began research on developing a safer and more efficient method of drug delivery. Rather than focusing their efforts on optimizing a delivery device to simply overcome the challenge presented by the stratum corneum's barrier, the team took an innovative approach to solving the problem by creating an entirely new hypothesis based on the notion that delivery of large complex drug- and carrier-systems was possible.

This approach required an investigation into what sorts of compounds could transmigrate the skin readily and rapidly. The TDSC team found that a variety of organic compounds, petro-chemicals, and physiological substances such as hyaluronic acid and dimenthyl sufoxide (DMSO) inadvertently or intentionally already possessed this ability.[1,2] From this observation, TDSC researchers deduced that the physical size of the compounds was not the key barrier; however, they believed that certain aspects of the physical chemistry of these compounds, when balanced in appropriate ratios, made them invulnerable to the skin's defense mechanisms.

In order to protect the drug from the skin and vice-versa, the team looked for a formulation technique that would employ nutritional and food supplement compounds to achieve the optimal physical chemistry effect

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during the drug delivery process. This research, conducted at the William Harvey Institute at St. Bartholomew's hospital in London, led to the formulaic discovery that would become the benchmark for the TDS patented system.

TDSC TECHNOLOGY

The TDSC platform was designed under the guiding principles that the system must: (1) rapidly move the drug through the skin in an intact, bioavailable form, (2) Employ GRAS or near-GRAS compounds that are compatible with the biological nature of the existing dermal barrier, and (3) modify the solute to enable temporary disruption of the skin's ability to recognize it as foreign and defend its transmigration.

In 2002, the Transdermal Delivery System (TDS®) officially became a patented process. Simply put, the patented TDS process combines compounds for dissolving drugs with a dose of the drug, to create a liquid or semi-solid vehicle that safely transports the Active Pharmaceutical Ingredient (API) through the skin and releases it into body in an intact, bioavailable form. Like gels, no patch or application appliance is required other than unit-dose packaging or a metered pump sprayer.

In February of this year, TDSC

FIGURE 1

scientists reached an agreement with the FDA Division of Reproductive and Urological Products (DRUP) to conduct the 22-Day Repeat Challenge Cumulative Dermal Irritation study outlined in the FDA Guidance to assess the safety of the individual ingredients, as well as the system as a whole. The system and, by inference, all of its inclusions proved neither toxic nor irritating to the skin. The TDSC transdermal delivery system's toxicology study report is scheduled to be submitted to the FDA in the second quarter of this year, along with extensive data on the safety of all the excipients.

TESTAGEN™

In July of 2012, TDSC announced it was in the later development stages of its first product, Testagen™, a spray-on treatment for low testosterone levels in men. Approximately 13.8 million men in the United States suffer from low testosterone levels, commonly referred to as "Low T," which has been linked to common ailments ranging from hypertension to low sex drive. Of the 13.8 million men suffering from low testosterone, it is estimated that only 1 million are currently undergoing treatment. Testosterone Replacement Therapy (TRT) drug sales have increased significantly throughout the past decade, from approximately $552 million in 2006 to $2.1 billion in 2012.

The safety and efficiency of transdermally delivered testosterone for hormone replacement has been extensively researched; however, there are currently product safety issues with all current forms of transdermal testosterone hormone replacement, including site-of-application

reactions in patches and roll-on gels, and dangers of inadvertent dosing to third parties by contact with gel preparations remaining on the skin.

Testagen TDS has been designed to address these problems of transdermal hormone replacement therapies. The patented treatment formulation is expected to revolutionize topical testosterone application as the system provides faster absorption and lowers transferable concentrations left on the skin. To ensure the drug's delivery is safe and as efficient as possible, the formulation process produces an extremely stable dose-specific and drug-specific formula, and has a quick-to-dry ethanol base that mitigates transference.

Testagen has been under evaluation for more than 10 years and has completed two human trials, and Phase IIb/III clinical trials are expected to begin later this year. ◆

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BIOGRAPHIES

Mr. Kenneth Kirby is the President, CEO and Founder of Transdermal Delivery Solutions Corp (TDSC), where he oversees both operations and technical development. Mr. Kirby has been a pioneer in transdermal delivery since 1990 and is the primary inventor of TDSC technology. In 2001, he formed the Langford Research Institute and started a fully funded academic and research collaboration with the William Harvey Research Institute at St. Bartholomew's and Queen Mary's Medical College, University of London. Mr. Kirby has personally directed the preclinical and clinical research efforts with the Harvey encompassing 19 trials of 17 varied compounds and 7 human trials. He is a cum laude graduate of the Florida State University's College of Arts and Sciences.

Dr. Chandan A.S. Alam is the Executive VP and Chief Science Officer of Transdermal Delivery Solutions Corp. (TDSC). Dr. Alam earned his Bachelor of Biological Sciences degree with Honors from London Guildhall University. He earned his MD at St. Georges University School of Medicine in Grenada for preclinical training, and clinical training at The Royal London Hospital School of Medicine. Dr. Alam is currently a member of East London Research Ethics Committee and is employed as a Senior Research Fellow with the Bone and Joint Research Unit at the William Harvey Research Institute at St. Bartholomew's Hospital Medical College in London . In this role, he is actively researching the transdermal delivery of drugs in both in vivo preclinical and clinical trials. He has published more than 45 papers, posters, and book chapters on angiogenesis, various animal models of disease, and transdermal delivery of drugs.

MARKET BRIEF

Trends & Opportunities in Particle Design Technologies – Life Sciences & Biopharma in the Spotlight

By: Cecilia Van Cauwenberghe, MS, Technical Insights Senior Research Analyst, Frost & Sullivan

PARTICLE DESIGN & ENGINEERING OVERVIEW

This article discusses the observed trends in particle design and engineering technologies, as well as the main factors and opportunities driving the principal technological advances in the biopharmaceutical industry around this topic.

Microparticles govern many solid dosage forms in the pharmaceutical and biotechnology industries. Successful instances of this include different dry powders for inhalation in the form of aerosols for the treatment of respiratory affections, as well as certain microformulations for delivery into the lungs or nose. Capsules and tablets filled and pressed for oral applications and transdermal delivery patches also represent examples of microparticles.

Interestingly, the design of novel particles and, particularly, microparticles, a decade ago was mainly related to their use as carriers, usually consisting of micronized dry material. Today, this conception has suffered many changes, and the overall perspective regarding particle design in the biopharmaceutical industry has significantly changed. These technologies are currently seen as novel drug delivery strategies. Particles are no longer seen as passive carriers, but rather as critical elements in the drug delivery system. This phenomenon in part is due to the advancements of therapeutic approaches, which every day require more complex dosage forms to meet the desired behavior of the drug response in the patient. Specifically designed particles are engineered to address a spectrum of functional responses and meet the conventional parameters of active stabilization, drug transport, modulation release, and dose targeting.

Under this scope, particle design and engineering constitutes a novel discipline capable of smartly combining different technologies and disciplines, ranging from elemental chemistry and colloid and interface science, to advanced materials and nanotechnology. This novel approach has allowed the industry to face important challenges, such as poor solubility and absorbability, the need for controlled-release applications, improved taste-masking, enhanced targeting, degradation protection, etc., through the development of new pharmaceuticals technology and novel dosage forms.

Particle design techniques capable of modifying certain properties to dote them with new functionalities are becoming essential in the growth of the biopharmaceutical industry. This fact gains special attention due to the crucial need for new drugs or reformulations of established molecules to be improved and efficiently delivered.

CHALLENGES & DRIVERS IN BIOPHARMA INDUSTRY

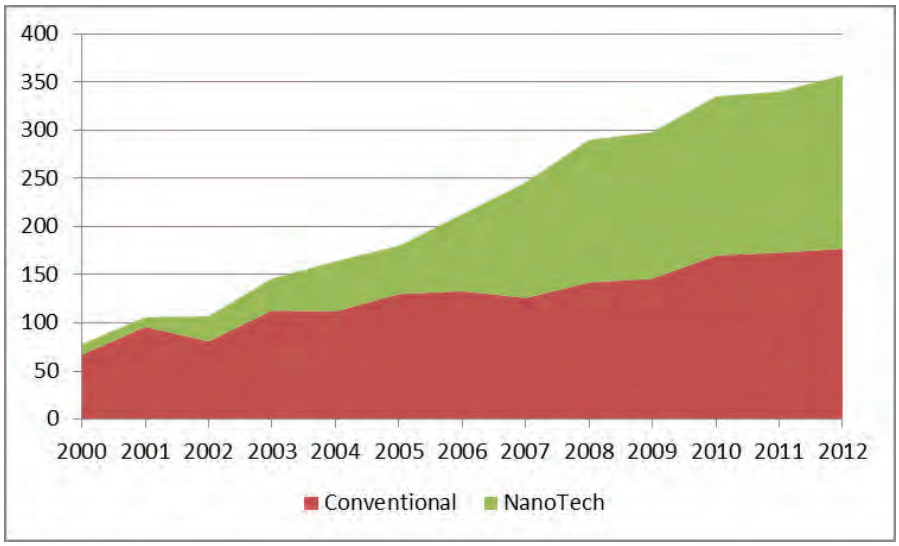
The aforementioned requirements additionally suppose the emergence of novel manufacturing technologies. Conventional methods consisting of the formation of fine particles, including solvent crystallization or precipitation followed by harvesting, drying, and micronization, constitute important tools aimed at achieving different targeted particle sizes. Nevertheless, such methodologies imply multistage processing sequences, so that more efficient technologies are required. Similarly, such methodologies used to involve high-energy inputs related to the damage of crystals, amorphous domains, and lack of physical stability, among other drawbacks directly impacting the product quality, which also requires novel approaches.

In addressing this concern, recent years have seen the appearance of supercritical fluid (SCF) methods for engineering drug particles. Through this methodology, well-defined crystallographic, chemical, and physical properties have been observed. We will

now look at several methods associated with this technology. The solution-enhanced dispersion by supercritical fluids (SEDSFs) process has demonstrated the broadest acceptation for biopharmaceuticals applications. Generally speaking, the technique consists of the use of the SCF as a dispersing anti-solvent, as well as an extraction medium for the solvent, which derives in the efficient precipitation of the solute. This technique serves equally for both organic and aqueous solutions. Through this methodology, important milestones were achieved, scaling the process to large manufacturing scale and clinical trials procedures under the Current Good Manufacturing Practice (cGMP) regulations enforced by the US Food and Drug Administration (US FDA) and the European Commission (EU).

However, the researchers communicate several inquiries about the expectations of this technology. The basic dichotomy is evidenced by taking into consideration that at this scale, some variables cannot be controlled by current practices in particle engineering, processing, and characterization. This observation enters in conflict with the fact that critical sources of variability may be identified using a cGMP approach. On that note, concerted efforts to understand product engineering through a broader conception should take place in order to guarantee a successful regulation and control of product properties and process attributes. This fact gains special importance under certain normative, such as the International Conference on Harmonization (ICH) Q8 (R2) Pharmaceutical Development, published on November 20, 2009. This provides information on how to present knowledge gained when applying scientific approaches and quality risk management for developing and manufacturing a product. Indeed, the ICH privileges the quality at design levels instead of at product level. For that reason, an integrated relationship, or harmonization, as the rule suggests, between different processing operations, product development stages, components, and product quality, etc., results are essential.

FIGURE 1



The incremental increase in the number of granted patents from 2000 to 2012 for relatively more conventional techniques consisting of microparticulates and micronizing, and the incremental growth due to the advent of nanotechnologies in the life sciences and biopharma industry. Source: Frost & Sullivan.

The following paragraphs focus on providing pharmaceutical and biotech actors with a broader landscape regarding the role of particle design and engineering in the industry from a competitive perspective.

TECHNOLOGY ADVANCES & COMPETITIVE TRENDS

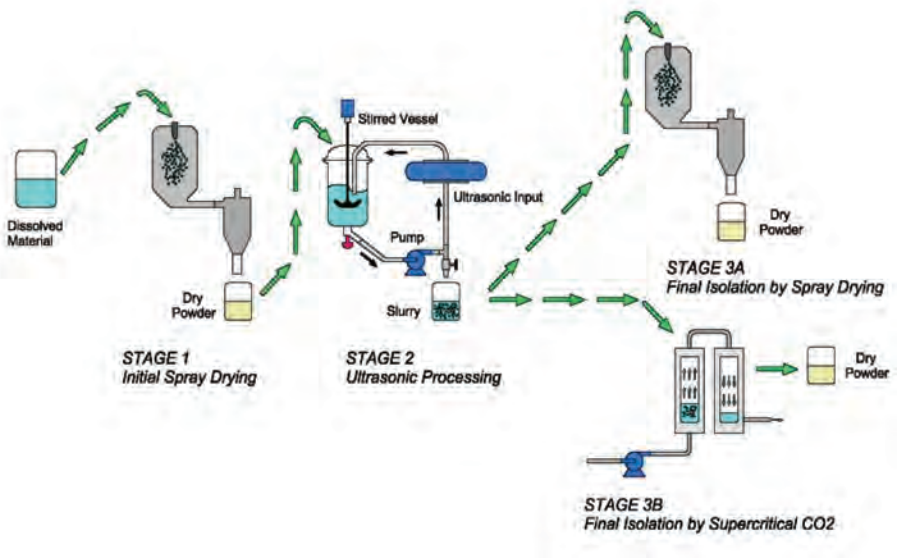
Particle design engineering methodologies can be derived from the modification of crystal forms to confer them the desired properties, as well as the alteration of the micro/nanometric properties to generate micro/nano particles of interest. On the other hand, particles can be obtained by self-assembly or incorporating biological pieces, as in the case of engineered antibodies (EAs) and virus-like particles (VLPs).

