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# Drug Development & Delivery

April 2014 Vol 14 No 3

www.drug-dev.com


# Early-Stage Development & Manufacturing Partnerships On The Rise!

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

**Robyn Barfield, PhD**
ADC Development Using SMARTag™ Technology

**Cindy H. Dubin**
Outsourcing Formulation Development & Manufacturing: Early-Stage Partnerships Are On The Rise

**Claudia Roth, PhD**
Use of Disposable Technology in Clinical Fill & Finish Manufacturing: Benefits & Considerations

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LAURENT MEUNIER, PHD

OUR CAPABILITIES JUST WENT FROM

# BROAD TO BROADER

FROM SEMI-SOLIDS & LIQUIDS TO SOLIDS

FROM NON-STERILE TO STERILE

FROM CONCEPT TO COMMERCIALIZATION

FROM VIRTUAL TO LARGE PHARMA

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Drug Development & Delivery

**April 2014** Vol 14 No 3



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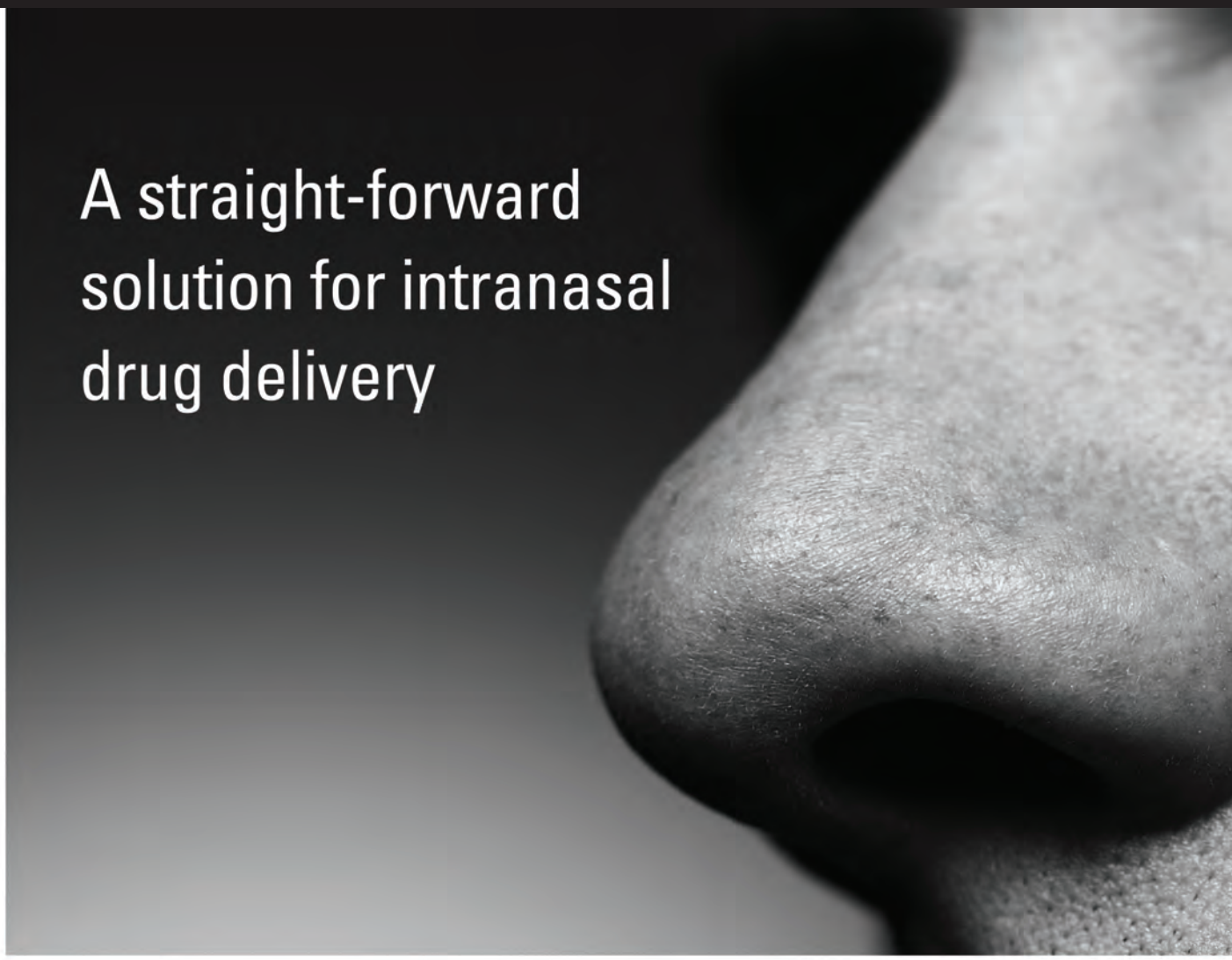
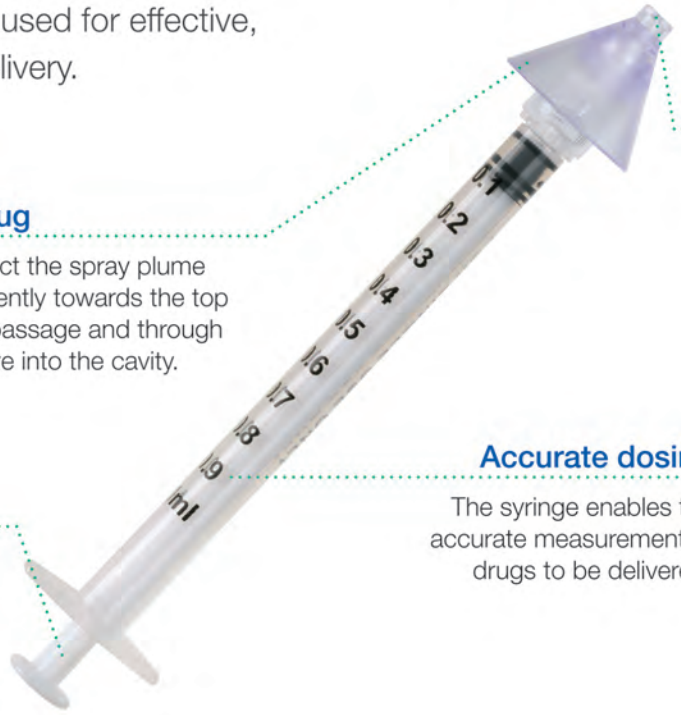
# A straight-forward solution for intranasal drug delivery



The Teleflex VaxINator™ is used for effective, easy-to-use nasal drug delivery.




## Atomization spray

The spray atomizes drugs into a fine mist of particles 30-100 microns in size.

## Conical plug

An aid to direct the spray plume more consistently towards the top of the nasal passage and through the nasal valve into the cavity.

## Accurate dosing

The syringe enables the accurate measurement of drugs to be delivered.

## Pressure

High applied pressure ensures that drugs are atomized into a fine mist of particles through the tip of the plug.

For use with drugs approved for nasal delivery.

Patent pending.

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*** In last month's issue, we incorrectly spelled SOLUBILIZATION on our cover, which goes to show you just how difficult SOLUBILIZATION really is!**

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# Early-Stage Partnerships

"The pharmaceutical industry likes to outsource. And that fact is blatantly obvious when one considers the outsourcing activity within the formulation development and manufacturing sector. According to a 2013 report from Frost & Sullivan, on a global scale, pharma spent $13.43 billion on contract manufacturing services. That number is expected to reach $18.49 billion by 2017."

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## Departments

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# Market News and Trends

## Marina Biotech Continues to Build Worldwide Patent Protection for SMARTICLES

Marina Biotech, Inc. recently announced that a decision to grant a patent has been issued for the company's fundamental SMARTICLES delivery technology in Japan (Ser. No. 2010-211089). The claims of this National Stage Application cover fundamental amphoteric liposomes made with preferred amphipathic components, and are a combination of a weak, but variable, anionic charge carrier and a weak cationic charge carrier.

The granted claims cover amphoteric liposomes that are suitable for designing specific formulation systems for both the controlled- and sustained-release of nucleic acid therapeutic cargos, including RNA, DNA, antisense, and nucleic acid decoys. In addition, the granted claims cover pharmaceutical preparations made from the amphoteric liposomes, a key to successful commercialization of the therapeutics.

"In view of our other intellectual property announcements over the past 6 months, it is clear we have established a rapid pace for the grant and issuance of patents covering the heart of our therapeutic capabilities - nucleic acid delivery," said J. Michael French, President and CEO at Marina Biotech. "With this decision to grant from the Japan Patent Office, Marina Biotech continues to expand the scope of granted intellectual property covering the fundamental components of our SMARTICLES delivery technology. To date, similar claims in this patent family have been granted for SMARTICLES technology in Europe and the US. Thus, this decision to grant reflects worldwide market coverage of our SMARTICLES delivery capabilities. The expanding patent coverage for both our DiLA(2) and SMARTICLES delivery technologies continues to establish our competitive advantage in delivering nucleic acid-based therapeutics."

SMARTICLES is currently in clinical development through licensees ProNAi Therapeutics, Inc. and Mirna Therapeutics, Inc. in both a Phase II trial delivering a single-stranded DNA decoy and in a Phase I trial delivering a double-stranded microRNA mimic, respectively. In December 2013, at the 55th Annual Meeting of the American Society for Hematology in New Orleans, ProNAi presented safety and efficacy data from its ongoing Phase II study. ProNAi presented data demonstrating that PNT2258, their first-in-class BCL2 targeted drug, exhibited single agent anti-tumor activity in patients with recurrent or refractory Non-Hodgkin's Lymphoma. Further, PNT2258 is safe at a dose of 120 mg/m2 IV administered for 2 to 3 hours on days 1 to 5 of a 21-day schedule. No tumor lysis syndrome or major organ toxicities were observed. No occurrences of elevated liver enzymes, hyperkalemia, hyperphosphatemia, hypocalcemia, renal failure/dysfunction, or infections were noted.

## Rexam's SOF'BAG: the Airless Package Now Available in 50 ml

Rexam Healthcare recently announced the latest version of its industry reference in airless package – the 50-ml Sof'Bag – in anticipation of the worldwide growth in demand for nomadic airless packaging systems. Rexam Healthcare presents a total packaging system for transdermal and topical applications. The Sof'bag is easy-to-use for patients while keeping filling simple and logistics easy for drug manufacturers.

Developed by Rexam Healthcare to ensure that pharmaceutical formulations are delivered with extreme accuracy, the Sof'bag is shipped in two components: a bag and bottle assembly and a pump and cap assembly.

The multilayer bag in the plastic bottle guarantees a maximum protection against contamination and oxidation. The metering pump dosing from 0.70 ml up to 1.50 ml was developed especially for pharmaceutical use. The packaging, dispensing creams, lotions, and gels, can also be used in all positions, making it a smart choice for easing consumers' lives. The Sof'Bag is currently on the market both in the US and in Europe for hormonal treatments and anti-inflammatory gels for example. The container can be supplied in 100 ml and more recently, in 50 ml.

The key benefits of the new 50-ml Sof'Bag include: 1) easy to carry in a bag due to its compact size, 2) nomadic, much more compatible with today patients' active lifestyle, and 3) easy to dispatch, simplifies the patients' life by keeping one product at home and taking another one with them.

# Caisson Biotech Expands Drug Delivery Deal With Novo Nordisk

Caisson Biotech, LLC recently announced it has expanded the scope of its partnership with global healthcare leader Novo Nordisk A/S. This latest license agreement gives Novo Nordisk exclusive rights to commercialize insulin conjugated to HEPtune, and non-exclusive rights to leverage the HEPtune technology across other core therapeutic areas, including other diabetes care products, human growth hormone therapy, treatments for obesity, and for inflammatory diseases, such as Crohn's, lupus, rheumatoid, and psoriatic arthritis.

Under the terms of the agreement, Caisson will be eligible to receive up to $167 million in milestone payments upon achievement of certain predefined clinical, regulatory, and commercial objectives plus potential long-term residual royalties.

"Novo Nordisk has completed feasibility studies that preclinically validate Caisson's heparosan-based drug delivery technology for product pharmacokinetics and enhanced half-life," said Dr. Paul DeAngelis, Chief Scientist of Caisson. "The HEPtune technology uses heparosan, a naturally occurring sugar polymer produced by the body that is stable and inert in the bloodstream while being biodegradable. Furthermore, HEPtune can be customized with respect to polymer size and conjugation chemistry, thus providing flexibility to enhance a variety of therapeutic proteins and peptides."

"As a respected healthcare leader, Novo Nordisk has been an ideal partner and provides the infrastructure and expertise necessary to develop these much-needed therapeutic products," added Thomas Harlan, CEO of Caisson. "We look forward to our continued collaboration under this new license and to assisting Novo Nordisk in achieving its goal of developing these products and helping more patients."