In turn, complex hybrid systems conformed by the association of dissimilar approaches have led to remarkable advances in therapeutics. This is the case, for instance, of nanoparticulate drug delivery systems for pulmonary administration of antiasthmatic agent, insulin, and many other medicines. Furthermore, pulmonary p-DNA, siRNA, and nucleic acid as gene delivery systems considered as micro/nano-particles can also be mentioned. Remarkably, this novel discipline requires a smart comprehension of the phenomena governing the mechanisms of action aiming to address, as well as an in-depth understanding of the particle formation or assembly process. Evolution and innovation engines must be crucially concerted to facilitate the emergence of new, cost/time effective, and even personalized, therapeutic approaches.

In Figure 1, the trend in the number of patents granted during the period 2000-2012 for particle design and engineering regarding biopharma products and processes can be observed, as well as the impact in the synergy that results from the evolution of nanotech developments focused on the life sciences and biopharma industry.

Beyond therapeutics, particles design and engineering has reached a unique niche in life sciences and biotech as services tools. New miniaturized, high throughput technologies for DNA sequencing, flow cytometry, drug discovery, and –omics (genomics, proteomics, metabolomics, etc.) and photonics applications are basing part of their work principle in the attachment of functional biological molecules to micro/nano-particles, usually spheres. Thus,

FIGURE 2



Depiction of the UMAX processing flow of the product via spray drying with cGMP in FDA-approved facilities. Source: Frost & Sullivan. Picture Credit: Prosonix Ltd.

for example, principal uses for microspheres in life sciences research applications rely on molecular diagnostics; fluorescence and enzyme immunoassays (FI, EIA); capture reagents for lateral flow devices and diagnostic assays; nucleic acid separation and protein separation; surfaces for immunoprecipitation; fluorescence microscopy; flow/image cytometry; magnetic cell separation; agglutination tests; among many others. As a result, a plethora of small and medium companies, most of them evolving from start-ups and spin-outs, are currently playing an important role by providing services to bigger pharmaceutical and biotechnology companies worldwide.

For instance, ReSyn Biosciences (Pty) Ltd, a start-up enterprise incubated by CSIR Biosciences, a South African bio-tools company, has developed a novel microsphere technology platform, which consists of a loosely linked polyethyleneimine polymer matrix allowing penetrating biological and synthetic molecules throughout the microspheres. According to the researchers, this technology offers exceptional capabilities, especially regarding their high surface area for binding of molecules and increases in the overall performance in several orders of magnitude.

Similarly, SiTec PharmaBio, a technology-based company based at Parc Cientific de Barcelona, Spain, offers pharmaceutical and biotechnology companies a variety of services in key areas of R&D, from lead and drug candidate selection to early clinical development based on micro/nanoparticulates.

Hovione is a leading international group dedicated to the cGMP development and manufacture of active pharmaceutical ingredients (APIs) through the use of different proprietary, cutting-edge technologies. Hovione's particle design technology platform offers real-world solutions enhancing drug delivery and bioavailability challenges by spray drying and congealing, hot melt extrusion, co-precipitation for solid dispersions, emulsification, controlled crystallization and co-crystallization, jet milling, wet polishing, and inclusion complexes generation.

On the other hand, Particle Sciences, Inc. became a leading contract research organization (CRO) based on particle design technologies to support analytic, bioanalytic, physical characterization, and manufacturing services for the pharmaceutical industry. Successfully identifying common obstacles in achieving cost-effective drug product developments, the company addresses important challenges through different technological approaches that include particle design and nanotechnology applications.

Naturally, top players in the life sciences industry, such as Life Technologies, Sigma-Aldrich, among many others, are also innovating this technology to enhance the performance of their products and offer top solutions in life sciences arenas. However, the appearance of new tech niches with the consequent participation of new companies create a cross-pollination environment in which different actors from diverse sectors can play, significantly enriching the partnering and alliance models and strategic behaviors.

On the other hand, regarding therapeutics approaches and involving medical devices development, Prosonix, an Oxford-based specialty pharma company specializing in respiratory diseases, has patented UMAX ultrasonic particle engineering and technology. In a few words, this innovative approach involves the operation of a complex and highly controlled disposal, coupled with the application of ultrasound in the also proprietary Prosonitron reactor system (PRS). According to the researchers, the UMAX process (Figure 2) achieves these means by optimal particle design, while facilitating the manufacturing of spheroidal and more regular-shaped crystalline particles for both dry powder inhalers (DPIs) and pressurized metered-dose inhalers (pMDIs). In this manner, UMAX technology is capable of providing a powerful and potential platform to produce multi-component particles for combination therapy for respiratory disorders. In the researchers' opinion, such multi-component co-associated particles could provide a synergistic effect at the molecular and cellular level, as in the case of inhaled steroids (ICS) and long-acting beta agonists (LABA), as well as different combinations of them, while delivering a predetermined ratio of APIs collocated to the target site in the lung.

Indeed, the opportunities of particles design and engineering technologies in the life sciences and biopharma industry is enormous. Although in appearance some new

developments could seem to have limited success, alternative options are constantly emerging for services or novel tools for research. Moreover, excipient manufacturers could also play a preponderant role around this technology. For instance, therapies associated with the gastrointestinal tract (GIT), such as those indicating the use of cyclodextrins, can additionally serve as solubility enhancers, the same as inhalers could present similar characteristics in treating respiratory disorders.

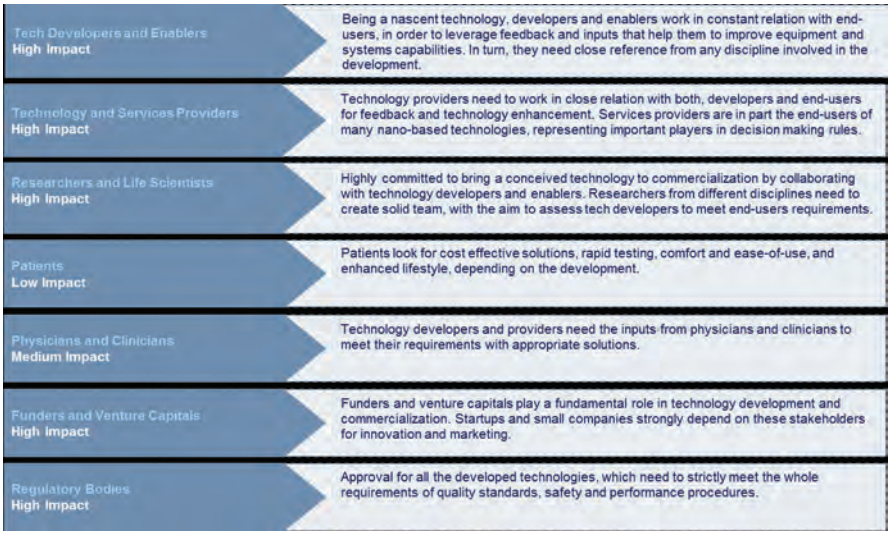
Nevertheless, the current trend of particles design embraces the solution of the problem at the design and engineering state, avoiding particles post-processing to reach their desired functionality. According to this, the goal is focused on advanced material sciences and engineering.

Protein-coated microcrystals (PCMCs) have also proven to improve therapeutics through the particle engineering of biomolecules. The approach broadly consists of the formulation and stabilization of proteins, nucleic acids, and vaccines through the co-precipitation of water-soluble carriers, typically amino acids or carbohydrates, with dehydrated biological macromolecules. By these means, the product results are perfectly suitable for delivering biomolecules in different ways, principally pulmonary and parenteral. Boehringer Ingelheim has excelled in the development of this technology.

Leveraging nanotechnology approaches, Hosokawa Micron Group, a leading supplier of the latest powder and particle technologies, and particularly, nanotechnology approaches, has rapidly advanced to encompass their strong expertise in traditional powder sciences with novel nanotech approaches. Hosokawa, which possesses an unmatched position in the marketplace, has launched an aggressive R&D program to penetrate other industries and participate in joint projects with public organizations and joint agreements with other companies.

Along the same line, Q Chip, a Cardiff-based biotechnology company strongly focused on drug delivery, especially through the development of long-acting injectable

FIGURE 3



The size of the innovation ecosystem around particle design and engineering. Source: Frost & Sullivan.

therapeutics, has developed its Q Chip's proprietary platform, Q-Sphera, a breakthrough microsphere manufacturing and formulation system that is compatible with small molecules, peptides, and proteins. Q Chip development offers unique functionalized microparticle delivery systems, aiming to meet the requirements for sophisticated life science applications, products and services. Among the main goals, the company faces the development of new delivery methods for therapeutics with controlling release, thus substantially improving drug formulations. In the opinion of the researchers, such multi-disciplinary and multi-targeting approaches also come along with the encompassed development of new equipment and medical devices. As part of its services programs, the company also offers an important portfolio of new functionalized bead-based assays.

Another remarkable case regarding technology providers is constituted by Liquidia Technologies, started as a University of North Carolina - Chapel Hill (UNC) company, which has established a powerful and versatile nanotechnology-based product development platform - PRINT. Such a nanotech platform has significantly contributed to revolutionizing the concept of engineered therapeutics. Liquidia has leveraged its approach to fabrication techniques from the semiconductor industry to effectively design and engineer novel particles in a broad spectrum of sizes, shapes, and compositions. According to the researchers, novel developments in particle design and engineering extrapolate the frontiers for new product developments, which is remarkable. The PRINT platform enables Liquidia to address the creation of precisely engineered vaccines, therapeutics, and other health-related products.

Associated with SCF technology, SEPAREX, a French high-tech suppler, which provides its customers with high-pressure components, standard and tailor-made systems for R&D, has penetrated the market with its recently designed and built equipment for SCF technology. The company has addressed the challenge of scalability, performing work at different scale levels, from lab-scale for screening new chemical entities or biomolecules available in very limited amounts, as well as pilot-scale equipment and semi-industrial plants for manufacturing clinical lots operating under cGMP rules. Similarly, different pilot-plants for inorganic powder formation capable of operating either with supercritical carbon dioxide (and co-solvents) or supercritical water have been developed.

Finally, in reference to virus-like particles (VLPs) and engineered antibodies (EAs), the synergy among self-assembly technologies and protein engineering advancements has been very fruitful. VLPs demonstrate significant potential in eliciting stronger and more efficient immune responses in comparison with conventional recombinant protein vaccines. In general words, VLPs mimic the external protein structure of a virus, avoiding the inclusion of the genetic material, and thus inhibiting viral replication. For that reason, VLP vaccines are not able to cause any infection by themselves. Rather, VLPs present viral antigens in the most authentic configuration possible, so that the human immune system responds to a VLP vaccines in the same manner as if the virus is present, without the danger of infection, and also can build its immune defenses.

LigoCyte, a private, clinical-stage biopharmaceutical company focused on developing novel vaccines for gastrointestinal and respiratory indications, has focused its expertise in VLPs technology, supporting a pipeline of enhanced product candidates, including vaccines against norovirus, influenza, respiratory syncytial virus, and rotavirus. The company, recently acquired by Takeda Pharmaceuticals, has developed an important portfolio of core technologies to efficiently produce a broad spectrum of VLPs vaccines. Other instances of VLPs vaccines include the recently licensed vaccines against human papillomavirus (HPV), Merck's Gardasil and GSK's Cervarix.

Particle engineering approaches in biomolecules are addressed through EAs. This is the case of Ablynx NV and its nanobodies. Nanobodies are antibody-derived therapeutic proteins consisting of the unique structural and functional properties of naturally occurring heavy-chain antibodies. The seed idea derived from the discovery of fully functional antibodies that lack light chains, such as in the case of camelidae (camels and llamas). Later, a single variable domain (VHH) and two constant domains (CH2 and CH3) were identified in the heavy-chains antibodies, conferring their unique structural and functional properties to form the basis of a new generation of therapeutic antibodies.

FINAL INSIGHTS & REMARKS

One of the most amazing phenomena observed along the implantation of this technology relies on the technology condensation/expansion capability. As a physics phenomenon, particle design and engineering approaches were defined several decades ago. However, as a discipline of science and engineering, leveraged to serve as new innovative tools and products in the life sciences and biopharmaceutical arenas, the technology is relatively nascent.

In this regard, advance manufacturing techniques allowing building structures with the desired properties, practically selected according to the specific behavior of a device and its application, or therapeutic response, have begun to play a highly dynamic role.

Beyond the structure, micro/nano-particle systems and devices constitute powerful tools, applicable not only to study fundamental life sciences, but also for practical biochemical and clinical applications.

The convergence of a plethora of technologies suggests the creation of new technology clusters that leverage the synergy among several disciplines. Predictions for 2020 include claims of a total restructuration of both tech and business clusters and niches favoring innovation and technology translation from R&D institutions to industry sectors. This convergence can be strongly evidenced in terms of products, as referenced in the earlier paragraphs.

A direct correlation with business development activities is exhibited by evaluating the evolution and dynamics of business models in time, taking as a reference research, development and tech transfer tasks. ◆

BIOGRAPHY

Cecilia Van Cauwenberghe is a Senior Research Analyst with Frost & Sullivan's Technical Insights practice. She has more than a decade of professional expertise in chemical and biomedical engineering arenas, including life sciences, biotechnology, healthcare, and biomedical devices, as well as biomedical and clinical engineering. Her particular expertise in leading and executing projects relate to biopharmaceutical and biochemical modeling, simulation, and optimization; microelectronic implantable devices design; and studies in metabolic syndrome and cardiovascular diseases applications. Her expertise and professional development has grown through work with academic and healthcare institutions as well as leading firms, including the Dr. Rene G. Favaloro Foundation University, South National University, Comahue National University, YPF SA, Techint Group, and the National Institute of Industrial Technology. She has performed Doctoral Studies in Chemical Engineering, Master of Science in Biochemical Sciences, as well as a Bachelor of Science in Chemical Engineering and Mathematics.

Development of Autologous Cell Therapies: Keys to Clinical & Commercial Success

By: Ronnda L. Bartel, PhD, Tod Borton, and Brian S. Hampson

INTRODUCTION

Throughout the past decade, there has been a steady increase in studies of cell therapies for clinical use, with approximately 47 industry-sponsored clinical trials in pivotal or late stages using autologous cells.[1] Autologous cell therapies involve taking a cell sample from a patient and manipulating those cells, and then administering them back into the patient. Such therapies have been shown to aid in the repair of tissues in many therapeutic areas, including cardiovascular disease, peripheral arterial disease, liver disease, diabetes, neurodegenerative disorders, bone repair, and spinal cord injuries.[2-5]

The patient-specific nature of autologous cell therapies can make large-scale production extremely challenging because a separate batch must be produced for each patient. Companies often struggle to scale up manufacturing as necessary in clinically and commercially viable ways. Cell therapies also often carry higher manufacturing risks than most small molecule pharmaceuticals. An error in the production of an autologous cell therapy directly translates into a failed treatment for a patient. And the often complex cell manufacturing process must meet both FDA regulations and the requirements of a successful business model.

Some companies are exploring the use of allogeneic cell therapies, which derive treatments or doses for multiple patients from the cells of a single donor. This approach can help to make manufacturing more efficient, leading to potential cost savings. However, the use of cell therapies derived from one donor in a different recipient must address the risk of immune response and rejection. With autologous therapies, patients receive cells that come from their own body, which virtually eliminates the risk of rejection. In addition, cells for allogeneic therapies must be extensively cultured and cryopreserved for long-term storage. This prolonged culture increases the risk of cell transformation (eg, tumorigenicity) and often the frozen product requires further manipulation prior to administration.

Many autologous cell therapies are produced with ex vivo culturing to increase the number and/or modify the therapeutic cells within the patient's cell sample. In this way, therapies derived from a cell sample will include a higher number, ratio, or type of cells known or believed to play a role in

FIGURE 1

Aastrom Manufacturing Platform.
Left: single-use cell cassette.
Right: highly automated instrument platform.

disease treatment. This process can add additional complexity to manufacturing because cell culture conditions must be optimized and extensively tested and monitored to maintain the regenerative potential of the cell.

Drug developers targeting autologous cell therapies must identify the optimal strategies to commercialize cell therapies safely while being able to manufacture therapies at a high volume without compromising quality. Aastrom Biosciences, one of the approximately 47 companies with an autologous cell therapy in late-stage development, has developed the innovative processes necessary to reduce risk throughout the manufacturing process. The company is now preparing for future commercialization for its investigational therapy ixmyelocel-T, derived from a patient's own bone marrow stem cells. The company has advanced ixmyelocel-T into Phase III clinical development in critical limb ischemia (CLI), which is a severe form of peripheral arterial disease.

OVERCOMING CHALLENGES IN CELL COLLECTION

Bone marrow contains two important types of stem cells: hematopoietic stem cells (HSCs) and stromal cells, which include mesenchymal stem cells (MSCs), multipotent stromal cells, and endothelial progenitors. Bone marrow stem cells are known to support cell regeneration and regrowth, and are being tested in several cell therapies, including ixmyelocel-T. Yet only 1 in 10,000 to 20,000 cells in bone marrow are HSCs, while MSCs are ten-fold less abundant.[6,7] Taking a large-volume sample of bone marrow is one approach used to ensure that a sufficient supply of these essential but rare stem cells is present in the cell sample. However, large-volume collection is typically painful for patients, requires hospitalization, and can cause side effects that include bone marrow inflammation.

Aastrom has identified a way to take a smaller bone marrow sample (about 60 mL) from the patient and then expand the hematopoietic and stromal cells during the manufacturing process using ex vivo culturing. The bone marrow sample is withdrawn from the patient under local anesthesia during a 20-minute outpatient procedure.

Though a smaller sample is beneficial to patients, the quality of the cell sample could be compromised if the sample is not collected properly. To achieve controlled outcomes and the best possible cell sample for manufacturing, Aastrom has developed a unique collection process, a detailed training program, and a kit with all of the materials for collection and shipping of the bone marrow to the manufacturing site.

STEPS TO REDUCE MANUFACTURING RISK

Once a cell sample is collected, it is typically shipped at a controlled shipping container to a centralized manufacturing site for processing. There are many manufacturing risks companies need to address once the sample arrives on site, including potential cross-contamination, cell damage, or improper labeling and record keeping that could lead to loss of patient identity. Because cellular products are regulated by the FDA as biologics, they require a Biologics License Approval (BLA) after commercialization. They also need to comply with Good Manufacturing Practice (GMP) regulations.

To minimize risk, there are several steps that can be taken in alignment with GMP regulations. Using closed-system technology with single-use disposables is one way to help minimize contamination risks. At Aastrom, each cell sample is placed in a single-use, sterile disposable cell cassette, and then an instrument uniformly distributes the cells over the culture surface for optimal growth. Each cell cassette also has an electronic memory device that identifies the cell product, instructs instruments through the cell production process, records the cassette status, and collects data. All instruments continually update status so that when a cassette is inserted into the incubator unit or when power is restored after interruption, the device knows exactly which point the cassette has reached in the production process. The electronic device helps to reduce the risk of mix-ups and operator errors.

Each cell cassette at Aastrom is placed into a dedicated incubator during the 12-day incubation process. As a therapy is prepared, the system controls all aspects of the culturing process, including temperature, culture medium exchange, and

gas exchange and confirms that all functions are operating correctly. It can also automatically place a process into a "safe state" in the rare event of an equipment or utility failure.

When the incubation is complete, Aastrom manufacturing personnel then harvest the cells from the cassette, again using an automated process, which helps to achieve the highest attainable levels of reliability, consistency, and cost-effective manufacturing.

POST-CULTURE PROCESSING

Typically, cells harvested from a cell culture are not suitable for direct patient administration. The cells need to first undergo several manufacturing steps to remove process residuals, achieve an appropriate product volume, and formulate the cells for delivery, which could include excipients to extend shelf-life. These steps are not easy to integrate into product manufacturing. The post-culture phase is also relatively time-consuming and subject to increased risk of error, contamination, and excessive holding times. In the case of a complex mixture of cell types, as in ixmyelocel-T, this process can cause a shift in the cell profile. And the transfers in this phase can result in cell loss or decreased cell viability.

Traditional approaches to cell harvesting produce cells mixed with culturing byproducts that need to be washed away in an additional processing step before cells can be sent back to the patient. Aastrom employs its automation system to drain away the culture medium and rinse the cells within the bioreactor before the cells are harvested. This removes two cell transfer steps and also leads to a lower rate of cell loss and cell damage. The company's closed system methodology also helps to reduce product volume and introduce storage excipients to prepare the therapy in a form suitable for administration. The system is not highly complex and also helps make the manufacturing process more efficient.

FINAL PRODUCT TESTING

Testing a cell therapy before it is injected back into a patient can be challenging for several reasons. First, all tests must be conducted rapidly because ixmyelocel-T has a 72-hour shelf-life. They should also be relatively inexpensive because the same tests will be repeated for every dose. The tests should only require a limited amount of cell sample volume to avoid excessive product loss. And testing must be able to screen a complex product composition.

In final product testing, critical quality attributes of the final product must be confirmed, including identity, potency, viability, dose, sterility, and purity. Careful selection of test parameters, testing method, and sample requirements for each of these attributes is essential to minimize product loss, test time, and cost.

COST SAVINGS & FUTURE EFFICIENCY CHALLENGES

While most pharmaceutical manufacturing processes, as well as allogeneic cell therapies, can take advantage of the efficiencies of "sharing" a single production batch among multiple patients, this is not the case for autologous cell therapies. The core steps for manufacturing cannot be shared, so companies need to look into other ways to achieve efficiencies. For example, labor-saving strategies, computerization, process automation, and engineered integration can each drive cost-savings. Increasing the number of cell products that can be manufactured in a given amount of time is necessary and often referred to as "scale out" rather than scale up.

Simplifying and integrating manufacturing steps also provides significant cost-savings. Aastrom's integration of washing and cell harvest is one example. The integration of automated cell sampling or quality control into manufacturing can reduce labor and processing times as well. This would additionally help to improve consistency. High-volume screening and multiplexing technologies in pharmaceutical companies might also be examined to help to address challenges in high-volume autologous cell therapy manufacturing. ◆

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BIOGRAPHIES

Dr. Ronnda L. Bartel serves as Chief Scientific Officer at Aastrom Biosciences and is responsible for the scientific direction of the company, including research, development, and technical operations. She has more than 20 years of research and product development experience and most recently was Executive Director, Biological Research at MicroIslet and Vice President, Scientific Development at StemCells Inc. Earlier in her career, she was Senior Principal Scientist and Director of Research at Advanced Tissue Sciences and was involved in the development and approval of some of the first cell-based products approved by the FDA. She has also worked as Senior Director, Science and Technology at SRS Capital, LLC evaluating life science investments and has held positions in clinical development, drug delivery, business development, and manufacturing. Dr. Bartel earned her PhD in Biochemistry from the University of Kansas, has completed post-doctoral work at the University of Michigan, and earned her BA in Chemistry and Biology from Tabor College.

Tod Borton has served as the Vice President of Technical Operations at Aastrom Biosciences since 2006 and has more than 25 years of product development and quality experience in the domestic, international, biotechnology, and medical device industries. Prior to joining Aastrom, he held the position of Director of Quality at Terumo Cardiovascular, where he was responsible for quality assurance, document control, and sustaining engineering. Prior to Terumo he held the position of Vice President, New Product Development and Advanced Engineering at Pall Corporation, where he developed and commercialized many biotech and medical filtration devices. Mr. Borton has authored many patents in the area of biotechnology and medical filtration device technologies and earned his BS in Plastic Technology from Eastern Michigan University.

Brian Hampson has over 25 years of experience in the development and engineering of novel culture systems, cell processes, and related control system and automation technology. He has held several executive and technical management positions at Aastrom Biosciences and was a Principal Leader in the development and engineering of the AastromReplicell Cell Production System, a first-of-its-kind automated manufacturing platform for culture-derived cell therapy products. He currently holds the position of Senior Engineering Fellow, where he is responsible for strategic planning and development of high-throughput technology for cost-effective, commercial-scale manufacture of Aastrom's cell therapy products. Previously, Mr. Hampson was at Charles River Laboratories, where he managed a number of programs to develop and commercialize novel bioreactor systems to support large-scale biomolecule production. Mr. Hampson has authored or co-authored a variety of abstracts, publications, invited presentations, grants, and patents. He earned Bachelors and Masters degrees in Engineering from Cornell University.