# Depomed Earns $10-Million Milestone

Depomed, Inc. recently announced that the US FDA approved Mallinckrodt plc's New Drug Application (NDA) for XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets (CII), previously known as MNK-795, for the management of acute pain severe enough to require opioid treatment and in patients for whom alternative treatment options (eg, non-opioid analgesics) are ineffective, not tolerated or would otherwise be inadequate. The release profile of XARTEMIS XR combines Mallinckrodt's newly patented technology, including design, formulation, pharmacokinetic and release characteristics, and Depomed's advanced Acuform drug delivery technology.

The NDA approval triggers a $10-million milestone payment to Depomed under Depomed's license agreement with Mallinckrodt. Depomed will recognize the entire milestone payment in Q1 2014. Depomed will also receive high single-digit royalties on net sales of XARTEMIS XR.

"We are pleased the FDA has approved XARTEMIS XR and that our Acuform technology has contributed to this important new therapy option for patients and their physicians," said Jim Schoeneck, President and CEO of Depomed. "We expect to receive significant recurring royalty revenue from Mallinckrodt's commercialization of XARTEMIS XR. Mallinckrodt has also licensed the Acuform delivery technology under equivalent royalty and milestone terms for its MNK-155 product candidate, which has been studied for moderate to severe acute pain. Mallinckrodt has indicated that it expects to file an NDA for MNK-155 in the second half of their 2014 fiscal year. FDA acceptance of the MNK-155 NDA would trigger a $5-million milestone payment to Depomed, and approval by the FDA would trigger an additional $10-million milestone payment to Depomed."

# Next-Generation Therapeutics for Infectious Diseases Conquer Global Spotlight

The available antivirals for commonly occurring infections, such as respiratory syncytial virus (RSV) and influenza are characterized by variable response, poor tolerability, and suboptimal dosing regimens, limiting their regular use and efficacy. Likewise, the development of resistance to almost every recommended antibiotic for bacterial infections like chlamydia and gonorrhoea makes treatment complicated.

Successful commercialization of next-generation therapeutics and the imminent arrival of novel innovative vaccine technologies are expected to address these issues and generate strong growth in the infectious diseases therapeutics market.

New analysis from Frost & Sullivan's *Global Infectious Diseases Therapeutics Market - Influenza, RSV, Chlamydia, and Gonorrhoea* finds the influenza vaccine industry is witnessing a shift from conventional egg-based vaccines, which use live attenuated and inactivated viruses, to novel DNA-based, recombinant, sub-unit, and even microbial vector-based approaches. These technologies are becoming popular for their cost benefits and potential for mass production in the event of a pandemic.

"Several new antiviral agents, including short-interfering ribonucleic acids (siRNAs), antimicrobial peptides, and other anti-inflammatory drugs, are being evaluated in clinical trials for viral infections," said Frost & Sullivan Healthcare Senior Research Analyst Aiswariya Chidambaram. "These ongoing clinical programs targeting newer classes of antivirals, vaccine technologies and improved diagnosis are likely to result in more sophisticated levels of treatment."

While resistance to current drugs and viral/bacterial breakthrough remain key obstacles to effective treatment, the asymptomatic nature of sexually transmitted bacterial infections makes even diagnosis difficult. In many cases, genital infections caused by Chlamydia trachomatis and Neisseria gonorrhoea go unnoticed, as they are asymptomatic in up to 70% of infected women and up to 50% of infected men.

"Since preventative therapies can help control infectious diseases effectively, vaccines are the way forward, particularly for viral infections," noted Chidambaram. "In fact, the global infectious diseases therapeutics market will be geared in this direction, as a way to significantly control disease burden."

# Eveon & Leti Advance Smart Bolus-Type Micro-Pump for Drug Delivery

Eveon and CEA-Leti recently announced the demonstration of liquid-pumping for smart drug delivery in the bolus mode using a silicon-based micro-pump fabricated with a standard MEMS process.

The milestone is the first functional micro-pump integration using MEMS standard process on Leti's 200-mm line. It is a result of FluMin3, Eveon's and Leti's 3-year joint-development project to produce an automatic drug delivery system integrating a MEMS micro-pump that reduces patient discomfort by delivering medicine with very high accuracy, minimal loss, and high flow rates.

FluMin3 is a major R&D program supported by the Rhone-Alpes competitive cluster MINALOGIC in collaboration with CEDRAT TECHNOLOGIES and IMEP-LAHC, the Institute of Microelectronics Electromagnetism and Photonics, and Microwave and Characterization Laboratory.

The micro-pump is based on core technology initiated by Eveon and IMEP-LAHC. The pump demonstrator is made from silicon wafers, which include a thin deformable membrane sealed over a fluidic cavity and fluidic valves determining inlet and outlet. A dedicated electromagnetic actuator developed by CEDRAT TECHNOLOGIES shapes the membrane.

First fluidic characterization of this device showed very promising pumping results with typical water-flow rates of 12 ml/min without any counter-pressure, and up to 6 ml/min under 1 bar counter-pressure. These results surpass the performance of state-of-the-art commercial micro-pumps whose typical water-flow rate capacity currently is 6 ml/min without any counter-pressure and 2 ml/min under 0.5 bar counter-pressure.

These encouraging results already match bolus-mode injection requirements. In addition, new designs under development by Eveon and Leti are expected to improve fluidic performances. At the same time, MEMS flow sensors designed to be finally integrated in the micro-pump have been fabricated and used to achieve an accurate liquid dosing using micro-diaphragm pumps with a dosing error below 5% for different counter-pressures.

Eveon, which coordinated this project, and Leti are continuing their work to stabilize relevant MEMS processes before industrialization and to integrate MEMS sensors inside the micro-pump to demonstrate an automatically controlled smart drug delivery device. More technical details concerning the architecture, the process of fabrication, and performances of this new micro-pump will be published and presented in coming conferences.

# Ensysce Biosciences Receives Patent for siRNA Delivery

Ensysce Biosciences Inc. recently announced the US Patent Office has issued a Notice of Allowance for US Patent Application No. 13/175,314: Single-Walled Carbon Nanotube/siRNA Complexes & Methods Related Thereto. The application has claims covering methods of delivering single-walled carbon nanotube (SWCNT) complexes with siRNA for therapeutic applications.

The patent will extend the intellectual property coverage of Ensysce and add to the extensive package of patents for the use of SWCNT for therapeutic applications licensed to Ensysce worldwide. Carbon nanotubes provide a means to deliver large biologically active agents through natural barriers within the body and readily into cells in a number of tissues that have previously been difficult to deliver to.

"Our demonstration of SWCNT delivery of siRNA into tissues and specifically tumors in animal models has allowed us to begin moving this delivery platform into clinical development," said Dr. Lynn Kirkpatrick, CEO of Ensysce. "We have optimized the formulation of our complexes and have begun studies to support our IND that will lead to a clinical trial in the next 12 to 15 months. This Notice of Allowance confirms the novelty of our approach and significantly enhances the scope of our protection."

"siRNA has issues with adequate cellular delivery, yet is one of the most intriguing and promising approaches to cancer therapy today," added Dr. Garth Powis, Director of the NCI Designated Sanford Burnham Cancer Center and member of the Ensysce Scientific Advisory Board. "Ensysce's success in using carbon nanotubes to deliver these macromolecules providing biological activity in tumors is a major accomplishment."

# Gerresheimer Extends Medical Devices Operations in US

Gerresheimer AG, one of the world's leading partners of the pharma and healthcare industry, is extending its production capacity for medical plastic systems at its plant in Peachtree City, GA. The production area will be increased by an additional 60,000 sq ft. Production of new medical devices will start right after completion of the infrastructural enlargements. Gerresheimer is investing millions of dollars in the project in Peachtree City, which will create around 120 additional jobs in the medium-term future.

"We're experiencing worldwide growth in demand for user-friendly, safe, and easy-to-use medical devices, such as inhalers and insulin pens. As a result of this growth, and new customer projects, our excellent plant in Peachtree City will be significantly increasing its production capacity. There are a great many opportunities for us in this business segment in the US, and our Peachtree City facility will play a crucial role in helping us to exploit them. We greatly appreciate the generous support of the state and local authorities in Georgia in this challenging project," commented Andreas Schütte, member of the management board of Gerresheimer AG with responsibility for the Plastics & Devices Division.

The additional production area will significantly increase Gerresheimer's Peachtree City plant's production capacity. Two thirds of the additional production area will be ISO class 8 cleanroom.

Gerresheimer is taking advantage of Georgia's internationally acclaimed workforce training program, Quick Start. The approximately 120 new jobs to be created in the medium term will include executive, adminis-trative, supervisory and production positions.

"Georgia's healthcare industry is uniquely poised to help Gerresheimer grow," said Nathan Deal, Georgia's Governor. "This leading global company is taking advantage of an eager, skilled workforce and an advanced life science and healthcare ecosystem. Our state is the ideal location to support Gerresheimer's newest expansion."

Gerresheimer established its first Peachtree City production facility in 1993 and expanded it in 2009 with the establishment of a Technical Competence Center (TCC). The plant in Peachtree City is part of Gerresheimer's Medical Plastic Systems business unit. Gerresheimer Headquarters is based in Düsseldorf, Germany. Peachtree City and the other plants in this business unit develop, industrialize, manufacture, and assemble customer-specific devices, such as inhalers, insulin pens, lancets, and various diagnostic systems.

# Gem Pharmaceuticals Announces $4.5-Million Financing for Phase II Trial

Gem Pharmaceuticals recently announced that current Gem board members/investors Diane Hendricks and Karl Leo have agreed to provide up to $4.5 million in new capital in order to fund the company's upcoming Phase II clinical trial of GPX-150 in sarcoma patients. These funds will be invested over the course of the trial.

GPX-150, Gem's lead anthracycline analogue, is a patented, chemically modified version of doxorubicin that is designed to eliminate this widely used anti-cancer agent's dose-limiting cardiotoxic side effects. GPX-150 has successfully completed a Phase I dose-escalation clinical study that demonstrated anti-tumor activity in some late-stage cancer patients without causing measurable cardiotoxicity. The maximum tolerated dose was determined based on the occurrence of Grade 3 and 4 neutropenia, which was resolvable upon dose reduction and is thought to be an on-target effect of the compound's anti-cancer activity. GPX-150 has been specifically designed to improve the therapeutic window as compared to doxorubicin; part of the way in which this is believed to be achieved is by GPX-150's increased selectivity at inhibiting the enzyme topoisomerase-2 alpha versus topoisomerase-2 beta. This key feature means that GPX-150 has the potential to be the first-ever targeted anthracycline compound.

"We certainly appreciate the continued support shown by our current investor group, and we may also seek to supplement this new funding with additional financing from venture capital investors or a corporate partner in order to expand our clinical development program," said Gem CEO Arthur Klausner.

"This financing represents a seminal event in Gem's development," added Gem board member Donald Drakeman, former CEO of the biotechnology company Medarex. "The Phase II study should be able to demonstrate whether the promising preclinical and early clinical results seen with GPX-150 can in fact translate into a cancer patient population that is truly in need of improved therapeutic options."

Gem Pharmaceuticals is a clinical-stage biopharmaceutical company developing proprietary anthracycline derivatives specifically designed to eliminate the critical cardiotoxicity side effect of this powerful class of chemotherapeutics while maintaining their well-documented anti-cancer efficacy. In so doing, Gem seeks to transform traditional broad-spectrum cytotoxic drugs into modern – and biochemically targeted – anti-cancer agents that hold the potential for higher dosing and correspondingly improved therapeutic utility.

# Novozymes Biopharma Announces Major Collaboration With Janssen

Novozymes Biopharma, part of Novozymes A/S, a world leader in bioinnovation, has recently announced a collaboration with Janssen Research & Development, LLC (Janssen). The agreement will enable Janssen to evaluate Novozymes Biopharma's engineered albumin-based VELTIS technology for potential drug candidates.

"We are delighted to be working with Janssen on this important collaboration," said Svend Licht, Senior Director, Novozymes Biopharma. "The VELTIS half-life extension technology can be linked to a broad range of drug candidates and the agreement is central in our continued strategy to demonstrate its potential to facilitate greater control across many therapeutic fields."

Novozymes' VELTIS technology represents a series of engineered human albumins which, in combination with a drug candidate, offers the potential for tunable control of the therapeutic half-life. The extended half-life of the albumins opens the door toward reducing the dosing frequency of drugs from daily to every 2 weeks or monthly.

"The VELTIS platform is a transformative technology that offers real potential to revolutionize the delivery of treatments," said Mr. Licht. "Working with partners across a wide-range of medical conditions, we are continuing to highlight the benefits of the solution in improving the lives of patients."