SPECIAL FEATURE

Prefilled Syringes and Parenteral Contract Manufacturing: Improving for Flexibility and Customization

By: Cindy H. Dubin, Contributor

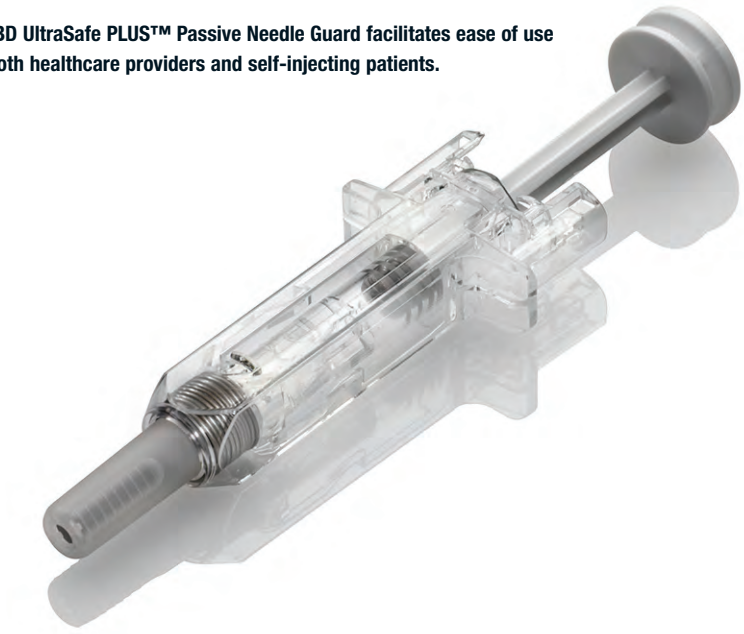
A rise in biologics and complex compounds–specifically in large-molecule drugs that require innovative injection methods–is driving the prefilled syringe market. The erosion of the blockbuster model, expiring patents, and growing competition have also increased the need for differentiation in drug delivery, while changes in demographics, particularly in the growing homecare sector, increase the need for convenient and safe administration forms that are user friendly, reliable and cost conscious. Prefilled syringes may offer intelligent and efficient answers for these current and upcoming needs.

FIGURE 4

Gerresheimer serves the pharmaceutical industry with ready-to-fill (RTF®) syringes and accessories for direct use on filling lines.

FIGURE 1

The BD UltraSafe PLUS™ Passive Needle Guard facilitates ease of use for both healthcare providers and self-injecting patients.



Many vaccines are transitioning to prefilled syringes, and with established markets such as anticoagulants and biologics, there will continue to be steady growth. According to the report, "*Global Prefilled Syringes Market: Trends & Opportunities (2012-2017)*," in 2011, 2.45 billion syringe units were sold and are predicted to hit unit sales of 3.59 billion in 2015.

Also growing is the sterile parenteral contract services sector within the total sterile CMO market. According to Frost & Sullivan, sterile parenteral contract services make up about 82.8% of the total sterile CMO market. This includes small-volume parenterals (vials, ampoules, and syringes), which make up the majority of sterile CMO services with 88.9% of market share, and large-volume parenterals (bags and bottles). Thus, the sterile parenteral manufacturing subsegment is expected to reach a market size of $6.5 billion by the end of 2016.

In this exclusive *Drug Development and Delivery Magazine* annual report on the prefilled syringe and parenteral manufacturing markets, leading drug delivery and contract development and manufacturing organizations (CDMOs) offer their insight into how the devices are evolving—from closure to container.

BD MEDICAL – PHARMACEUTICAL SYSTEMS—NEXT-GENERATION TECHNOLOGIES

The exposure of healthcare practitioners to blood-borne pathogens as a result of injuries caused by needlesticks is a significant public health concern. BD, which provides prefillable syringes, self-administration solutions, and safety and shielding systems, has seen an increase in legislation on a global scale with respect to this concern. The EU passed mandate 2010/32/EU, which requires all EU member countries to address the danger of accidental sharps injuries (including needlesticks) by enforcing this legislation by May 2013. It is anticipated that this increasing legislation will impact the presentation of injectables, especially those in prefilled syringes. Although this legislation has not specifically targeted 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, explains Sarah Baer, Marketing Product Manager.

Add to this the fact that 7 of the 10 top-selling drugs worldwide, and more than 60% of drugs in development are biologics, with an increasing number planned for the self-injection market. These drugs require the most advanced primary and secondary container technologies due to their heightened sensitivities, high development costs, and increasing needs from patients suffering from the chronic diseases they are meant to treat.

BD Medical – Pharmaceutical Systems is focused on improving healthcare worker safety, and offering higher-value products, which has been demonstrated by its recent acquisition of Safety Syringes, Inc.

The company's latest product is the BD UltraSafe PLUS™ Passive Needle Guard, which is designed to facilitate ease of use for both healthcare providers and self-injecting patients when manual injection control is preferred. In addition, this safety device is

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designed to meet increasingly complex biotechnology drug requirements, including higher viscosity. The BD UltraSafe PLUS Passive Needle Guard includes a plunger rod to help support injection of viscous drugs, a larger drug inspection window to improve drug visibility, extended built-in finger flanges, and an enhanced plunger head for improved injection support and stability.

BD also introduced the BD Vystra™ Disposable Pen within the last year. This self-injection pen has been designed for use with a range of therapies that require frequent, low-volume injections or variable dosing, according to Megan Lan, Worldwide Strategic Marketing Manager.

The BD Neopak™ Prefilled Syringe is the company's next generation glass prefillable syringe engineered to specifically meet the needs of the biopharmaceutical injectable drug market, explains Amanda Davis, Senior Product Marketing Manager.

BD is now developing the BD™ Microinfusor patch injector to address the delivery needs of next generation biologic therapies. According to Surya Viswanathan, Strategic Marketing Manager, it is a single-use, disposable, prefilled, automatic injection system that is hands-free during drug delivery, leveraging the company's container technologies.

BATTELLE—DELIVERING HIGH-VISCOUS AND HIGH-VOLUME FLUIDS

Improving the usability of prefilled syringes is the dominant trend in the industry.

FIGURE 2

Drug delivery devices designed by Battelle are born from the global R&D company's cross-disciplinary experience in device design, formulation, and usability and user testing.

Even devices that have been on the market for years need to be reassessed to ensure they are actually being correctly used by patients. But pharma often is driven by a need to innovate without making changes. While this appears contradictory, prefilled syringes are a stable platform that can be used as a foundation to build new delivery technologies. This allows pharma to keep what they know, while allowing the industry to move forward with devices that provide a better patient experience.

For companies bringing new combination products to market, Battelle's Drug Delivery service provides a cross-disciplinary approach that combines capabilities in device development, formulation, human factors testing, and usability studies, explains Alexa Konstantinos, Battelle's Director of Business Development for Medical Products. By focusing on the entire system (formulation, device and patient) during development, this approach can reduce the risk of innovation and overcome the challenges with delivering viscous formulations. "By integrating our human-centric design capabilities with our engineering and formulation teams, Battelle has helped clients develop intuitive devices that address human factors testing the first time without delaying a product launch," said Ms. Konstantinos.

Battelle is developing technologies to address the challenges of delivering high-viscosity and/or high-volume therapeutics, particularly for patients with compromised dexterity and strength who must self-inject. "We are developing a chemical reaction-driven injection 'engine' technology that could be used to deliver a high-viscosity formulation in a short time period without changes to the primary container closure of the prefilled syringe. The same technology could also be tuned to deliver a larger volume over a longer time frame for use in a bolus injector-type device," said Chris Muenzer, Principal Research Scientist for Battelle.

Battelle has renewed its alliance with Zogenix to continue the development of DosePro®, a prefilled, needle-free, disposable, subcutaneous delivery technology. "We will continue working with our existing clients to

FIGURE 3

In addition to aqueous formulations, Coldstream Labs has employed organic solvents in lyophilization to overcome solubility/stability issues.

design and develop new prefilled pens and auto-injectors and seek opportunities to partner on our new technologies related to high-viscosity delivery," said Ms. Konstantinos.

COLDSTREAM LABORATORIES, INC.—FLEXIBILITY IN LIQUID AND LYOPHILIZED FORMULATIONS

Flexibility in manufacturing is more important than ever in contract manufacturing, particularly in the parenterals space. Coldstream leverages its flexible, mobile isolator technology to offer aseptic manufacturing solutions to allow it to carry out processes that previously may not have been deemed practical. Through its isolator system, Coldstream accommodates a variety of processes, including complex formulation procedures in a high-containment environment. Coldstream is a CDMO focusing on the cGMP manufacture of injectable products, with a full platform of analytical, microbiology, and formulation development capabilities.

Irrespective of the nature of the products being manufactured, the first step in every project at Coldstream is to evaluate the potency of the active ingredient to be handled. This process includes a gap analysis to assess the information available about the product and the process to be used to manufacture the finished product. A risk assessment process helps identify appropriate handling procedures in order to ensure safe operations.

A typical project at Coldstream involves identification of a suitable process to safely and efficiently manufacture drug product to be used in early clinical trials. Challenges at this stage vary and frequently timelines are tight. The company has invested heavily in equipment and personnel in order to ensure the processes are developed and transferred efficiently to plant scale.

Mobile isolator technology serves as the heart of Coldstream's manufacturing facility, which is suited for manufacturing small-volume parenteral products for clinical trials and niche commercial products. "Our isolator system allows Coldstream to work with a variety of active pharmaceutical ingredients, including potent materials in both liquid and lyophilized presentations," says Eric W. Smart, President and CEO.

Coldstream's isolator technology provides a high degree of control of the manufacturing environment including a means of preventing microbiological contamination. In addition to engineering controls, a key part of the sterility assurance program includes maintenance of well-developed microbiology testing capability.

Coldstream develops and operates lyophilization processes. In addition to aqueous formulations, the company has increasingly employed organic solvents in lyophilization to overcome solubility and stability issues with compounds that are incompatible with aqueous environments.

Coldstream has invested in upgrades to its lyophilization capabilities, including the installation of cryogenic solvent traps and other engineering controls to enhance its flexibility to handle organic solvents in its plant-scale lyophilizer.

GERRESHEIMER AG—ROOM FOR IMPROVEMENT

Prefillable syringes are intuitively and easy-to-handle products. Nevertheless, administration can still be improved by changing properties of the basic components such as the glass syringe barrel, plunger stoppers, and siliconization levels. When implementing improvements, prefillable syringe manufacturers are dependent on the pharmaceutical companies that bring the final products to the market, explains Bernd Zeiss, Manager, Technical Pre-Sales Support for Gerresheimer AG.

"We know that the syringe as the interface between drug and patient gains importance, and hence, Gerresheimer offers an early and close development partnership to the pharmaceutical industry," he says.

Gerresheimer serves the pharmaceutical industry with ready-to-fill (RTF®) syringes and accessories for direct use on filling lines. Gerresheimer RTF syringes are characterized by high standards such as low cosmetic defects, low crack, and low break force values for cone and finger flange, consistent pull-off forces of needle shields, and siliconization levels. Gerresheimer's RTF syringes are available in a range from 0.5 ml to 3 ml long.

Progress development in the prefilled syringe industry is revolving around their design, properties, and accessories, such as manufacturing syringes in tighter dimensions or enhancing break resistance for auto-injectors. There is also a focus on minimizing cracks and improving pull-off forces of tip caps and needle shields. TELC® (Tamper Evident Luerlock Closure) improves the classical luer lock adapter and the TERNS® (Thermoplastic Elastomer Rigid Needle Shield) is a Gerresheimer proprietary closure system for syringes with a cannula.

Adding to the need to evolve the dimensional design of prefilled syringes, there is rising demand from new drugs that need to be administered by injection. Biotech drugs are challenging the existing syringe systems. "On one hand, syringes need to be adapted and specified for these demanding drugs, such as by reducing silicone oil levels," says Mr. Zeiss. "On the other hand, we see the rise of generic drugs as an important development, where cost is critical and customers aim at economic solutions."

He adds: "The syringes we know today will still be there in a decade or two, completed by a range of new and handy specialized application systems and combination systems. Continuous improvement through carefully and thoroughly developing the existing platforms is what we see for the future."

FIGURE 5

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

UNILIFE—DIFFERENTIATED AND CUSTOMIZABLE DEVICE PLATFORMS

Pharmaceutical customers are seeking to use prefilled syringes to differentiate their drugs from branded, generic or biosimilar competition. In essence, commodity off-the-shelf prefilled syringes are no longer desirable.

"Unilife does not do 'me-too' devices. We specialize in device platforms, not rigid devices, so that we have the flexibility to customize each product to customer needs," says Stephen Allan, Vice President,

Marketing and Communications for Unilife.

Unilife prefilled syringes feature automatic, integrated needle retraction. Other proprietary platforms include dual-chamber syringes with ventless, orientation-free mixing, precision-therapy wearable, disposable injectors for the subcutaneous delivery of doses 1mL or larger in volume, disposable and LISA electro-mechanical reusable auto-injectors with user-controlled injection speed needle-free removal of the used syringe, novel devices for targeted organ delivery, and the Ocu-Ject for the delivery of microliter doses.

"Each of our device platforms has proprietary technology that is disruptive within its class," says Mr. Allan. "We are in the process of delivering customized devices to a number of pharmaceutical customers from across all of our technology platforms," says Mr. Allan. "We are also developing additional game-changing technologies that will address other unmet or emerging needs for injectable drug delivery."

VETTER PHARMA INTL.—A NEW WAY OF LOOKING AT MANUFACTURING AND DELIVERY

An important single trend in the pharmaceutical and biotech industry is the erosion of the blockbuster model and the strengthening of the overall injectable market. Biologics are predicted to be a major contributor to this growth. And while

Vetter's Peter Soelkner: "Changes in the industry will require strategic partnerships in the prefilled syringe segment that respond to the numerous challenges."

manufacturers will enjoy opportunities in the emerging area of complex biologics, the new opportunities will also present challenges as well. Due to their biochemical composition, complex biologics require a wholly different way of manufacturing and administration. The monoplant model will no longer be viable in this area, leaving a growing need for production sites that allow for efficient manufacturing of complex and sensitive biologics in syringes. These sites should be able to operate fast and flexible, with the ability to scale up rapidly and allow for a quick switch of products being manufactured.

As a CDMO, Vetter anticipated the growth in biologics. Vetter has a new commercial aseptic filling line RVS 3 for pre-sterilized/nested syringes, capable of manufacturing up to 1 million units per day. "RVS 3 was designed to meet the respective needs and demands of our different customers," said Peter Soelkner, Managing Director of Vetter Pharma International. "The development and installation of this new line represents excellence in outsourcing, providing intelligent and efficient solutions to specific challenges in aseptic manufacturing."

According to Mr. Soelkner, RVS 3 meets the high quality standards and efficient performance needs for the market while offering customers a competitive solution for commercial manufacturing of medium- and large-scale products. "Through intelligent processes for handling the tubs under aseptic safety, the line enables reliable, premium quality for economically intelligent conditions. It also offers back-up possibilities to existing customer products."

In addition, Vetter's modern facility for secondary packaging addresses the growing demand for administration devices, like auto-injectors, pens, and other safety devices. And its tamper-evident closure, V-OVS®, protects the integrity of the drug product before administration.

"The key to success is achieving high sterility while offering innovative products that enhance compliance and improve accuracy of delivery, all in a time of rising costs and shorter lead-time," said Mr. Soelkner. "As a full-service provider, Vetter provides fast, flexible and cost efficient manufacturing of a customer's product. Its state-of-the-art filling lines, as well as manual and fully automatic visual inspection enable product safety."

Looking ahead, Mr. Soelkner believes that pharmaceutical and biotech companies will focus greater attention on their core competencies, continuing the trend towards outsourcing. At the same time, complexity will grow further in active ingredients and production processes. "These important

changes in the industry will require strategic partnerships in the prefilled syringe segment that respond to the numerous challenges in the industry – from loss of patent protection to increasing competition and higher regulatory demands."

WEST PHARMACEUTICAL SERVICES—THE IMPORTANCE OF THE CONTAINER AND CLOSURE

Drug delivery devices and systems are becoming increasingly essential because of the growth in injectable therapies driven by increased incidence of long-term diseases such as diabetes and auto-immune diseases. Many of these treatments require regular injections, which are often performed by the patient or caregiver in the home setting. Understanding the needs of these patients or caregivers is essential when considering designs for drug delivery systems.

Also, there can be a cost benefit when transitioning health care delivery from the hospital environment to the home environment or other health care facilities. Effective drug delivery devices and systems that enable a patient to self inject can aid this transition. For example, it is now possible to transition from hospital IV to home-administered subcutaneous injection through the use of an electronic patch injector or auto-injector. Pharmaceutical and biotech companies are working closely with drug delivery device manufacturers at an early stage to ensure that there is efficient development of an overall system to enable cost-effective drug delivery.

FIGURE 6

The SmartDose® electronic patch injector system from West enables higher volumes of drug to be injected slowly.

prefillable syringes may aid in patient compliance, but most are still based around conventional glass syringes, which may cause safety issues such as breakage. Newer drugs, including those with high viscosity or that need to be administered in high volume, can present administration challenges.

Delivery system companies, such as West, have introduced new materials for prefillable syringes, including break-resistant cyclic olefin polymers, such as the Daikyo Crystal Zenith® polymer. "Manufactured from a polymer that reduces the risks of breakage, the dimensional tolerances, quality standards, and freedom from materials such as silicone oil, tungsten or adhesives helps to ensure that the systems provide the combined benefits of plastic with the features necessary to contain a sensitive biopharmaceutical," explains Graham Reynolds, Vice President, Marketing and Innovation, Pharmaceutical Delivery Systems, West. "Understanding the interactions between all elements of the drug delivery system (including the drug, container, delivery device and the patient) is a key factor in ensuring success. If any one of these factors is not adequately considered, the success of the overall treatment may be compromised."

After several years of development, West, along with partner Daikyo Seiko in Japan, has scaled-up manufacturing of a 1mL Daikyo Crystal Zenith syringe system. The fully validated syringe system is provided in a sterile tub and nest format, and has been designed to be compatible with existing filling equipment. Developed more than 20 years ago, the Daikyo Crystal Zenith polymer is currently in use with more than 30 marketed drug products. "However, the transition to polymer syringes has been slow in a very conservative market," explained Mr. Reynolds. "Recent trends are driving a wider adoption, so we anticipate strong focus on these types of syringe systems in the coming years."

West has also collaborated with Vetter

FIGURE 7

Three vented ViaLok vial access devices from Yukon Medical: 13 mm ViaLok (left), 20 mm ViaLok (right), and vial spike (center).

YUKON MEDICAL—MAKING THE CONNECTION

Pharma to provide customers with a fully integrated system for obtaining a filled syringe that is ready for stability studies. "Several customers are at various stages within their marketing application processes, and we expect that this system will become a syringe of choice for many new or existing biologics where problems of quality, breakage, extractables and drug interaction could be a challenge with traditional glass syringes," says Mr. Reynolds.

West is continuing to scale-up the SmartDose® electronic patch injector system, which is designed to deliver higher volumes of drugs to the patient at a controlled rate. This is a great example of an integrated delivery system based on a Daikyo Crystal Zenith cartridge that incorporate research around user needs and preferences.

Connection issues and unwanted contaminants are affecting the prefilled syringe market today. ViaLok® vial access devices allow for needle-free access into standard drug vials via a standard luer connection. The products have been designed to provide a secure connection to the vial using materials that are BPA-, PVC-, and latex-free. Yukon Medical received 510k clearance and CE mark registration for several ViaLok access devices in the past year.

Another trend Yukon identifies is extractables and leachables in plastic prefilled syringes. "This particular issue diminishes significantly when using Yukon products due to the short duration contact with the syringe when using a glass vial as the primary package," says Yukon Medical CEO, Todd Korogi.

Yukon also sees that drug commercialization costs are a significant and rising trend. Yukon addresses this trend by making it easier to use a standard primary container such as glass vials to access, which in turn saves its clients significant development costs and reduces time to market.

In addition to launching a ViaLok with in-line fluid filtration in 2014, Yukon Medical will release the SmartMix™ reconstitution device, which allows the user to reconstitute a diluent and a lyophilized drug (or viscous solution), again using standard glass vials as the primary packaging. "This device eliminates many of the problems associated with prefilled syringes such as compatibility issues, connection issues, development costs, and filling capacity while still reducing the number of steps to prepare and deliver the medicine," says Mr. Korogi. The device is intended for standard dose products where the lyophilized drug vial is sealed under vacuum.

"Consider devices that utilize standard glass vials as potential new technologies that warrant further investigation," advises Mr. Korogi. "With the introduction of prefilled syringes, vials have been considered old technology when it comes to primary packaging. However, if we can find a way to use glass vials as the primary package and access them in a new way; the technology may be something that can get companies to market more quickly, save development dollars, and provide the clinician/user with a great user experience." ◆

DRUG DEVELOPMENT
µco Executive
by SNBL

SNBL, Ltd.: Innovation in Drug Delivery Enabled Through a Unique Business Model

Shunji Haruta, PhD
Founder,
NDS Division
Executive Officer,
SNBL, Ltd.

Drug development companies are abuzz regarding alternative routes of delivery. Current buzzwords, such as buccal, nasal, parenteral, and pulmonary are stirring the nest, and for good reason. It is difficult to read an article about the biopharmaceutical industry without being reminded of the massive paradigm shift currently in midstride. Within this shift, the necessity of easy-to-use and effective self-dosing medications is underscored and at this juncture, these buzzwords are seen as imperative solutions. Healthcare costs as a whole are rising. Hospital-only administered treatments are becoming more expensive and burdensome on an already strained system, and demand for therapeutically relevant medications for diseases with high unmet needs (as opposed to incrementally better me-toos) continues to grow. Pharma and biotech companies are falling behind; R&D budgets of the 90s for a single project are rare, cut-and-run decisions are being made sooner in early development than ever before. Hospitals, pharma, and biotech alike need to save money, as does the consumer during this economic depression, and the consumer has grown aware of power in demanding more affordable price points. The immense in-flux of patent expiries and the subsequent market flood of generics have only further highlighted the "price gouging" of the biopharmaceutical industry to consumers. Unfortunately, many have too little understanding of the need for companies to regain the amount spent in upfront R&D, a hard feat without considerable marketshare and blockbuster status. In response, pharma and biotech are searching for de-risking partnerships and cost-minimizing development options. Thus is the dilemma of the aforementioned buzzwords, and creators of said drug delivery platforms are providing previously underappreciated solutions through innovative science, novel business models, and advantageous partnerships. Drug Development & Delivery recently interviewed Dr. Shunji Haruta, founder of NDS (Nasal Delivery Systems) Division and Executive Officer, SNBL, Ltd. to discuss how NDS Division and its powder nasal delivery platform, µco System™, fit into this new paradigm.

"As stated earlier, our parent company is a CRO, and preclinical services are truly our bread and butter. Licensing of the µco System inherently comes with the know-how and background of our CRO experience. SNBL is the largest worldwide provider of CRO NHP expertise, and this knowledge is invaluable during the drug development process."

Q: For our readers who are not yet familiar with your technology, can you briefly describe the µco System?

A: The µco System is a nasal drug delivery platform stemming from two breakthroughs. The first breakthrough is our muco-adhesive carrier technology. The carrier technology lays the groundwork for API effectiveness. Holding the API on the nasal mucosa for an extended period of time, the carrier allows for absorption into the blood stream. Our carrier consists of GRAS excipients and is virtually inactive and non-absorbable. Natural mucocilliary clearance eventually removes the carrier from the nasal cavity and is then moved through the GI tract and cleared from the body.

The second breakthrough technology of the µco System is our line of in-house designed nasal delivery devices, Fit-lizer™. We have designed both single- and multiple-use devices, which achieve 100% delivery of the formulation into the nasal cavity with every use; usability studies have confirmed this delivery across a variety of patient actuation pressures. We wanted a user-friendly, simple, and effective delivery device and we have been able to achieve that.

Q: You are the inventor of the µco System; tell us about why you chose to pursue powder delivery instead of the popular liquid and gel route?

A: The nasal cavity is an opportune drug delivery route because of its rich vascular capillary bed situated directly beneath the surface, but it was frustrating to see nasal medications consistently fail in effectiveness. Biology shows the nasal cavity is ideal for many types of therapies, but it is clear to anyone who has ever used a traditional liquid nasal product that the medication is not staying in the nasal cavity. Liquids simply run too quickly. Without time to absorb nasally into the blood stream, minimal effect is seen and by looking at PK profiles of liquid nasal medications, you typically see a double-peak; initially for absorption through the nasal mucosa and the second through the GI tract. This is why I chose to begin looking at muco-adhesive carriers for increased nasal absorption. There had to be a better way, and muco-adhesive carriers were the logical next step.

Q: Is it uncommon that a delivery technology offers both a carrier and device? Why did SNBL develop both? Why not just the carrier?

A: We saw the problem with nasal delivery as two-fold: medications that run out of the nasal cavity after delivery and poor delivery of the formulation. If we developed a fantastic, enabling carrier, we knew it could only be as good as the device used to deliver it. The majority of nasal delivery devices deliver inconsistently and/or less than 70% of the formulation into the nasal cavity. That results in inconsistent absorption (efficacy) and is costly to both the pharma company and the patient. On top of that, devices seem to become more and more complicated; some devices can only be used by certain patient populations and not by others. We wanted to design a universal device with simple operation and complete delivery that can be used by virtually any adult; we have been able to do just that. I am very proud we have two technologies that complement one another so well.

Q: You founded NDS Division in SNBL, Ltd., a CRO. It is unusual for a CRO business to develop a drug delivery platform? Why did SNBL make the commitment to the µco System?