Together with this new collaboration, Novozymes Biopharma announces a new brand name for its half-life extension platform. Now known as VELTIS, the technology enhances the pharmacokinetics of peptide and protein drugs, potentially reducing dosing frequency of therapeutics to once-per-month, while contributing additional benefits through decreased dosage levels and reduced toxicity.

# Catalent Launches Advanced Technology for Glass-Free Delivery

Catalent Pharma Solutions recently announced the launch of its new ADVASEPT technology, for the advanced aseptic filling of injectable drugs, at the INTERPHEX exhibition, March 18-20, at the Javits Center, New York City, NY. The new platform provides a glass-free, aseptically filled, primary container that reduces or eliminates many concerns associated with traditional glass vials, including the risk of injuries to treatment providers and patients, the potential for glass particulate contamination, and accidental breakage in transit and subsequent product wastage.

"This new technology eliminates the risk of glass particulate contamination, significantly reduces the risk of breakages and minimizes container weight through the use of an ultrapure plastic design," said Catalent's Jonathan Arnold, Vice President and General Manager of Advanced Delivery Technologies. "Catalent also brings analytical expertise in areas such as biologic substance testing, extractables and leachables, and stability, and we have scientifically shown comparability of a monoclonal antibody between traditional glass and ADVASEPT vials."

ADVASEPT vial production leverages proven Quality by Design manufacturing techniques that have optimized the blow-fill-seal manufacturing process. Leveraging this form of advanced aseptic processing, a stopper is inserted during the blow-fill-seal process to create a next-generation, glass-free injectable solution, minimizing the risk of contamination by reducing particles, process steps, and human interaction. Significant reductions in controlled space requirements also drive out the operational and fixed costs of traditional vial filling while decreasing the risk of contamination.

Available with safe, easy-to-open pop-off or twist-off tops, the ADVASEPT stoppered vial is currently produced in 10-mL, 50-mL, and 100-mL sizes. ADVASEPT vials are manufactured at Catalent's Woodstock, IL, facility and are highly customizable. Containers can be tailored to meet the unique needs of customers across many markets, such as biologics, pharmaceuticals, generics, and animal health.

# The Second Quadrant

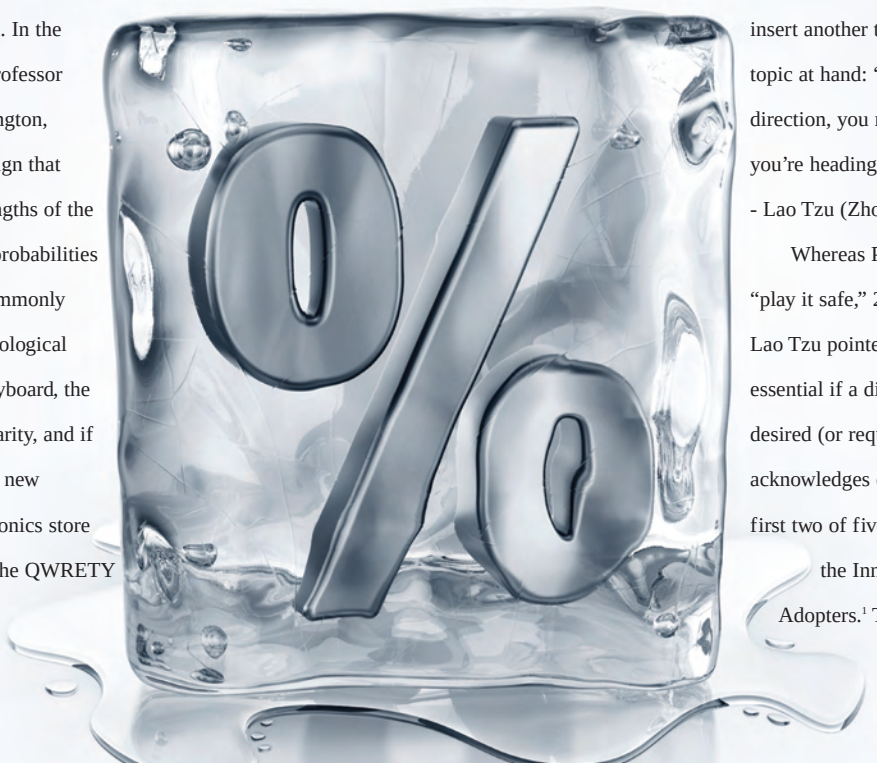
## Diffusion of Innovation & the Adoption of Solubilization Technologies

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

*"Be not the first by whom the New are try'd, Nor yet the last to lay the Old aside." - Alexander Pope, An Essay on Criticism (1711)*

Adoption of new technology, even when it has obvious advantages, is a difficult undertaking. Like everyone else writing in English, I am typing this column on a QWERTY keyboard. Have you ever wondered how we all ended up with this particular layout? As you might expect, there are other designs that are much easier to learn and allow much faster typing with lower error rates. In fact, the QWERTY keyboard was specifically designed by Christopher Sholes in the 1870s to slow down the typing rate so as to not jam the keys on a mechanical typewriter.[1]

With the early design of typewriters, this had the effect of actually speeding up the typing process because one didn't have to deal with the jammed keys. However, as the mechanical design of typewriters improved and the typing style evolved to touch typing instead of hunting and pecking (for most of us), there was a significant driver to move away from the QWERTY design. In the 1930s August Dvorak, a professor at the University of Washington, introduced a keyboard design that took advantage of the strengths of the fingers and the statistical probabilities of which keys are most commonly typed. No matter the technological advantages of Dvorak's keyboard, the design never gained popularity, and if you are in the market for a new keyboard, your local electronics store will be stocked only with the QWRETY version – a result that the famed economist W. Brian Arthur termed "lock-in."[2]



Modern, complex technologies often experience rapid, exponential growth rates. Arthur's hypothesis for this phenomenon was published in the 1980s with his pioneering theory of increasing returns. In short, the theory states that the adoption of a technology has an inherent positive feedback mechanism wherein the more a platform is adopted, the more users gain experience, and this adoption proliferation drives improvements in the technology.

According to Everett M. Rogers, the process of adoption of a new technological innovation follows a process in which the innovation is first made and then communicated via a particular medium to a network of potential adopters over a period of time.[2]

Even with rapid growth of a new technology, the users do not all adopt the innovation at the same time. At this point, I feel compelled to insert another thought critical to the topic at hand: "If you don't change direction, you may end up where you're heading."

- Lao Tzu (Zhou Dynasty)

Whereas Pope's admonition is to "play it safe," 20 centuries earlier, Lao Tzu pointed out that change is essential if a different destination is desired (or required). Rogers acknowledges change agents in the first two of five groups of adopters, the Innovators and Early Adopters.[1] The first group is

## FIGURE 1


**The lifecycle and categorization of technology adopters for a new innovation.**

obviously composed of the Innovators, individuals that recognize the need to solve a particular problem, who find the solution and then present it to those that have the need. At this point, a risk-taking group, referred to as the Early Adopters, latches on to the technology and applies it to a problem they have identified and that stands in their way toward progress. Given the success of this group, others take notice of the benefits of the innovation and recognize that much of the risk has now been removed due to the improvements made by the Early Adopters. Ultimately even the risk-averse become convinced the technology has merits and has been "de-risked" so they adopt the technology. The lifecycle of the technology continues toward maturation as the market becomes saturated. (Pope's recommended stages would most likely be compatible with Early Majority and Late Majority users.)

## FOCUS ON SOLID DISPERSIONS

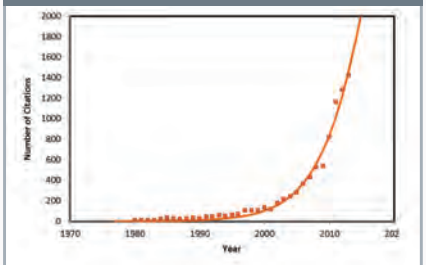
How can we apply this thinking to the growth of solubilization technology in pharmaceutical drug delivery? In this column, I'll focus on one technology, spray-drying. As shown in the Second Quadrant column in the January/February 2014 issue of *Drug Development & Delivery*, solid dispersion technology was first applied in the 1990s. The cumulative number of approved drugs that use the technology is approximately 20. While it is clear the technology is being adopted at a more rapid rate in the past few years, it is interesting to consider the factors that are governing this growth. Table 1 lists a few of the drivers shaping the adoption rate of solid dispersion technology.

Starting with the obstacles to change, I believe it is fair to say that one of the major factors preventing widespread adoption of solid dispersion technology is the early on perception of inherent risk in the technology for pharmaceutical applications, and the pharmaceutical industry's culture of caution. And no wonder there is trepidation when the path from discovery into the clinic can be perceived as already treacherous and somewhat unpredictable. Second to that, there are a number of key drivers that slow the adoption rate, including competition from alternative delivery platforms (namely lipid vehicles), the incremental added cost of development, and the significant capital investment required to deploy the requisite spray-dry equipment. In addition, the relative lack of experience and formulation expertise with solid dispersions influences the selection of the technology at early stages due to the perceived complexity of the technology.

As for factors driving the adoption of solid dispersion technology, it goes without saying that the number one reason is the increasing numbers of poorly soluble molecules coming from discovery. But many other factors exist. For example, the commercial success of companies such as Vertex stands out as a leading example of what can be accomplished with the technology. However, equally important are the continued innovation in the field and the rapidly growing, collective knowledge base in the industry.

As a measure of the industry knowledge in the solid dispersion space, we at Agere analyzed the number of literature citations that include "solid dispersion" and "pharmaceutical." Figure 2 shows the results of this analysis, and that the

## FIGURE 2




**The rapid growth in the number of citations referencing solid dispersions since 1980. Agere analysis: citations were determined from Google Scholar, patents excluded, search term: solid dispersion and pharmaceutical.**

literature in the field is growing at an exponential rate. Further analysis of this curve leads one to conclude that we as an industry are somewhere in the Early Majority category of adopters. This implies that the utilization of solid dispersions has many years left before the technology becomes mature.

Assuming that poorly soluble molecules are here to stay, and that history repeats itself, I have no doubt that eventually new innovations or completely new technologies will emerge that will eclipse current solutions. I'm curious about when and what these might be. ◆

**To view this issue and all back issues online, please visit www.drug-dev.com.**

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1. For a more complete description, see Diffusion of Innovations, 5th Ed., Everett M. Rogers, 2003 ISBN 978-0-7432-2209-9.
2. Arthur BW. Competing technologies, increasing returns, and lock-in by historical events. The Economic Journal. 1989;99(394):116-131.
3. Agere analysis

## TABLE 1

| Factors Increasing Adoption | Factors Slowing Adoption |
|---|---|
| Increasing # of insoluble compounds | Culture of risk aversion |
| Rapidly growing knowledge base | Competing platforms |
| Success of early adopters | Lack of experience/expertise |
| Industry shift to outsourcing model | Cost of development |
| Strengthening supply chain | Capital investment requirements |
| Continued innovation | Natural attrition |

**Factors influencing the adoption of solid dispersions in the market place.[3]**

# Use of Disposable Technology in Clinical Fill & Finish Manufacturing: Benefits & Considerations

**By:** Claudia Roth, PhD

## INTRODUCTION

Use of disposable technology - from pump systems to filling needles - is gaining traction in the clinical manufacturing of injectable drugs. Traditional stainless-steel equipment is expensive, takes a long time to procure, and requires lengthy qualification/cleaning validation. But successful use of disposables doesn't simply mean swapping out stainless-steel parts for plastic. The following will review not only the benefits of using disposables, but the real-world variables to consider when converting to single-use technology. The pathway begins with the question, why use disposables?

## CLEANING VALIDATION OUT; MORE API IN

One of the clear benefits to disposables is that their use eliminates the need for cleaning validation. Use them once; throw them out. Poof - 1 to 3 months is cut instantly from the timeline to first batch (Figure 1).

Once clinical manufacturing is underway, disposables also eliminate the additional 1 to 3 months per year, approximately, required to requalify the cleaning procedure and equipment.

But perhaps even more important, precious API need no longer be "wasted" on cleaning validation studies. Five hundred milliliters of API - the amount that would fill a small soda bottle - can be valued at $500,000 or more. Moreover, that may be all the drug a company has produced in the early stages of development, following years of work. In larger-scale traditional compounding equipment, two-thirds of that initial API may be consumed in a single cleaning validation run. So for many companies, disposables are not merely nice to have; they can be a must-have in order to be able to proceed with drug development.

**FIGURE 1**

| Type of equipment | Time in months[1] Procurement of equipment[2] | Cleaning validation | TOTAL |
|---|---|---|---|
| Traditional stainless steel | 4 to 12 | 1 to 3 | 5 to 15 |
| Disposables | 1 to 1½ | N/A | 1 to 1½ |

4 to 13½ months saved to first batch by using disposables

[1] Approximate. Depends on drug, complexity of equipment and other variables
[2] Includes initial qualification.