A: As a CRO, SNBL has done copious amounts of testing throughout its now 55 years. We began to recognize that the industry standard models for nasal delivery were not producing predictive results. Preclinical testing is to prove safety before entering volunteers, but for pharma and biotech companies that are investing limited R&D dollars, the preclinical results are too often misleading in terms of PK.

SNBL has some of the world's most extensive experience working with NHPs and recognized the problem with using rat and dog models: anatomy and physiology are too distinct from that of humans. There is no way to get an accurate and predictive PK from rats and dogs. However, SNBL soon realized that the nasal anatomy of NHPs is comparable to that of humans. So we designed and validated a nasal NHP model, along with an in-house designed nasal testing mechanism, which synchronizes with the breathing cycle and automatically administers upon inhalation. This allows PK testing of nasal drugs on unanesthetized NHPs while maintaining lower stress levels, producing exceptional data and, consequently, fewer animals and decreased cost per study. Simply put, SNBL's CRO capabilities complemented the development of the µco System. Management saw the potential and made the choice to move forward and support it.

Q: You said that initial development of the µco System was for insulin, but that the course changed after you learned more about its characteristics and capabilities. What pilot program(s) did you run instead? What kind of regulatory hurdles did you encounter?

A: Insulin is a White Whale for many drug delivery systems, so we learned a lot about the capabilities of our carrier by trying to overcome hurdles with insulin. Ultimately, we chose to pursue other paths for proof-of-concept, and we chose granisetron with the µco System (TRG) as our first pilot program. For the treatment of chemotherapy-induced nausea and vomiting (CINV), we have taken TRG through Phase II clinical trials, aiming for a 505(b)(2) approval. Our initial proof-of-concept came in a Phase I study, where we achieved 100% absolute bioavailability against IV injection of marketed granisetron. The preclinical data generated using our NHP model, which I previously touched on, proved predictive.

Our second pilot program is zolmitriptan with the µco System (TRZ). TRZ, for the treatment of migraine headaches, recently completed a successful Phase I clinical trial, also aiming for a 505(b)(2) approval, with promising results. Cmax was reached by 20 minutes after dosing, and relative bioavailability compared against a marketed tablet was 136%; relative bioavailability to marketed nasal spray was 182%. We have been very happy with the results from our clinical trials, and it has certainly been a learning experience for our small NDS team.

SNBL has GLP preclinical capabilities as well as clinical capabilities, so being able to conduct our preclinical and Phase I work in-house has been very helpful. But in terms of CMC work, we had never done anything like this previously. That was a challenge, and the NDS team was on a steep learning curve, but we now have a well-equipped lab for delivered-dose testing, particle size measurements, and plume geometry. In addition, we have gained a lot of regulatory know-how having compiled the IND filing in-house, as well as oversaw the Phase I

studies at our clinical facility in Baltimore.

The biggest regulatory hurdle we have come across is the lack of precedent in powder nasal drug delivery. Aiming for a 505(b)(2) approval pathway for powder nasal delivery is something that the Agency had not previously dealt with. It has been a good experience speaking and meeting with the Agency at each step of development, and the Agency has given the NDS team great depth in understanding what is expected from a regulatory standpoint.

Q: NDS offers licensing of the µco System. What is different about partnering with NDS?

A: As stated earlier, our parent company is a CRO, and preclinical services are truly our bread and butter. Licensing of the µco System inherently comes with the know-how and background of our CRO experience. SNBL is the largest worldwide provider of CRO NHP expertise, and this knowledge is invaluable during the drug development process. Partnership with NDS has a consultancy aspect to it. We are not manufacturers, every partner is not coming from the same mold, and we understand that. Each project and compound has specific needs, and our in-house capabilities from assay development and validation to tailored study designs and formulation optimization supports these needs. We also have regulatory experience, which means we are able to provide insight regarding strategy.

Q: Overall, what success has the µco System had, and what is your 3-year projection?

A: Thus far, we have licensed the µco System to Pastorus Pharma for use with oxytocin for the treatment of autism. We are also in talks with a number of other companies regarding licensing of the µco System and are very excited about our future working relationships with these companies.

As for our 3-year projection, we realize that it is necessary to always continue improving and innovating. We have confidence in the µco System and are driven to use it for bringing therapeutically relevant and improved treatments to patients; the relief and safe treatment of patients is what NDS and SNBL value most. Making a positive impact in patients' lives excites us, and we will achieve that by partnering the system for systemic delivery of small molecules and peptides. Following will be the use of the µco System for powder nasal delivery of vaccines, which will be groundbreaking in its own right. Finally, we will be adding to our CRO capabilities through the development of a self-inhalable pulmonary delivery system for NHPs and other species; this system is currently under development, and we are pleased by the progress it is making.

NDS and SNBL are really a prime example of how out-of-the-box business models can be harnessed for mutual benefit. NDS has this very unique technology that could not have been created without SNBL's expertise and in return, the development NDS spearheaded gave SNBL a one-of-a-kind model and testing mechanism; there are multitudes of mutual benefit. NDS and SNBL have become leaders in nasal drug delivery development and testing, both in their own right, and it is due to the relationship and business model. I am confident that NDS will continue to progress with development and partnering of the µco System, and through this progress will persist in contributing to SNBL's CRO capabilities. There are always improvements to be made and new discoveries to be had, and the biopharmaceutical industry is constantly changing to adapt to these discoveries. NDS and SNBL are adaptive, innovative players that will contribute to advancements in the industry over the coming years. ◆

Technology & Services Showcase

Solid Dosage Forms

Agere Pharmaceuticals offers clients formulation design and development, cGMP analytical, and solid oral dosage form services. Solid dosage forms supported include tablets, capsules, powder for inhalation, and alternative dosage forms. We can select excipients, drug excipient ratios, and process development, as well as prepare immediate and sustained-release forms for the clinic. In addition to characterization of unit operations, Agere offers a broad spectrum of analytical and physical measurement capabilities. All services are offered on a fee-for-service basis. For more information, please contact Agere at (541) 639.8397 or info@agerepharma.com or visit **www.agerepharma.com.**

HPMC Capsules

Capsugel's Vcaps Plus HPMC (hypromellose) capsules are non-animal capsules with low-moisture content that also meet global pharmaceutical standards. A proprietary capsule-manufacturing process eliminates the need for gelling agents and delivers gelatin-like consistent disintegration and dissolution properties. The unique performance characteristics of Vcaps Plus HPMC capsules expand the range of applications for two-piece capsules. The proven properties of Vcaps Plus capsules make them an excellent alternative to gelatin or traditional HPMC capsules for optimizing delivery, performance, and stability of over-the-counter, New Chemical Entities, and off-patent products, as well as reduce development timelines. For more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com**.

Technology & Services *Showcase*

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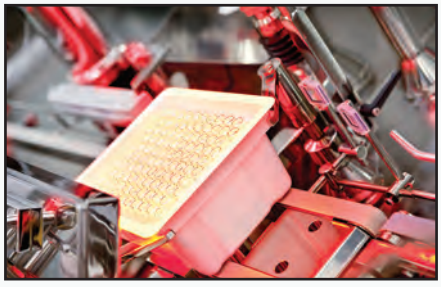
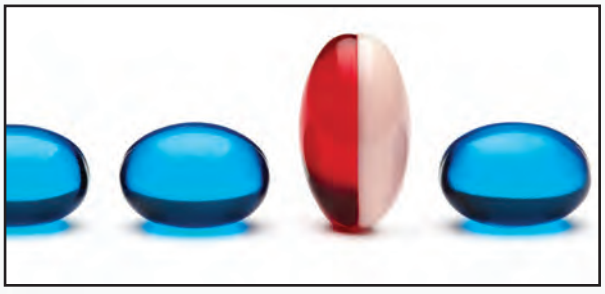
Twister® is a new capsule-based DPI, designed specifically to address unmet medical needs in fast-growing markets. During its development by a dedicated Aptar Pharma multi-disciplinary technical team, Twister was tested and validated with a number of different dry powder drug formulations. Twister has a simple and robust design with few components, making it cost-attractive for asthma and COPD treatments in fast-growing markets. Twister is designed to be patient-friendly and easy to use, allowing patients easy access to their medication in three simple steps: Insert, Twist, and Inhale. To help improve patient compliance with the prescribed treatment, Twister is transparent, allowing the capsule and powder to be seen in the device as they are processed. In addition to these visual cues, the patient is also guided by audible feedback during inhalation. For more information, visit Aptar Pharma at **www.aptar.com/pharma**.

Integrated CDMO



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

Softgel Technology



Catalent RP Scherer softgel boasts more than 75 years of development expertise and manufacturing experience. RP Scherer improves solubility and optimizes performance in all of its capsules. RP Scherer is supported by a global infrastructure of cGMP, FDA, and EMA. RP Scherer Softgel technology improves solubility, increases bioavailability, and offers valuable product differentiation of different shapes colors and sizes. This technology also helps bring compounds to market faster using a proven dosage form and helps reduce regulatory risk. RP Scherer capabilities continue to expand. In Q1 2013, Catalent announced two major joint ventures in China significantly expanding it RP Scherer softgel innovations, proven operational excellence, and regulatory compliance in the Asia Pacific region. To learn more about Catalent's global RP Scherer Softgel technology capabilities, call (877) 587-1835 or visit **www.catalent.com/index.php/offerings/softgel/softgel-tech**.

Innovative Syringe Systems

The Gerresheimer Group is the leading manufacturer of glass and plastic products for the pharmaceutical and life science industry. The product portfolio ranges from pharma¬ceutical vials to complex drug delivery systems. Gerresheimer is also known for excellence in the area of RTF® (Ready to Fill) syringes, which are supplied completely washed, siliconized, assembled, nested, packed in tubs, and sterilized to the customers. A range of proprietary acces¬sories, such as the rigid needle shield with thermoplastic elastomer (TERNS) and the tamper-evident Luer lock closure with twist-off motion (TELC), facilitate safety and convenience for the end-users of these syringe systems. Gerresheimer partners with customers worldwide to meet specific market needs. For more information, contact Burkhard Lingenberg of the Gerresheimer Group at +49 211 6181-250 or visit **www.gerresheimer.com**.

Technology & Services Showcase

Development & Manufacturing

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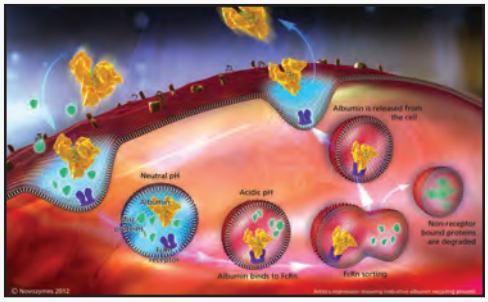
Multidose Eyedropper

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

Tunable Half-Life Extension Technology



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

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Technology & Services *Showcase*

Device Manufacturing

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

Development Services

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

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Unilife has developed a flexible, scalable portfolio of wearable, disposable injectors for the subcutaneous delivery of large-dose volume therapies with optimal patient comfort and convenience. Multiple customization options are available to address specific therapeutic, operational, branding, and patient needs, including dose volume and controlled bolus, constant or variable delivery duration rate. Each device leverages human factors data with target patient populations to provide a highly intuitive, effective, and confident user experience. Designed for seamless integration with approved manufacturing methods and primary container materials, Unilife is ready to support customer needs for the commercialization and lifecycle management of their injectable therapies. For more information, call (717) 384-3400, email info@unilife.com ,or visit **www.unilife.com**.

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Vetter Development Service (VDS) provides expert support for your drug development projects, from inception to market launch. Our services include state-of-the-art clinical manufacturing at our facilities in Chicago and Europe, with scale-up and transfer to our large-scale manufacturing facilities. Thanks to the latest technology and innovative processes, we help increase your API yield. Vetter Development Service provides Formulation Support, Process Development, Clinical Trial Manufacturing, Analytical Service, and Regulatory Support. For US inquiries please contact +1-847-581-6888 or infoUS@vetter-pharma.com. For EU inquiries please contact +49-751-3700-0 or info@vetter-pharma.com. Visit **www.vetter-pharma.com** for more information.

Market Forecasting

Monte Carlo-Based Forecasting: How to Deal With Uncertainty

By: Jemma Lampkin and Gerard Loosschilder, PhD

Introduction

Imagine that you have just wrapped up the Phase II trial of your new drug. The results are promising, yet the launch is several years out. R&D costs are significant, and healthcare budgets are under pressure. Your CEO is expressing concerns about critical success factors like FDA approval, potential changes of payer policies, and a chance that competition beats you to market. A market forecast may help your business decide whether to continue with the development. Yet, when so many factors going into the forecast are uncertain, there is doubt surrounding the value of conducting a forecast at all. Before you know it, conditions may change, the forecast could be rendered invalid, and you could be forced to start anew. But why not turn uncertainty into a virtue? In this paper, we show how Monte Carlo-based forecasts are better at handling uncertainties, turning them into valuable tools for product managers and marketers engaged in strategic business planning.