**Time saved from procurement of equipment to first batch.**

## QUICKER TO GET, LESS EXPENSIVE TO BUY

It's easy to spend $100,000 for tanks, needles, and other components of traditional, dedicated fill-and-finish equipment. Some complex custom systems can cost as much as

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a half-million dollars.

That's too much for companies, especially small ones, to invest before even knowing their drug will work. They also need product in hand within 4 months to be competitive and maintain economic viability. This timeline simply is not possible with stainless steel. Off-the-shelf models generally take 4 to 5 months to procure, and custom equipment up to 1 year, including qualification.

Conversely, single-use systems can be procured in 4 to 6 weeks and cost around $5,000 per 1,000-unit batch. The cost of disposables can add up with increasing numbers and sizes of batches. But because cleaning validation is eliminated, the savings in API almost always eclipse equipment costs (Figure 2).

## PROVIDES FLEXIBILITY DURING A TIME OF UNCERTAINTY

During the early stages of development, knowledge is still limited about the drug product and processes. Adjustments are inevitable. With traditional equipment, the moment a formulation is changed, for example, that $50,000 dedicated stainless steel compounder that took 9 months to procure will instantaneously turn into a hunk of useless metal.

Disposable equipment enables quick and inexpensive last-minute "tweaking" - or wholesale changes. It's also highly economical when scaling up batch sizes from 100 units to 10,000 to 100,000, compared to purchasing dedicated equipment for each increase.

**FIGURE 2**

| Type of equipment | Cost in $US[1]: Procurement cost of equipment[2] | Cost in $US[1]: Cost of API[2] used per cleaning validation |
|---|---|---|
| Traditional stainless steel | $20K to $500K (one time only) | 50 ml to 500 ml used per validation = $50K to $500K |
| Disposables | $5K per 1,000-unit batch | N/A |

With disposables, the **value of API saved* typically outweighs cost of equipment.**

* both in dollars & preservation of scarce drug

[1] Approximate. Depends on drug, complexity of equipment and other variables.
[2] Estimate assumes value of $500K/500 ml for initial API supply.

**Costs saved and API preserved.**

## CREATING A COMPREHENSIVE DISPOSABLE PATHWAY

Citing the benefits of disposables is easy. But making them a reality is harder and requires careful planning. Many companies have already incorporated disposable elements within their clinical manufacturing operations, but few have created a facility-wide disposable pathway. The general principle is that whenever an ingredient or solution is in direct contact with equipment or components, use disposables. That applies to activities involving weighing API and excipients, material preparation and assembly, compounding, filtration, and filling operations. Single-use technology is not required for equipment that is in indirect contact with the drug, such as lyophilizers or RABS gloves.

## CRITERIA FOR SELECTING SINGLE-USE TECHNOLOGY

The disposables market is already large and growing. Where to begin? Here are some considerations when choosing a supplier to meet your needs:

- What kind of validation data package does the supplier have readily available?
  - Have they checked material compatibility data?
  - What is the material's chemical resistance?
  - What is its leachables and extractables profile?
  - What is its shelf-life?
  - How easily can I access their quality documentation (extremely important)?
- Can the supplier work within your lead times?
- Are they willing to customize their platforms to fit your needs, when necessary?
- Do they have a solid track record in the bio/pharma industry?

## FIGURE 3


**A disposable ultra-/diafiltration system used at Vetter's clinical manufacturing facility in Chicago. Vetter, an international contract development and manufacturing organization (CDMO), established a site-wide disposable pathway for the facility, which became fully operational in 2011.**

## DELVING DEEPER INTO PRODUCTS

Once you locate a potential supplier, drill down on the technology itself. This is just a sampling of the type of questions to ask:

- Does the available equipment meet your specification requirements?
- Can materials be autoclaved (if applicable)?
- Do mixing systems cover a wide range of applications, including both slow and fast mixing (applicable to a platform technology)?
- What is bag quality? More certified features carry a higher price; lower standards carry risk of leaking. Risk mitigation requires a well-considered balancing act.
- Can parts and components be connected aseptically?
- Are components easy to mount, exchange, and disassemble within a RABS system (if applicable)?
- If components come in bulk, are they compatible with your cleaning procedures?

Don't stop at questions. Before committing, obtain samples from several suppliers and conduct trials to determine if their wares are truly compatible with your own operations and up to your quality standards. You may find that a mix of suppliers best serves your needs, depending on their various strengths and weaknesses.

## THE REAL-WORLD HURDLES OF DISPOSABLES: TWO CASE STUDIES

Theory is fabulous. Then there's real life. While the disposables market is growing fast, it's still in its infancy. Before making a commitment, conduct extensive examinations of both materials and suppliers to verify that both meet your requirements. Be ready for surprises, be patient, and above all, be vigilant. Here are two real-world tales of problems that one company encountered and what it did to solve them.

## MATERIALS TESTING

Test, test, and test again before selecting single-use equipment because the field of disposables is still so new. A company that was trying to establish a site-wide disposable pathway was in search of an acceptable disposable filling

needle. The first supplier provided a product that did not comply with established cleaning procedure. The glue failed. The second supplier's needle discolored with cleaning and did not properly seal to an adjoining component. As an intermediate solution, the company discarded stainless-steel needles following each batch, in keeping with the facility's single-use framework. Finally, the company found a third supplier that was able to provide high-quality disposable filling needles.

## SUPPLY CHAIN & DOCUMENTATION

The disposables supply chain can be complex. One of the suppliers the company had selected started subcontracting as it grew. Eventually, one subcontractor supplied manufacturing and parts assembly; a second, packaging; and a third, gamma radiation. Each subcontractor supplied its own quality documentation, which was in order, but the three were not compiled together as a single, complete package. The company worked closely with the supplier to tighten processes so that all documentation was properly packaged to fully comply with regulatory requirements.

These are just two of the hurdles the company encountered, but they were not unexpected. The world of disposables is evolving. Be ready to work as partners with your suppliers, while continuing to scan for new options and improvements in technologies.

## DISPOSABLES ARE NOT A PANACEA

Although they offer a clear technological advantage, don't count on disposables alone to drive success in clinical manufacturing. For example, using filling equipment with short tubing lengths to minimize line losses is critical to preserving API during early stage manufacture. And knowing how to develop the right processes during development for a smooth transfer to commercial manufacturing can cut many months off time-to-market.

Disposables, however, are already playing a vital role in the acceleration of clinical manufacturing. That can mean greater return on investment for life sciences companies, but more important, faster delivery of new therapies to the patients who need them. ◆

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## BIOGRAPHY

**Dr. Claudia Roth** was appointed President of Vetter Development Services USA, Inc. in 2010. She is responsible for the operations and administration of Vetter's early stage clinical manufacturing facility in Chicago, IL, the company's first US site. Dr. Roth joined Vetter, a leading contract development and manufacturing organization (CDMO), in 2000 at the company's headquarters in Ravensburg, Germany. Starting in the company's aseptic production group, she later moved to Vetter's research and development organization, where she built and led the division's first process development and implementation function. Dr. Roth studied chemical/process engineering at the Friedrich-Alexander University of Erlangen in Nuremberg, Germany, earning her PhD in Lyophilization, which she executed at Roche Diagnostics in Mannheim, Germany. A recognized expert in lyophilization, she regularly presents at industry forums on topics related to aseptic manufacturing.

# FIXED-DOSE COMBINATIONS

# Fixed-Dose Combination Products – A Review (Part 2 – Analysis)

**By:** Tugrul T. Kararli, PhD, MBA; Kurt Sedo; and Josef Bossart, PhD

## INTRODUCTION

An analysis of fixed-dose combination (FDC) products can provide insight into evolving therapeutic needs and point the way to new product opportunities. In the first part of this series (Drug Development & Delivery, March 2014) we defined what we meant by FDC products and provided a general sense of the magnitude of these products. A review of that first article will provide a useful introduction to the analysis offered here. Note that this review is restricted to products approved in the US from 1990 through the end of 2013, and information was sourced using the PharmaCircle Product & Pipeline and FDA Products modules.

Of the 131 FDC products approved by the US FDA since 1990, it was previously noted that the majority of these products comprise pharmaceutical actives that had been previously approved. This is not surprising as the approval process for a new chemical entity (NCE) is sufficiently challenging that combining two or more unapproved actives substantially increases the associated risks and the costs. It is perhaps better to gain approval as a single entity NCE, properly understand its characteristics in a large population, and then pursue additional combination opportunities.

## CORPORATE SPONSORS

Of the 131 approved FDC products, a total of 87 (66%) were developed by, or in active partnership with, Big Pharma companies. Among the leading companies were Merck with 10, Novartis with 9, and GlaxoSmithKline with 8 FDC products. A list of companies is provided in Table 1. Specialty Pharma companies accounted for an additional 42 FDC products. The leading companies in this regard were Gilead with 4 and Valeant with 3. The remaining Specialty Pharma companies for the most part developed 1 or at most 2 combination products. Emerging biopharmaceutical companies, those without any product revenues, accounted for the remaining 2 approved FDC products.

## THERAPEUTIC TARGETS

The most popular therapeutic indication for FDC products was cardiovascular with a total of 35 products (28 for hypertension). Endocrinology-related products followed with a total of 28 products. These endocrinology products covered a mixed bag of indications, including diabetes (13) and female health indications (12). The female health indications included contraception (9) and post menopausal indications (3). It's interesting to note how many "new" combinations of an estrogen and progestin have been introduced in the past 2 decades. This is a well-defined product opportunity path that is relatively low risk in terms of

**TABLE 1**

| Corporate Sponsor | Approved FDC Products |
|---|---|
| Merck | 10 |
| Novartis | 9 |
| GlaxoSmithKline | 8 |
| Abbvie/Abbott | 6 |
| Pfizer | 6 |
| Bayer | 5 |
| Boehringer Ingelheim | 5 |
| AstraZeneca | 4 |
| Bristol-Myers Squibb | 4 |
| Gilead | 4 |
| Takeda | 4 |
| All Others (<4) | 66 |

**Approved FDC Products by Sponsor**

approval outcomes; clinical endpoints and trial designs have been well refined throughout the past few decades.

Infectious disease FDC products are also well represented with a total of 17 products. This may be a surprising number until one considers that the treatment of Human Immunodeficiency Virus (HIV) infections has been revolutionized by the combination of multiple antiviral agents, rather than single agents as is common with antibiotic treatments. Combining these agents in a single dosage form significantly improves outcomes by ensuring better compliance.

The only other double-digit therapeutic class was central nervous system with 11 FDC product approvals. The majority of these products were targeted to the management of pain, often combining 2 synergistic analgesics, or an analgesic and an antagonist.

The one other therapeutic area worth mentioning, because it represents an outsized share of FDC product sales, is respiratory disease. The past couple of decades have seen the development, approval, and wide market acceptance of inhaled combinations of a steroid and a bronchodilator for the management of asthma, and a steroid plus an anticholinergic for the treatment of chronic obstructive pulmonary disease. The leader in this area, GlaxoSmithKline's Advair, a combination of fluticasone and salbutamol, has racked up more than $75 billion in worldwide sales since its first approval in 1999. The success of Advair has led other companies to introduce competing FDC products for the treatment of asthma and other respiratory indications, some of which have achieved sales in excess of $1 billion annually. A list of product approvals by therapeutic area is presented in Table 2.

## DELIVERY ROUTES

It will be no surprise that the majority of approved FDC products are oral dosage forms (98/131). This is followed by topical FDC products (8). Inhalation, injectable, and ophthalmic delivery each accounted for 6 approved products.

## BILLION-DOLLAR CLUB

Of the 131 FDA-approved FDC products, a total of 19 (15%) have managed to capture more than a billion dollars in annual sales. GlaxoSmithKline and Novartis each have 3 products in the billion-dollar club, as does Gilead with its enviable portfolio of HIV combination products. Merck and Boehringer-Ingelheim follow with 2 products each.

Cardiovascular and infectious disease are the leading indications for these billion- dollar products. Infectious disease products include 5 HIV/AIDS and 1 antibiotic combination product. The cardiovascular products are a mixed bag of antihypertensive products combining actives with complementary activities, for example, a calcium channel blocker and an angiotensin receptor blocker. In two cases, a hypertensive and diuretic combination

## TABLE 2

| Therapeutic Category | Approved Products |
|---|---|
| Cardiovascular | 35 |
| Endocrinology (All) | 28 |
| Infectious Disease | 17 |
| Central Nervous System (All) | 11 |
| Respiratory | 9 |
| Allergy | 7 |
| Ophthalmology | 6 |
| Dermatology | 5 |
| All Other (<5 approvals) | 13 |

**Approved FDC Products by Therapeutic Category**

product was able to crack the billion-dollar annual sales mark solely on the basis of the combination product's performance.

Although only 3 respiratory products managed to crack the billion-dollar annual sales mark, they did so with distinction. The many formulations of Advair (salbutamol/fluticasone) have achieved more than $8 billion of annual sales. Both Combivent and Pulmicort are members of the club and have proven to be very profitable products largely exempt from generic competition by virtue of their device-based delivery systems. Members of the Billion Dollar FDC Club are presented in Table 3.

## GLOBAL VERSUS REGIONAL

It's not surprising that the majority of the 131 FDA-approved FDC products have been approved in multiple markets around the world. What is surprising is that fully 41 of the total number of 131 products have only been approved in the US, or Canada and the US. Some of these US-only products are really not surprising and reflect the uniquely American attraction to opioid analgesics, often in combination formulations to deter abuse. But the US only status of Lotrel (amlodipine/benazepril), an antihypertensive, seems a bit odd. Looking a little more closely, there may be an opportunity for a company to take some of these US-only FDC combination products and see if there is an untapped international opportunity.

## INNOVATION & CREATIVITY

When one looks over the list of FDC products approved since 1990, it's hard to be impressed with the creativity of the developers. Many of the products seem to be slight variations on well-validated themes. Three common and decades-old themes stand out among the FDA product list. They are: the combination of a novel progestin with a validated estradiol analog (12 products), a novel antihypertensive with a diuretic, generally hydrochlorothiazide (20 products), and a novel antihistamine with pseudoephedrine (7 products). Together they account for 30% of all FDA-approved FDC products since 1990.

The past couple of decades have seen four new themes developed and validated, with a concurrent introduction of multiple products built on the themes. These newer themes are a novel steroid combined in a single dosage form with a validated beta-agonist, or a novel beta-agonist with a validated steroid (4 products), a novel antidiabetic agent with metformin (9 products), the combination of multi-specific anti-HIV agents (8 products), and the combination of a narcotic agent with a non-narcotic analgesic, most often, it seems to avoid unfavorable prescription scheduling (5 products).

The concept of combining two or more agents in a single dosage presentation to ensure better compliance has had a major impact on the improved outcomes seen with HIV medications. The combined use of these agents is critical, but no less than ensuring compliance in taking all of the products in the prescription "cocktail."

The FDC combination of a narcotic with a narcotic antagonist must also be considered as novel and therapeutically important. In the case of Pfizer's

## TABLE 3

| Product | Company | FDA Approval |
|---|---|---|
| Adderall | Shire | 1996 |
| Suboxone | Reckitt-Benckiser) | 2002 |
| Avalide | Sanofi | 1997 |
| Diovan HCT | Novartis | 1998 |
| Exforge | Novartis | 2007 |
| Lotrel | Novartis | 1995 |
| Micardis HCT | Boehringer-Ingelheim | 2000 |
| Vytorin | Merck | 2004 |
| Janumet | Merck | 2007 |
| Yasmin | Bayer | 2001 |
| Atripla | Gilead | 2006 |
| Combivir | GlaxoSmithKline | 1997 |
| Epzicom | GlaxoSmithKline | 2004 |
| Tuvada | (Gilead) | 2004 |
| Zosyn | Pfizer/Taiho | 1993 |
| Advair | GlaxoSmithKline | 2000 |
| Combivent | Boehringer-Ingelheim | 1996 |
| Symbicort | AstraZeneca | 2006 |
| Complera | Gilead | 2011 |

**Approved FDC Products Having Achieved More Than $1 Billion in Sales in at Least 1 Year**

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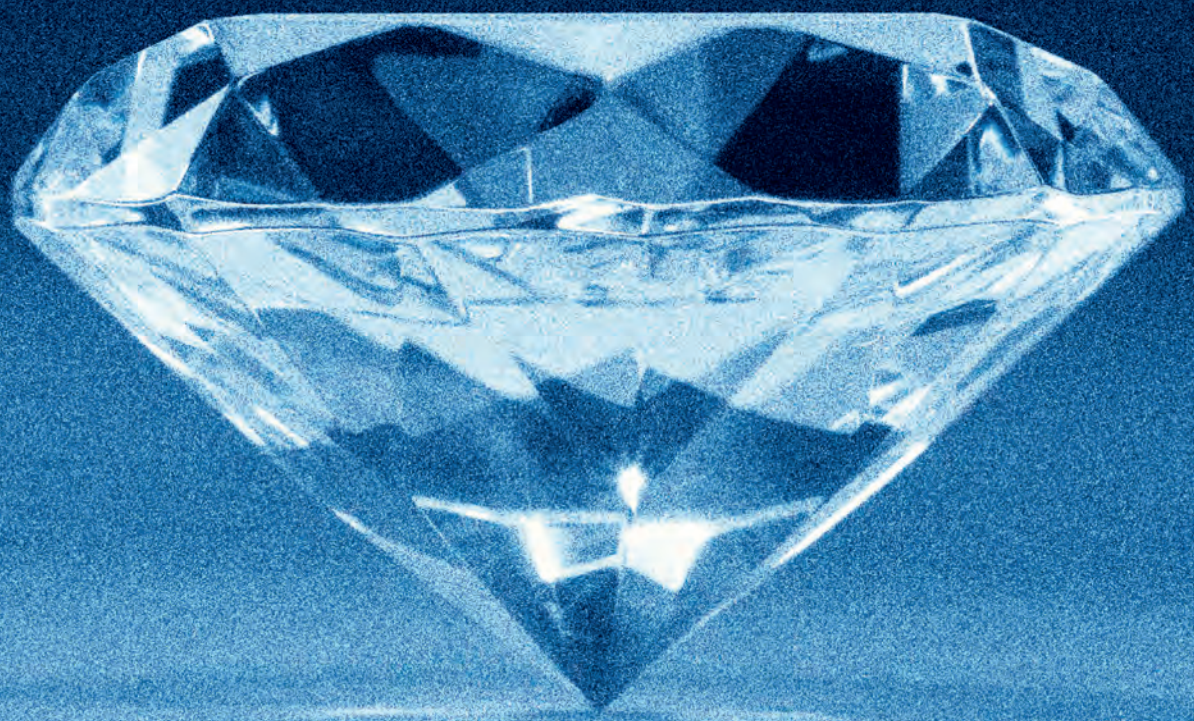

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Embeda, the intention is to limit abuse while providing a therapeutically meaningful analgesic effect. The commercial success of this product, a US-only item, has been significantly impacted by the on-and-off-again issues related to formulation integrity of the dosage form. A far greater success has been seen with Reckitt-Benckiser's Suboxone, a combination of buprenorphine and naloxone, targeted to the treatment of opioid addiction. This product is a member of the billion-dollar club.

Recognition should also be given to the increasing development of FDC products for the treatment of ophthalmic indications. Not only do these combined agents act in an additive or synergistic manner; they also help to ensure compliance by simplifying the dosing process. In the case of ophthalmic dosing, it's not a simple matter of taking two pills rather than one.

## FUTURE DEVELOPMENTS

The best way to understand what the future might bring is to look at the FDC products pipeline. That will be the focus of the third and final article in this series. We'll take a look at the pipeline products from Phase I to those filed for approval in the US and the European Union to see what new trends and themes are working their way through to approval. ◆

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## BIOGRAPHIES

**Dr. Tugrul T. Kararli** earned his PhD in Pharmacology from the University of Florida and his MBA from DePaul University. Dr. Kararli worked at Searle/Pharmacia for 18 years and held various positions and responsibilities within the Pharmaceutical Sciences department, participating in pharmaceutics, product development, and drug delivery activities. As the Chairman of the Global Drug Delivery Technology Team at Pharmacia, he was responsible for identifying, planning, and executing the drug delivery technology strategies for marketed and development products. Dr. Kararli has authored numerous articles on various aspects of pharmaceutics and drug delivery and holds more than a dozen US and international patents. Currently, he is the Founder and President of PharmaCircle LLC, a knowledge management service company in the drug delivery and pharmaceutical/biotechnology fields.

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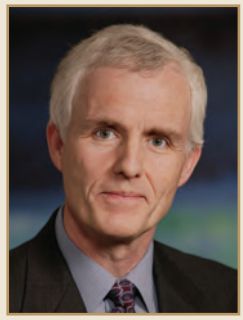

**Dr. Josef Bossart** is Managing Director of The Pharmanumbers Group, a boutique research and consulting group providing the biopharmaceutical industry with analysis and insights that improve business outcomes. He has more than 3 decades of experience in the biopharmaceutical sector, including senior sales, marketing, business development, and management positions within Big Pharma, Specialty Pharma, and Emerging Pharma companies. He earned his PhD in Medicinal Chemistry from The Ohio State University, College of Pharmacy.

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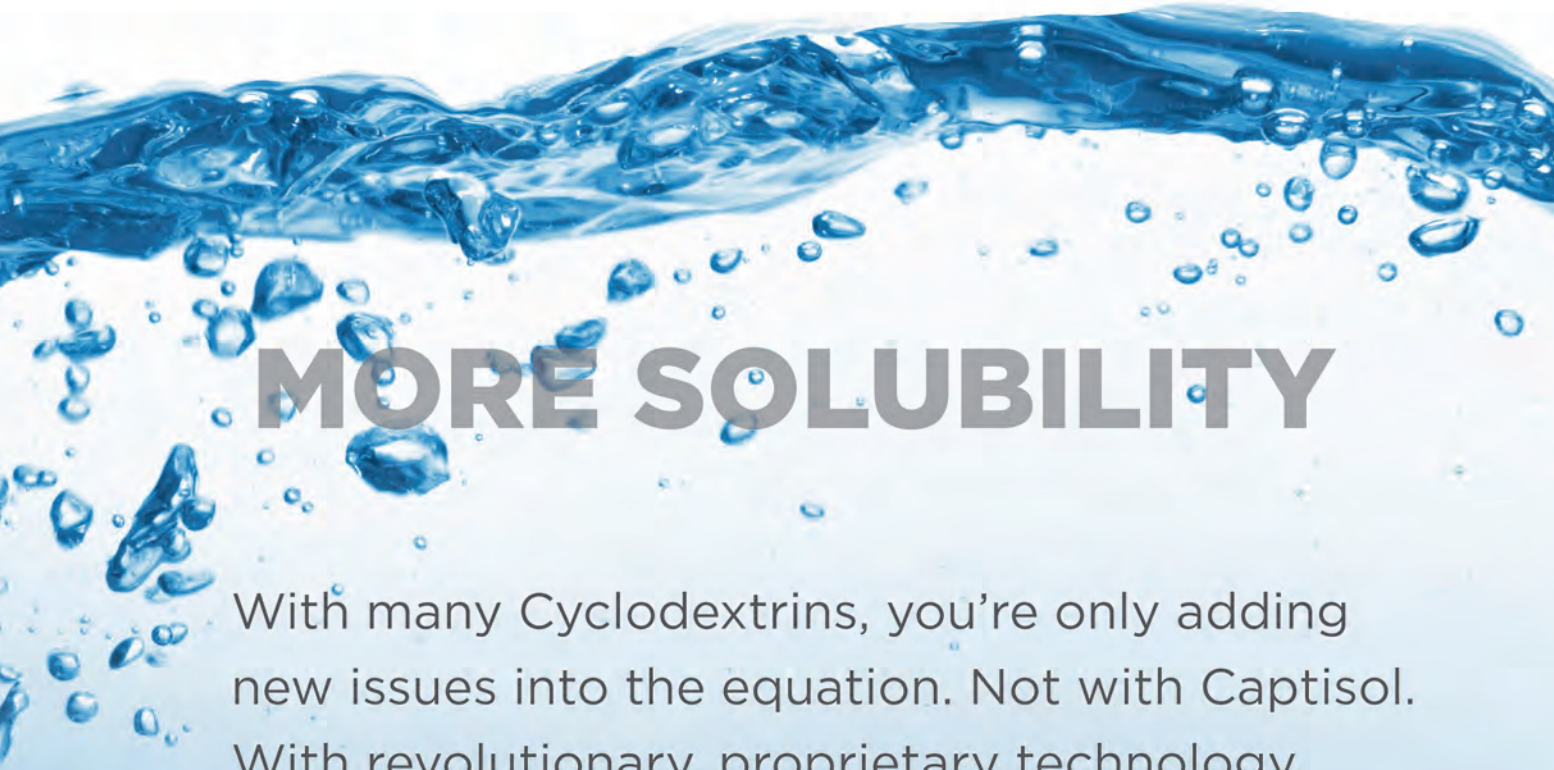