What is a Monte Carlo-based Forecast?

A traditional market forecast of a new drug or treatment produces a single revenue number, say $3 billion over a 5-year period following launch. It is computed by a multiplicative exercise: Revenue =

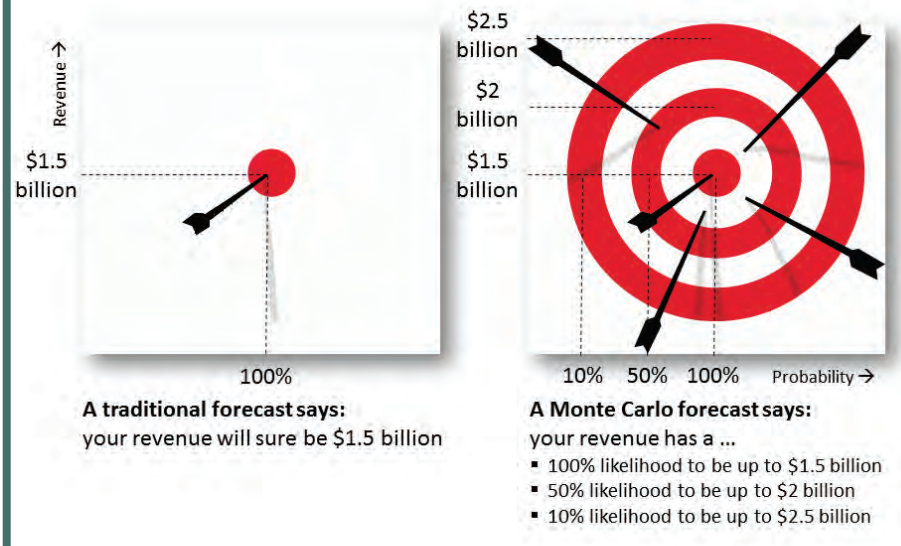


Figure 1. **From a Point to a Range Forecast.**

Certainty Level: High (normal distribution)	Minimum	Maximum
2016	35%	40%
2017	65%	70%
2018	95%	100%
2019	100%	100%
2020	100%	100%

Table 1. **Awareness of Periculum by physicians as % of peak share.**

Population x Awareness x Acceptance x Price x Compliance. Awareness is most likely to increase over time because of investments in above or below the line communication and sales force effectiveness. Acceptance is the healthcare professional's expected prescribing behavior of the new drug at the given price and taking into account payer policies for eligible patient groups. Usually, we also take into account the competitive context of alternative drugs and treatments, showing how much the new drug helps grow the market or how it can steal share from competition.

Unlike a traditional forecast, a Monte Carlo-based forecast does not produce a single number, but instead provides a range of possible outcomes at a probability distribution. For example, it indicates that sales over the 5-year period are likely between $2.5 and $3.5 billion. The probability distribution may show there is a 100% likelihood that sales will be $2.5 billion and still a 50% chance of sales being $3.5 billion (Figure 1).

A Monte Carlo simulator produces output ranges because the inputs are data ranges instead of data points. For example, instead of working with a single awareness number of 50%, we work with a range of 40% to 60%. Or, availability could be determined at 20%, 40%, or 60%, depending on payer policies. Taking into account all factors, the simulator multiplies range values instead of point values, producing an output range.

We believe that Monte Carlo-based forecasting is more realistic and intuitive. After all, who is expecting to make exactly $3 billion? Forecasts may always be slightly off, and most likely, they are off because of errors or uncertainties in the input variables. Therefore, it is better to explicitly account for them. In fact, Monte Carlo-based forecasting delivers a superior way of dealing with uncertainty because it helps provide a structure for contemplating what uncertainty looks like. It does so by allowing us to set the shape of the distribution of the range. A common example of this is the "normal distribution." For example, it says that the mean awareness at moment t is 50%, but the bulk of awareness values are distributed between 40% and 60% (Figure 2A). Its most common counterpart is the uniform distribution: it sets two extreme values (eg, 40% and 60% for awareness); every value in between has an equal likelihood of occurring (Figure 2B).

These ranges are used to deal with variables that have continuous values. Similarly, we can work with the likelihood of discrete events. For example, we can use this to model the effect of competitive launches. Imagine that we expect a first mover advantage; the first to enter the market puts up an entrance barrier and sets followers at a disadvantage. We can set the likelihoods that either we or the competition move first, and we assign the first mover advantage. This will impact the distribution of the forecasted variable. The rule is the higher the uncertainty in inputs, the wider the input ranges, and the more likely we choose a uniform instead of a normal distribution.

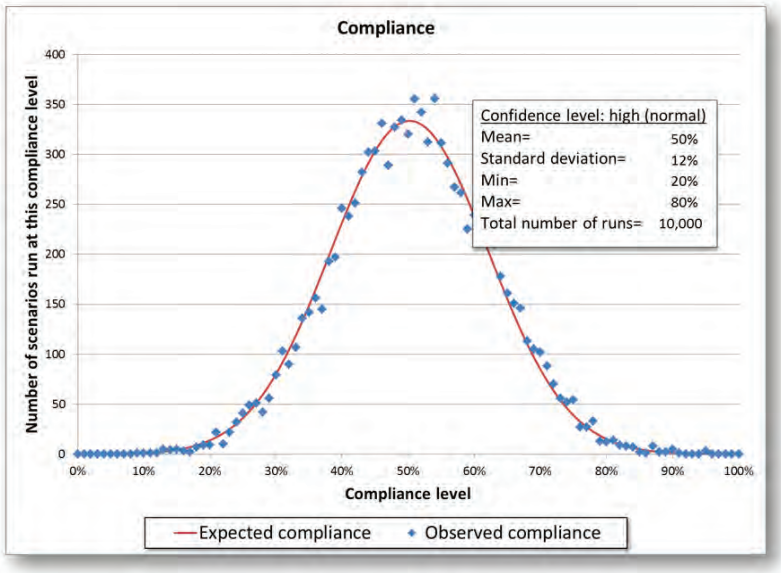
Why Do We Account for Uncertainty?

We account for uncertainty because the input variables in our forecasts are not always of good quality, and because specific events can render a forecast invalid if not accounted for. In the United States and other established markets, reliable data are widely available. Launches of new drugs and treatments in common disease states are well documented and provide for great analogues. However, there are several

	Certainty Level: Low (uniform distribution)	
Lower Bound	75%	Compliance is the patient's adherence to the prescribed dose per day
Upper Bound	85%	Persistence is the proportion of patients persisting with the prescribed therapy

Table 2. **Expected patient compliance x persistence.**

A



B

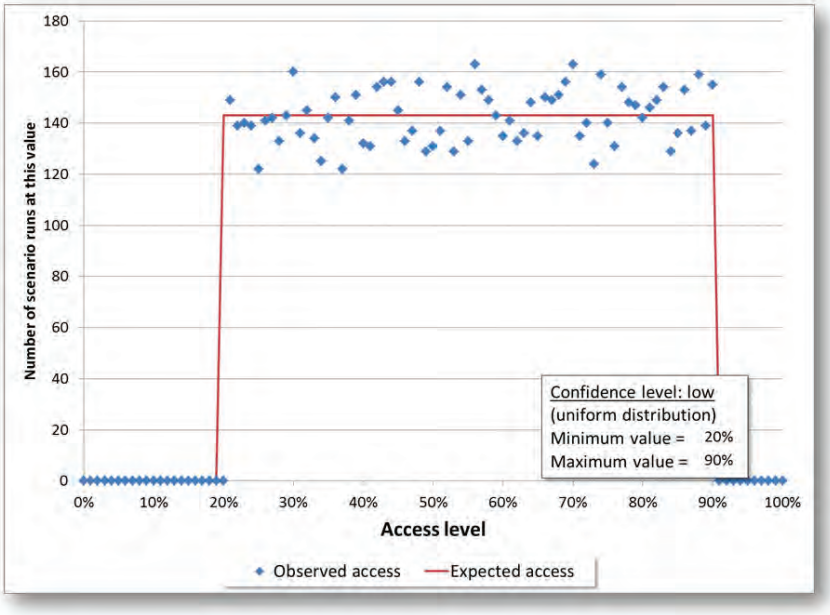


Figure 2 A. Normal Distribution **A normal distribution is used when the uncertainty associated with a variable is low. A normal distribution can either be specified by setting the mean and standard deviation, or by setting the minimum and maximum value. Values are randomly generated based on the normal distribution. The red line describes the expected distribution; the blue dots describe the frequencies of compliance values in the 10,000 runs of a Monte Carlo simulation.**

Figure 2 B. Uniform Distribution **A uniform distribution is used when the uncertainty associated with a variable is high. A uniform distribution can be specified by setting the extreme values. Values in between the two extremes are randomly generated. The red line indicates the expected distribution; the blue dots indicate the frequencies of compliance values in the 10,000 runs of a Monte Carlo forecast.**

situations for which there are no analogues or secondary data. Yet, that's where opportunities for new drugs and treatments often lie. Examples include emerging markets, less-explored disease states, and rare or orphan diseases.

Another reason is that inputs in forecasting often come from a variety of sources from different origins: syndicated research, expert interviews, government statistics, internal sales data, or simply anecdotal evidence and the hunches of business people. Data from different sources often contradict each other, and it may be impossible to get to a single, valid number. This may lead to researchers or business units to agree on just one data source to keep metrics aligned and avoid having to deal with conflicting data. This may work at face value, but is it really the way toward an accurate forecast and the best description of reality? Working with ranges or scenarios is a better solution.

Finally, one can be sure that competition will launch new products and that payer policies will change; the only question is when? Especially in a situation in which we believe that the order of events will impact our performance, it is important to do scenario planning and include the scenarios and their corresponding likelihoods in our forecast. Scenario planning needs to include input from business owners and stakeholders and involves answering three questions: (1) what could happen, (2) when might it happen, and (3) what is the likelihood of it

happening? True to the nature of scenario planning in a situation of uncertainty, the first two questions can have conflicting answers.

How Else Do We Deal With Uncertainty?

Monte Carlo-based forecasting does not help to deal with uncertainty by itself. On the contrary, the fact that it produces an output range instead of a single number can contribute to the uncertainty. That is why we set action standards. An action standard consists of two things: a threshold sales value or other KPI (key performance indicator) that the forecast needs to exceed before the business decides to proceed with the initiative (eg, $2 billion over 5 years), and the likelihood of making this number (eg, 100% sure to make $2 billion).

Action standards serve two purposes. First, they help us to set the expectations from the business. We do this as part of the study design and before sharing the results. Because the expectations are set beforehand, decision-making is usually more informed and of better quality. Second, we suggest setting the values, shapes, and ranges of the input variables in close collaboration with the business. It is here that the business learns to cope with the uncertainties associated with the input variables.

Through this process, we learn about the business' appetite for risk. Some (companies, functions, or persons) are rather risk averse and are more willing to accept a lower result at a higher likelihood (eg, 100% sure to make $2 billion). Others accept more risk and set a higher result at a lower likelihood (eg, 50% sure to make $3 billion). One only pursues an initiative if one meets or exceeds the action standard.

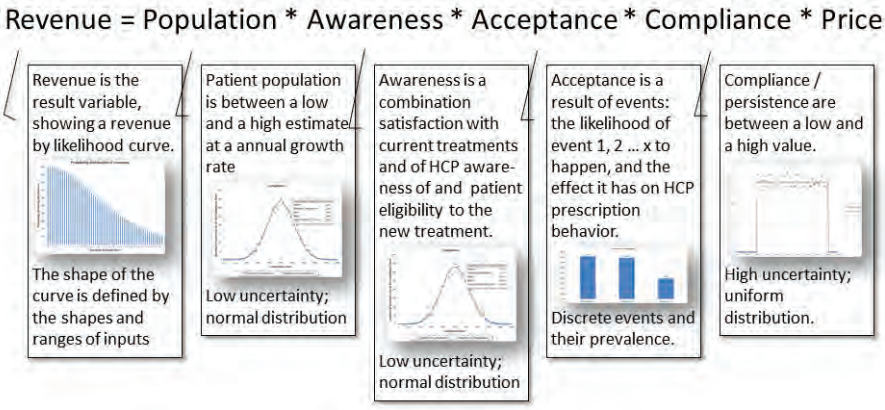


Figure 3. A Monte Carlo Forecast of Revenue **In a Monte Carlo forecast, thousands of scenarios are run. In each scenario, a value for each variable is drawn from the distribution of values, and the values are multiplied to compute a revenue number. The thousands of scenarios result in a distribution of revenue values, responsible for the likelihood curve used to determine if we make the target value set by the action standard.**

Exhibit 1: The Case of Periculum, a New Type 2 Diabetes Drug

Further, we present a fictitious business case to show the relevance of the approach in a business context. Ducendi Incorporated is a big pharmaceutical corporation, and type 2 diabetes is one of its main focus areas. Launching a new molecule will ensure Ducendi remains a strong player in this market. Always on the look-out for up-and-coming biotech companies with interesting innovations in the pipeline, Ducendi has focused its attention on Novus Pharmaceuticals.