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# ANTIBODY DRUG CONJUGATES

## ADC Development Using SMARTag™ Technology

**By:** Robyn M. Barfield, PhD, and David Rabuka, PhD

### INTRODUCTION

Bioconjugates are an emerging class of biologics that combine the favorable properties of proteins, such as specificity and the ability to target distinct protein interfaces, with the advantages of synthetic small molecules, such as potency, bioavailability, and synthetic tractability. Early examples of bioconjugates include proteins linked to water-soluble polyethylene glycol (PEG), small molecule drug/protein combinations, and small molecule imaging agents attached to proteins. The body of published research focused on bioconjugation methods and applications continues to grow, and the number of bioconjugate compounds in development or on the market is steadily increasing. Although bioconjugates show great promise to improve existing therapeutics and create entirely new methods of treatment, there are also obstacles to overcome. The defining element of bioconjugates – the combination of large biologic and small synthetic molecules – is also its key weakness, on account of the inherent differences in the chemical properties of these components. Additionally, the chemical complexity of protein surfaces impedes the development of improved conjugation methods. Despite these challenges, there has been progress in advancing these complex compounds through clinical trials and successfully treating patients. These bioconjugate compounds include a subset of molecules known as antibody-drug conjugates (ADCs).[1]

### ADCS: ADVANCED BIOCONJUGATES

ADCs are a class of bioconjugates that combine the target specificity of an antibody with the high potency of a synthetic small molecule. An ADC bioconjugate consists of a targeting component (a monoclonal antibody or mAb) that is chemically modified with a linker connected to a drug payload such as a cytotoxin (Figure 1A). The optimal ADC will leverage the innate characteristics of its distinct components to create a compound with an expanded therapeutic window, exhibiting increased potency with reduced toxicity and minimal side effects. After the antibody binds to its antigen on the target cell surface, the ADC is internalized by endocytosis. It eventually fuses with the lysosome and is degraded into its component parts, including the drug attached to a chemical linker. The active payload diffuses into the cytoplasm, where it induces cell death (or other desired activities) through mechanisms, such as tubulin destabilization and DNA alkylation (Figure 1B). ADC technology offers the promise of selectively reducing or eliminating tumors without affecting surrounding healthy tissue.[2]

There are currently two ADCs on the market. Brentuximab vedotin (Adcetris®, Seattle Genetics) was approved by the FDA in 2011 for the treatment of Hodgkin's and anaplastic large cell lymphoma. Adcetris is generated using maleimide chemistry to conjugate to cysteine (Cys) residues after mild reduction of the antibody. In 2013, trastuzumab emtansine (Kadcyla®, Genentech) gained FDA approval for the treatment of HER2+ breast cancer. The cytotoxic payload is conjugated to lysine (Lys) residues using a thioether linker system. Both Adcetris and Kadcyla have been successful at treating patients when other chemotherapies have failed. However, despite these successes, patients are still experiencing toxicity and significant side effects. The current ADC pipeline is large, with more than 100 ADCs currently in clinical trials; this effort underscores the industry's belief that ADCs will be effective biotherapeutics. However, many

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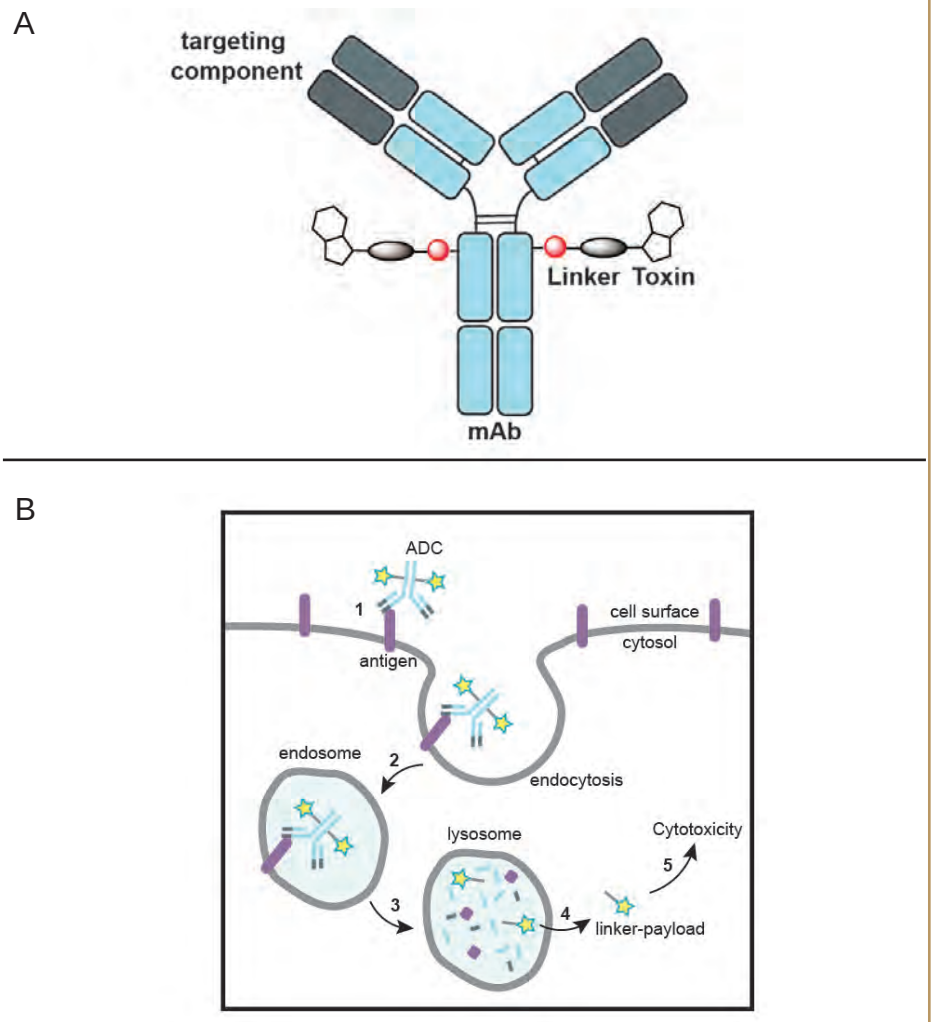
challenges remain within the field of ADC technology (www.clinicaltrials.gov).

## LIMITATIONS OF CURRENT ADC TECHNOLOGIES

The complications incurred with current ADCs are mainly a result of chemical promiscuity in the conjugate location on the protein peptide backbone. Traditionally, antibody-linker-drug conjugation chemistries have modified the thiol group of Cys residues, which can be targeted with maleimides, or the amino group of Lys residues, which can react with activated esters. Because antibodies contain multiple Cys and Lys residues, modifications using these conjugation methods are not site-specific. Therefore, placement of the payload cannot be precisely controlled. These random conjugation methods result in heterogeneous protein mixtures with variable drug-antibody ratios (DARs) and varied payload location on the protein peptide backbone. For example, with Cys conjugation, the reported DARs range from 0 to 8. With Lys conjugation, the location, or point of drug placement, is even more variable, with the resulting ADCs containing a statistical mixture of, potentially, hundreds of drug placement combinations.

The challenge with these methods is to ensure that product batches are reproducible from sequential production runs, considering the potential for ADC batches to have statistically varied drug payload placement. The ability to generate a consistent product is crucial for the regulatory approval of any drug. In addition, the analytics of such complex mixtures is tedious and costly. Furthermore, there are clinical ramifications caused by heterogeneous ADC mixtures. Any given ADC injection consists of a complex mixture of different chemical and therapeutically discrete active species. This heterogeneity creates significant therapeutic liabilities, with each distinct ADC having a different pharmacokinetic, efficacy, and safety profile. Conjugates with suboptimal toxin loads have reduced efficacy, while highly conjugated products are associated with increased toxicity. Additional complications are caused by the instability of the chemical linkages that are formed using conventional conjugation methods. For example, Cys-based maleimide bonds and Lys-based hydrazone bonds exhibit relatively short half-lives in vivo.[3,4] The first ADC to gain FDA approval was gemtuzumab ozogamicin (Mylotarg, Wyeth/Pfizer), which used Lys conjugation to generate a heterogeneous ADC. This heterogeneity, along with an unstable acid-labile hydrazone linkage, contributed to significant toxicity in patients, which ultimately led to the drug being withdrawn from the market.[2]

**FIGURES 1A&B**




**Key components of an antibody-drug conjugate (ADC).**
**A)** An ADC consists of an antibody (mAb), a membrane permeable drug payload (eg, a toxin), and a chemical linker that connects the mAb to the payload. The variable region of the mAb (shown in gray) provides the target specificity as it is the region that binds to the cell surface antigen.
**B)** The ADC binds its cell surface antigen on the target cell (1) and is internalized via endocytosis (2). The endocytic compartment eventually fuses with the lysosome (3). Lysosomal proteases degrade the ADC into its component parts. The small molecule drug payload then freely diffuses out into the cytoplasm (4) where it accesses molecular targets in the cytosol or nucleus to induce cell death (5).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## FIGURES 2A&B

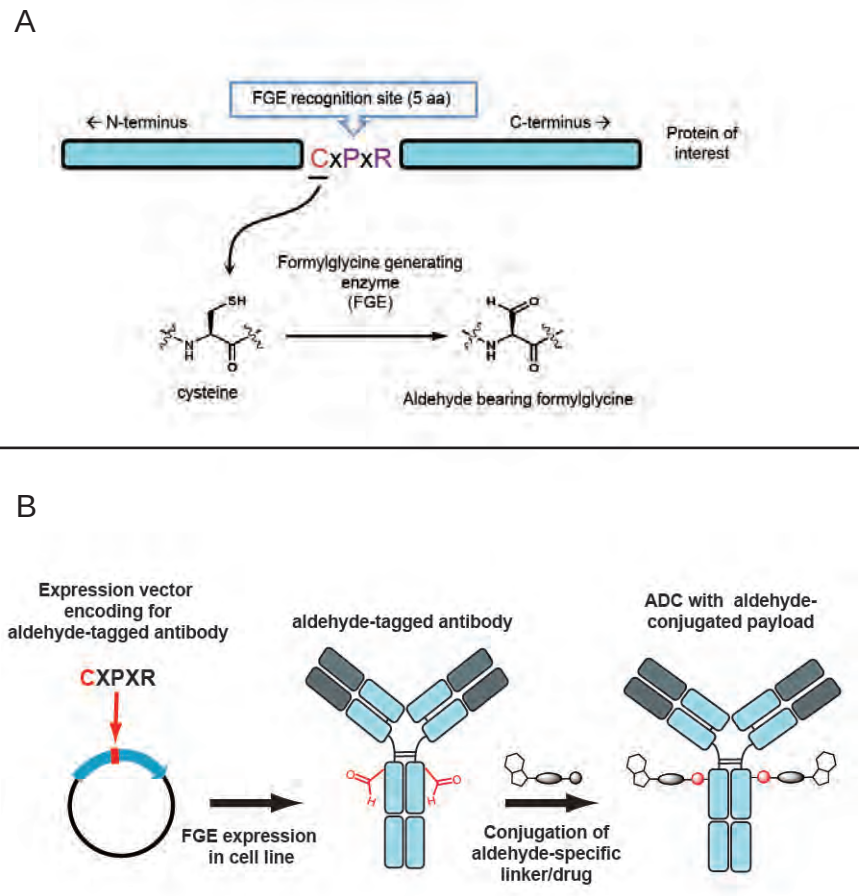



**Figure 2A & 2B. The creation of a uniquely reactive aldehyde on any protein of interest offers a simple and efficient chemoenzymatic approach for generating uniform ADCs.**
**A)** Formylglycine generating enzyme (FGE) enables site-specific modification of any protein through the oxidation of a Cysteine (Cys) residue contained within the FGE consensus recognition motif (CxPxR). FGE converts the Cys to a formylglycine (FGly) containing a chemically reactive aldehyde functional group.
**B)** The sequence encoding the minimal FGE recognition motif/aldehyde tag (CxPxR) is cloned into one or multiple sites within the coding region of the antibody. The antibody is then produced in an FGE overexpressing mammalian cell line, and an aldehyde-bearing antibody is purified. The purified antibody is then conjugated to drug-linkers using aldehyde-specific chemistry to generate a site-specifically modified ADC.

## SMARTAG TECHNOLOGY TO DEVELOP ADCS

One approach to solving the problem of ADC heterogeneity is to introduce chemistries that have tightly controlled reactivities in the context of a protein, resulting in site-specific conjugation. These bioconjugation reactions require bioorthogonal chemistries, or chemistries that are directed to a single chemical entity not found in naturally occurring polypeptides. To achieve chemical site-specificity, it is possible to incorporate a unique functional group, for example a novel side chain in an amino acid that has a distinct reactivity profile with respect to the 20 proteogenic amino acids. Several methods for the introduction of bioorthogonal reactive sites have been reported. These unconventional approaches include the introduction of exogenous Cys residues with enhanced reactivity, the incorporation of unnatural amino acids bearing synthetically derived side chains, and a number of chemoenzymatic approaches including the use of a microbial transglutaminase enzyme.[1,5,6] Redwood Bioscience is pioneering an alternate chemoenzymatic solution to site-specificity, leveraging the naturally occurring formylglycine generating enzyme (FGE) to generate a unique, aldehyde-bearing amino acid residue known as formylglycine (FGly). Redwood Bioscience and Catalent Pharma Solutions have joined together to develop bioconjugates that incorporate Redwood Bioscience's proprietary FGE/aldehyde tag technology and novel bioconjugation chemistry. This method, known as SMARTag technology, encompasses all the required components to produce best-in-class, site-specifically modified bioconjugates, including ADCs.

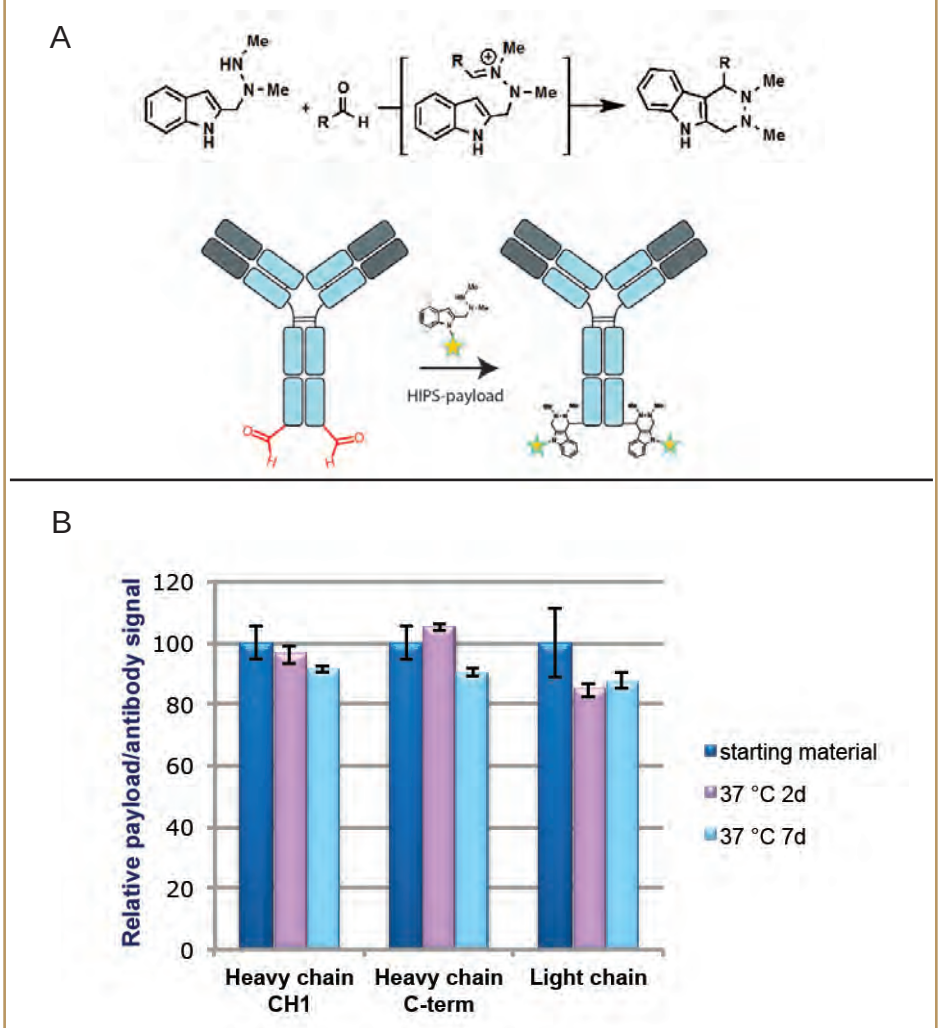
FGE is a naturally occurring enzyme endogenous to most prokaryotes and eukaryotes, including humans, that was discovered to be essential for the activation of a class of ubiquitous sulfatase enzymes that remove sulfate from biomolecules. Sulfatase activity requires an FGly residue, which is embedded in its active site. FGE is responsible for generating this FGly residue; it recognizes a consensus amino acid sequence, termed the sulfatase motif, and converts a Cys in the consensus sequence to an FGly through a novel oxidation process. The broadly defined minimal consensus motif recognized by FGE is the pentamer CxPxR, where x primarily consists of a neutral amino acid residue (Figure 2A). High conversion of Cys to FGly is possible when this small FGE target sequence, termed the aldehyde tag, is inserted into heterologous protein sequences and expressed using standard recombinant expression methods.[7,8] The ability to take the aldehyde tag out of its natural context and place it into any desired protein with

continued Cys to FGly conversion is the key element to SMARTag technology.

Recombinant proteins modified with the FGE aldehyde tag consensus sequence are produced in a wide variety of cell based expression systems including *E. coli* and mammalian cells.[9] In mammalian cell lines, such as CHO, FGE is expressed in the endoplasmic reticulum (ER). The generation of FGly occurs co-translationally before protein folding and glycosylation is complete, obviating the need to express and purify a recombinant enzyme along with the target protein to be modified.[10] In the context of producing high titers of recombinant protein, endogenous levels of FGE are often unable keep up with the high level of recombinant protein expression. However, FGE can be co-expressed with the aldehyde-tagged protein to ensure that Cys to FGly conversion goes to completion. Using standard cell culture techniques and cell line development to overexpress FGE, aldehyde-containing antibodies can be produced at high titers. Alternatively, conversion reactions can take place in vitro; purified aldehyde-tagged proteins can be incubated with purified recombinant FGE with robust Cys-to-FGly conversion. In vivo co-expression or in vitro incubation of FGE with an aldehyde-tagged protein yields products with complete conversion of Cys to FGly, which can be monitored and quantified using a mass spectrometry (MS)-based assay.[11]

The SMARTag technology platform offers a simple and efficient bioconjugation method to produce homogenous, enhanced biotherapeutics. Because the aldehyde tag is a short, six amino acid sequence, it can be genetically encoded into any heterologous protein of interest with minimal structural perturbation to the target protein. The aldehyde tag can be inserted at the N-terminus, C-terminus, or internally using standard molecular biology techniques. It can also be inserted at multiple locations at one time to specifically control not only the location but also the number of chemical attachment points. Conjugation of a toxin payload to an aldehyde-containing antibody protein, for example, using aldehyde-targeted conjugation chemistries, results in site-specifically modified proteins (Figure 2B).

## FIGURES 3A&B

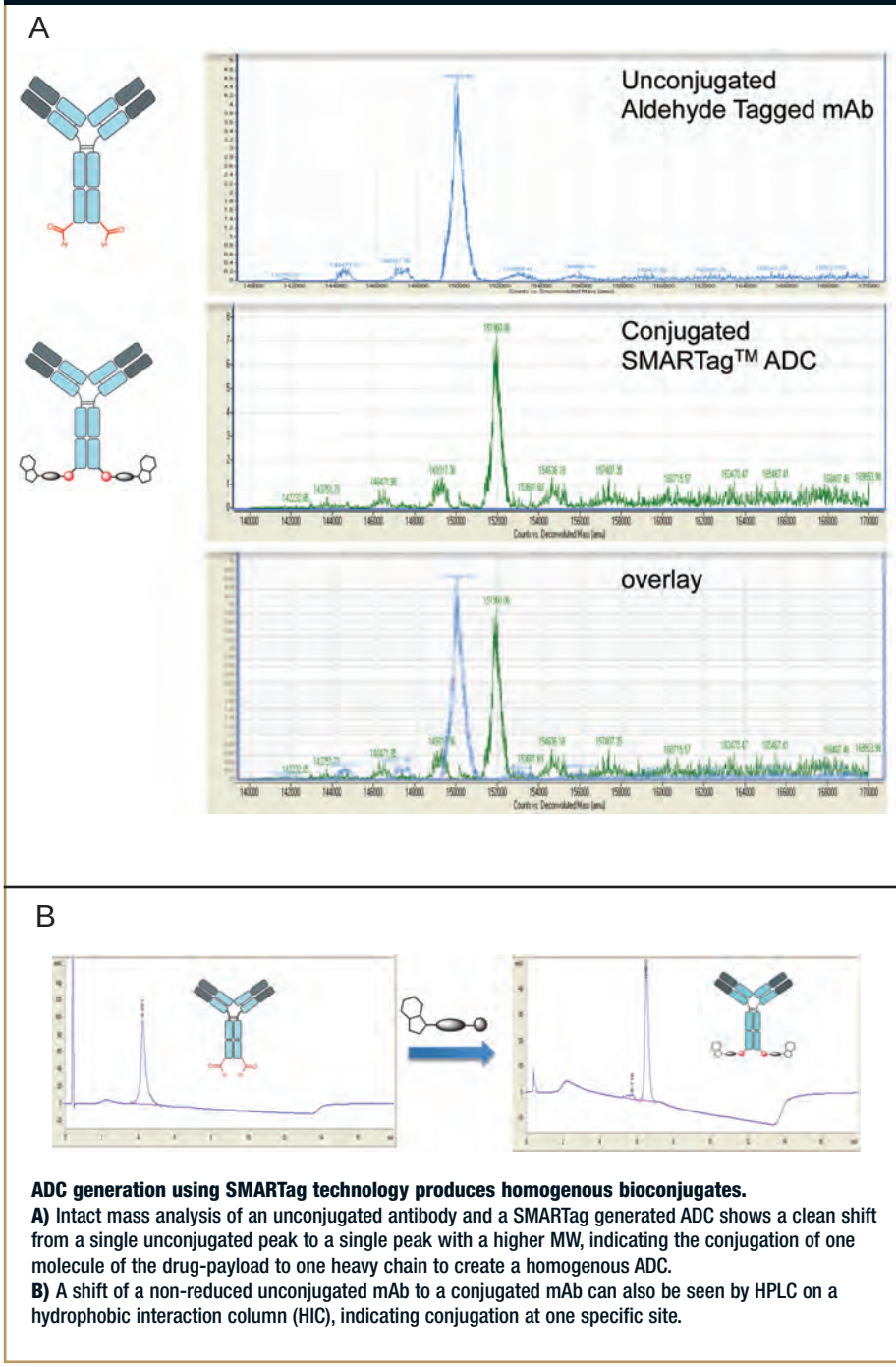



**SMARTag ADCs with varied cytotoxic payload placement generated using novel HIPS chemistry are stable in human plasma at 37 °C.**
**A)** Overview of the hydrazino-Pictet-Spengler (HIPS) ligation and a HIPS payload conjugated to an antibody.
**B)** ADCs conjugated to HIPS-linker-drug at either the CH1 or C-terminal regions of the heavy chain or internally on the light chain were incubated at 37 °C in human plasma. ELISA-based assays were performed after 2 days (purple) or 7 days (light blue) to determine the amount of conjugate loss. The y-axis shows normalized values for the total drug payload signal measured relative to the antibody signal. Minimal loss of conjugate is observed as compared to the starting material (blue).

## ALDEHYDE-TARGETING CONJUGATION CHEMISTRIES

The aldehyde generated by FGE on the target protein can be selectively reacted with alpha-nucleophiles, such as aminooxy- and hydrazide-bearing compounds, generating oxime- and hydrazone-ligated products, respectively. Traditionally, these aldehyde ligation strategies were used because of their chemical simplicity, their bioorthagonality, and because they can be performed under

## FIGURES 4A&B




**ADC generation using SMARTag technology produces homogenous bioconjugates.**
**A)** Intact mass analysis of an unconjugated antibody and a SMARTag generated ADC shows a clean shift from a single unconjugated peak to a single peak with a higher MW, indicating the conjugation of one molecule of the drug-payload to one heavy chain to create a homogenous ADC.
**B)** A shift of a non-reduced unconjugated mAb to a conjugated mAb can also be seen by HPLC on a hydrophobic interaction column (HIC), indicating conjugation at one specific site.

aqueous conditions. However, there are disadvantages to these chemistries. First, the C=N bond formation occurs slowly, and the bioconjugate products are susceptible to hydrolysis, undermining their utility in instances where long-term stability is required. The oxime has been identified as the most hydrolytically stable C=N linkage, but it is still thermodynamically unstable to hydrolysis under dilute conditions. A second disadvantage to oxime formation is the requirement for acidic reaction conditions in the bioconjugation step.[12]

The ideal bioconjugation reaction would form a stable C-C bond with protein aldehydes under neutral pH conditions. Redwood Bioscience recently described the development of an aldehyde-specific Pictet-Spengler ligation, a C-C bond-forming reaction that capitalizes on the bioorthogonality of hydrazone formation in an intermediate step (Figure 3A). This new ligation strategy, known as hydrazino-Pictet-Spengler (HIPS), utilizes the speed of alpha affect nucleophiles, a hydrazine moiety, to generate an electrophilic intermediate, which is then subject to nucleophilic attack by the indole. The nucleophilic attack forms an irreversible C-C bond, which is responsible for the high stability of this ligation technique. Therefore, HIPS chemistry alleviates the inherent instability associated with the aminooxy- and hydrazine-based aldehyde chemistries. The HIPS reaction forms hydrolytically stable conjugates with glyoxal- and formylglycine-modified proteins, including monoclonal antibodies.[13] This proprietary chemistry can be applied to the generation of chemically stable ADCs. In fact, ADCs generated using HIPS chemistry show >90% stability in human plasma after 7 days at 37°C, regardless of the conjugation site (Figure 3B). In addition to producing a very stable C-C bond with aldehydes, the HIPS reaction takes place at neutral or near neutral pH. The ability to generate stable bioconjugates using mild, near physiological pH conditions offers numerous advantages over other existing bioconjugation methods.