Novus has just met its Phase II clinical trial endpoint for a new drug to treat patients with type 2 diabetes called Periculum. Periculum is an oral drug with a novel mode of action that is believed to ensure minimal adverse events with an outstanding tolerability profile.

Novus and Ducendi are looking into a partnership agreement to take the drug from the current Phase II clinical trial to its launch a few years out. Novus asks Ducendi to fully fund the Phase III trial, set up a production plant, and launch Periculum globally. But there are

More	33%
Equally	33%
Less	33%

Table 3. **The likelihood of Periculum to be efficacious is…**

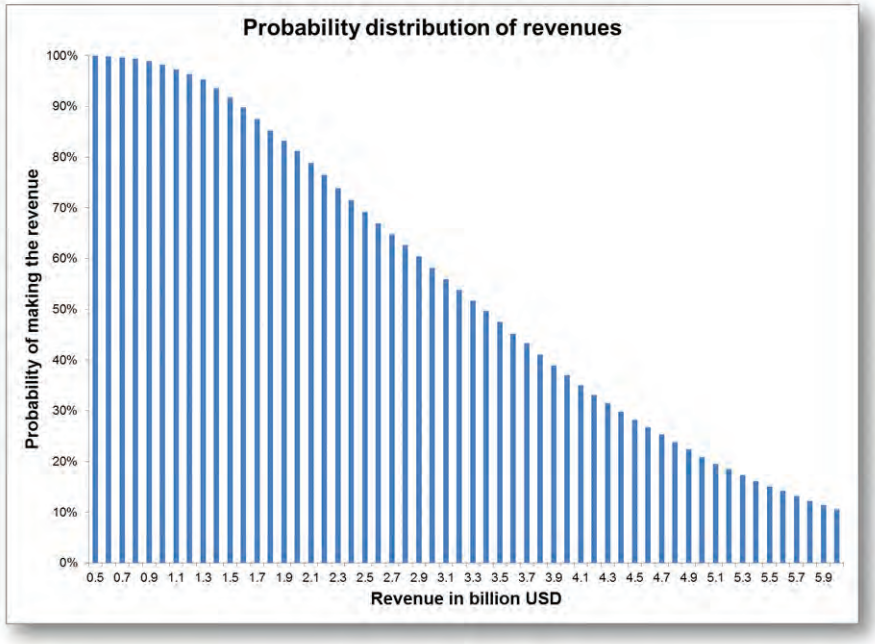


Figure 4. Revenue Forecast **This chart shows a Monte Carlo revenue forecast with on the horizontal axis the revenue value and on the vertical axis the likelihood value of making the revenue.**

uncertainties. While the efficacy data coming out of the Phase II trial look promising, the Phase III outcomes may disappoint. Also, rumor is that competition is going to launch a similar drug right around the same time. While Novus is keen on signing a license agreement, Ducendi wants to first assess the opportunity of Periculum.

Usually, Ducendi validates business cases in the US only, because succeeding there almost certainly generates a positive ROI. However, because of expected changes in the healthcare landscape in the US and global markets, Ducendi also wants to validate the business case in emerging markets. While validating a business case is easy in the US and other established markets because of the availability of analogues, it is more difficult in emerging markets. Analogues are less prevalent, and fewer data are available and of uncertain validity. Hence, the need for a Monte Carlo-based forecast.

The team sets out to collect data about key emerging markets. First, they commission a study to validate interest in the drug. They estimate the willingness of healthcare professionals to switch to the new drug under target product profile scenarios describing variations in efficacy and tolerability profiles. They also include similar drugs by different pharmaceutical brands to help the team get insight into the peak share of the new drugs under various launch scenarios. They define the size of the patient population and set the expected awareness curve, patient compliance, and persistence levels. Awareness is a compounded measure accounting for satisfaction with current drugs and treatment and the awareness or "buzz" associated with the new product. As input, they collect government statistics and syndicated data enriched by expert interviews with practitioners, opinion leaders, policy makers, and payers. Because there is no such thing as one truth, the team decides to include range forecasts of awareness curves (Table 1) and patient compliance (Table 2).

Before	**33%**
At the same time	**33%**
After	**33%**

Table 4. **The likelihood of Periculum to be launched; competition is…**

Next, they align about the likelihood of events and outcomes. They set the likelihood of Periculum to be less, equally, or more efficacious in the Phase III clinical trial compared with Phase II (Table 3).

They also set the likelihood of the competitor drug to be launched before or after Periculum, or for both to be launched at the same time (Table 4).

Then, acceptance levels for Periculum are determined under the various scenarios of efficacy and the competitive launch. Next, they convert study results into a market forecast (Figure 3).

The best way to ensure management buy-in for the outcome of the forecast is have them take part in the preparation. The team sits with Ducendi management to agree upon the expected revenue and whether or not to proceed with Periculum.

	Target		Forecasted	
	ROI Revenue	% Likelihood	ROI Revenue	% Likelihood
Lower Threshold	$1.5 billion	90%	$1.5 billion	93%
Higher Threshold	$2 billion	80%	$2 billion	81%

Table 5. **Setting the action standards.**

Ducendi's gold standard is to break even in 5 years after launch. The 5-year investment in Periculum is estimated at $1.5 billion, including payments made to Novus, royalties on sales, an upfront fee due upon signing the deal, and milestone payments. Therefore, the 5-year revenue of Periculum must exceed $1.5 billion to generate a positive ROI.

We know that a Monte Carlo forecast provides a range estimate (Figure 4).

So, the second thing management needs to decide is what risk they want to accept not to meet or exceed the target value. Having a low appetite for risk, we can set the likelihood of making $1.5 billion at 100%. But management is willing to take a higher risk of not making a large profit (eg, a 75% likelihood of making $2 billion). We take these values as the action standards to decide whether or not to proceed with a partnership between Ducendi and Novus.

When running the numbers including the uncertainty factors, it becomes clear that there is a 93% likelihood of making $1.5 billion and an 81% likelihood of making $2 billion (Table 5). The team makes a positive recommendation for an in-licensing deal between Novus and Ducendi.

Summary

The reality of the healthcare industry is that what happens around us is stochastic, but the state of mind is still deterministic. Decision-makers often want one answer and are not inclined to commit to a range nor to the associated probability. Deciding on action standards at the outset of a research study and accurately setting ranges for the parameters are crucial to the success of the forecast. Both of these require collaboration and careful thinking among market researchers and business intelligence managers. Ultimately, Monte Carlo simulations are a way to obtain more accurate forecasts in areas of great complexity and uncertainty - never deleting the uncertainties, but helping us to cope with them. ■

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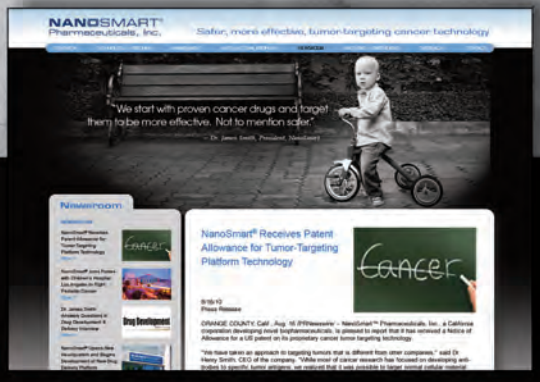

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M*A*S*H

By: John A. Bermingham

In May 1970, I arrived in Seoul, South Korea, at Kimpo Airbase and was transported by truck to the town of Chunchon, just south of the D.M.Z. I was stationed at Camp Page and was with the 226 Signal Company and assigned to the Communications Center.

While at Camp Page, our small movie theater showed a new movie by the name of M*A*S*H. We all found it interesting that here we were in Korea 18 years after the Korean War was put on hold due to the truce, and the rumor on Post was that there was a M*A*S*H unit during the war very close to where we were. In fact, the movie and television program M*A*S*H was set in Uijeongbu, which was close to Chunchon.

M*A*S*H stands for Mobile Army Surgical Hospital, and the purpose of a M*A*S*H unit was to get experienced medical personnel closer to the front, so that the wounded could be treated sooner and with greater success. Casualties were first treated at the point of injury through buddy aid or medics, then routed through Battalion Aid Stations for emergency stabilizing surgery by means of a triage process, and finally routed to the M*A*S*H unit for the most extensive treatment.

When companies run into trouble and the investors are looking for a quick fix to "stop the bleeding," it is incumbent upon the CEO and his/her management team to triage all functional areas of the company. Sometimes triage means taking the worst first or in the case of a company, looking at what areas are in the worst shape or causing the most detrimental problems. However, sometimes a CEO will go after the low-hanging fruit first, meaning the quickest and easiest problems to attack.

I don't agree with that strategy as I believe in what I call a modified comprehensive triage. That means that you should look very quickly at all of the issues that are affecting the company and focus on as many of them simultaneously as you can, giving special consideration to the more serious problems but not exclusively. This takes a lot of work and a lot of hours, but it has to be done if the company is going to survive.

The reason is that large complex problems can certainly take the company under. But small problems can become big problems, or multiple small problems can add up to a large problem, and either of these situations can take the company down. So you have to make very fast decisions on how to fix the "patient."

Leading the triage does not mean that you have to do everything yourself. That is what delegation is for. The rule that I always follow is to delegate everything that you don't have to do yourself. However, you also have to be in the leadership role at all times and be certain to make people that you delegate accountable for achieving the expected results.

While you are leading the modified comprehensive triage, make sure that you are communicating frequently with your owners or investors, such as a private equity firm. It is very important that they be completely aware of what you are doing and the progress that you are making. This is not the time to keep things close to the vest. Another benefit that I have experienced is that when you are going through this process, you will quickly learn who your star performers are, who you can delegate to and rely on, and who the people are who can't quite cut it.

At the end of this process you will have learned a great deal about your company and your people, and that is an invaluable benefit that will help you on the go-forward plan after you have saved the patient! ◆

Biography

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

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

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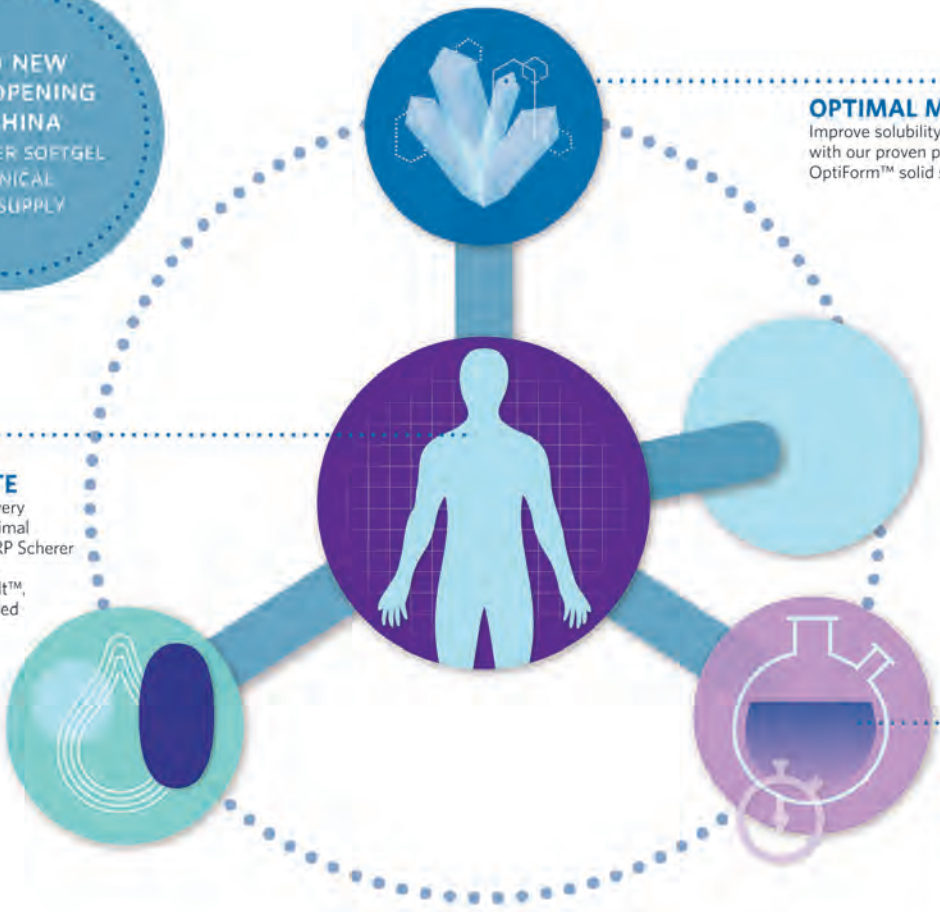

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