SMARTag technology is a broadly applicable platform that encompasses the use of aldehyde-tagged proteins and HIPS conjugation chemistry. It is a simple and robust system that can be used as a universal scaffold across many fields to generate site-specific, homogenous bioconjugates. Some of the reported applications of the aldehyde tag methodology include fluorophore conjugation, cell surface labeling, PEGylation, glycoengineering, and bispecific protein fusions.[7,8,14,15] Redwood Bioscience is specifically interested in applying this

proprietary and elegant technology to ADCs.

Using HIPS aldehyde chemistry, we can site-specifically modify antibodies at an extensive number of sites by engineering the aldehyde tag into the constant regions of any antibody of interest. HIPS conjugation chemistry applied to payload attachment requires mild, near neutral pH conditions with no refolding required. With respect to payload diversity, the HIPS system is compatible with a variety of payloads that have different cellular targets and modes of action, including microtubule disrupters and DNA alkylators. In addition, Redwood has developed an array of cleavable and non-cleavable linkers utilizing this novel chemistry. Because of the programmable and site-specific nature of HIPS chemistry, the analytics involved in determining the number and location of conjugated drugs to antibodies is significantly simplified relative to traditional, randomly modified bioconjugates (Figure 4). ADCs generated using the SMARTag technology are potent in vitro in the sub-nanomolar range against a variety of targets, using a variety of different payload and linker combinations. Moreover, SMARTag ADCs are efficacious in in vivo mouse tumor models. Together, Redwood Bioscience, Catalent, and SMARTag technology are providing a powerful next-generation solution to the development of optimized ADCs. ◆

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## BIOGRAPHIES

**Dr. Robyn M. Barfield** graduated from the University of Georgia with a BS in Cell Biology and Genetics. She earned her PhD in Cell and Molecular Biology from the University of Pennsylvania, where she studied the Ras signal transduction pathway during *Caenorhabditis* elegans development in the laboratory of Dr. Meera Sundaram. This work was recognized with an Outstanding Thesis Award. Dr. Barfield's post-doctoral work focused on the mechanism of protein transport to the cell surface in *Saccharomyces* cerevisiae under the mentorship of Nobel laureate Dr. Randy Schekman. She currently works as a Senior Research Scientist at Redwood Bioscience as part of the bio-conjugation team that generates site-specific antibody drug conjugates.

**Dr. David Rabuka** earned his PhD in Chemistry from the University of California, Berkeley, as a Chevron Fellow in the lab of Professor Carolyn Bertozzi. His research included developing and applying Redwood's platform technology to cell surface modifications. Prior to joining Professor Bertozzi's lab, Dr. Rabuka worked at the Burnham Institute, synthesizing complex glycans, followed by Optimer Pharmaceuticals, where he was an early employee, focused on the development of glycan and macrolide based antibiotics. He graduated with a double honors BS in Chemistry and Biochemistry from the University of Saskatchewan, where he earned the Dean's Science Award and holds an MS in Chemistry from the University of Alberta. Dr. Rabuka is an author on over 20 major publications, as well as numerous book chapters and patents.

# BUCCAL DELIVERY

# Dissolvable Film Format Evolves to Buccal Drug Delivery Applications

**By:** Scott D. Barnhart

## INTRODUCTION

The permeability of mucous membranes provides a convenient route for the systemic delivery of new and existing therapeutic drugs. Drug delivery through various mucosal surfaces may improve bioavailability by bypassing the first-pass effects and avoiding the elimination of the drug within the gastrointestinal (GI) tract.[1] Transmucosal drug delivery is being considered as an attractive delivery route for new and existing drug compounds, some of which are only available today through parenteral delivery. Of the various sites available for transmucosal drug delivery, the buccal mucosa and the sublingual area are the best suited sites for local as well as systemic delivery of drugs due to their physiological features.[2]

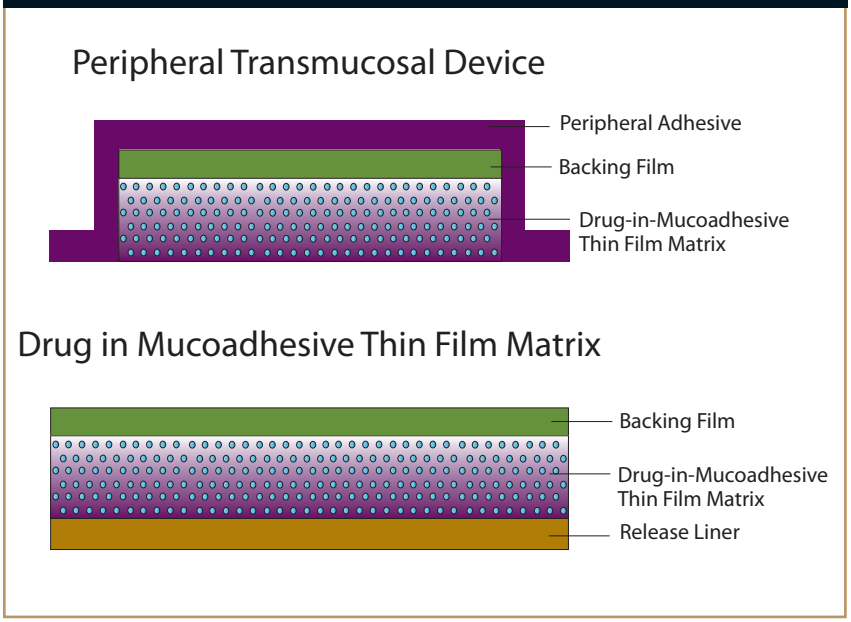
For compromised patient populations in which swallowing is difficult or the potential choking hazard is present, a buccal delivery device presents an effective dosage format with rapid onset and improved bioavailability compared to other oral formats. A number of buccal products are emerging for the treatment of chronic conditions, as well as breakthrough treatments for central nervous system conditions and pain therapies in the form of oral sprays, buccal films or tablets, and sublingual films or wafers.

As with transdermal applications, there are limitations to delivering higher molecular weight (Mw) compounds through buccal mucosal tissue. This is because the buccal and sublingual membranes contain a stratified (multilayered) epithelium that demonstrates differentiation of various cell layers. This is different than the single epithelium cell layer lining of the (GI) tract, thereby resulting in less resistance to permeability. Several approaches can be taken to increase the permeation of a drug through the buccal mucosal membrane. One of these approaches is to improve the bioadhesion properties to increase residence time and drug release of the device in the oral cavity. Another approach is to modify the physiochemical properties of the drug, such as a drug's partition coefficient. A third approach, which is also used in transdermal drug delivery, is to employ the use of chemical permeation enhancers.[3]

## FORMULATION FLEXIBILITY OF THE DISSOLVABLE FILM FORMAT

Dissolvable oral thin films (OTFs) are a proven technology for the systemic delivery of active pharmaceutical ingredients (APIs) and have been adopted as a practical alternative oral dosage format for over-the-counter and prescription drugs. The chemistry and art behind formulating drug-loaded films for

**FIGURE 1**



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buccal applications draws upon formulation expertise derived from traditional OTFs for GI delivery and from transdermal dosage forms.[4] Through an extensive understanding of these dosage forms and by leveraging their similarities, formulators can effectively tailor a dissolvable film platform to add therapeutic value for delivering drug compounds through the oral mucosa.

Dissolvable films are typically composed of an aqueous polymer matrix. Water solubility, good film-forming capability, safety, variety of molecular weight (Mw) range, and drug compatibility make these materials suitable in many applications, including buccal transmucosal drug delivery. The availability of polymers across a wide molecular weight range allows for formulation flexibility to achieve a variety of physical properties, including drug-release rate, film strength, and disintegration rate. Combining low molecular weight and high molecular weight polymers allows for the optimization of various physical properties.[5] The ability to adjust these ratios and formulate with a variety of polymer combinations provides substantial design latitude to the developer. Characteristics, such as thickness, dissolution rate, surface characteristics (texture), and mechanical properties (film strength), are customizable for each dissolvable film formulation.[6]

Dissolvable film employed in buccal systems may be designed as bioerodible mono- or multi-layer constructions, as well as non-eroding mono- or multi-layer systems, all featuring a mucoadhesive tailored for the desired dwell time. Bioerodible systems offer patients the convenience of rapid onset and complete system disintegration. Non-eroding systems are well suited for longer dwell time in the oral cavity (2 to 12 hours). A protective layer that may be designed into these systems reduces the variability of patient-to-patient bioerosion levels to deliver the active ingredient in a more predictable, controlled-release fashion. This protective outer layer also provides unidirectional drug release, reducing or preventing hepatic clearance due to GI absorption and metabolism.

The ideal transmucosal buccal film design would feature an API-loaded layer that bonds directly to the buccal site, while a second outer backing layer erodes at a designated rate equal to the time it takes for the entire drug concentration to be delivered to the system. Unidirectional drug release provides optimal bioavailability and negligible loss of drug to the saliva and GI tract. The slower eroding backing layer would offer

**TABLE 1**

| | |
|---|---|
| Acitretin | Acyclovir |
| Arecoline | Buprenorphine |
| Buserelin | Buspirone |
| Calcitonin | Carbamazepine |
| Captopril | Cetylpyridinium chloride |
| Carvedilol | Chlorpheniramine maleate |
| Chlorhexidine diacetate | Cyanocobalamin |
| Clotrimazole | Denbufylline |
| Danazol | Diltiazem |
| Diclofenac sodium | Ergotamine tartrate |
| Endomorphin 1 | Flurbiprofen |
| Fentanyl | Gonadotropin releasing hormone |
| Glucagon like peptide | Hydrocortisone acetate |
| Hydralazine | Insulin |
| Ibuprofen | Lactoferrin |
| Ketoprofen | Lidocaine |
| Leu-enkephalin | Melatonin |
| Lueinizing hormone releasing hormone | Metoprolol tartrate |
| Metaclopromide | Miconazole |
| Metronidazole | Nalbuphine |
| Morphine sulphate | Nicotine |
| Naltrexone | Nimesulide |
| Nifedipine | Octreotide acetate |
| Nystatin | Oxytocin |
| Omeprazole | Pilocarpine |
| Pentazocine | Piroxicam |
| Pindolol | Predinisolone |
| Pituitary adenylate cyclase-activating polypeptide (PACAP) | Propranolol |
| Propolis | Recombinant human epidermal growth factor |
| Protrelin (TRH) | Salmon calcitonin |
| Recombinant human interferon | Sodium fluoride |
| Silymarin | Terbutaline sulphate |
| Testosterone | Theophylline |
| Thiocolchicoside | Thyotropin releasing hormone |
| Triamcinolone acetonide | Verapamil |

**APIs Under Consideration for Buccal Delivery [11,12]**

protection to the drug-containing mucosal layer during eating, drinking, and exposure to saliva to prevent the API layer from dissolving into the oral cavity until completion of the desired drug infusion time.

The next generation of buccal product designs will evolve to include options for controlled release up to 12 to 24 hours. The general challenge for controlled-release applications is to design systems that slowly erode over time without becoming dislodged and swallowed as a result of normal activities, such as eating and drinking. Increased residence times of new buccal delivery devices may make it possible to deliver sensitive biological compounds that would otherwise be deactivated in the GI tract and thereby can only be dispensed currently through an injectable dose. Product developers must be cognizant of an increased potential for irritation to occur for longer-wearing devices - some of these concerns can be addressed through proper mucoadhesion ingredient selection.

## FORMULATING MUCOADHESION PROPERTIES

A number of unique factors must be taken into consideration when formulating bioadhesives for this challenging bonding environment. For example, the polymer layer that makes direct contact with the oral mucosa should demonstrate strong H-bonding groups to interact with mucus. Also, matrix polymers featuring a strong anionic charge with sufficient chain length and mobility will offer improved penetration of the mucosal layer to create chain entanglement with the mucus network. Formulations that feature surface tension characteristics similar to those of the mucosal tissue surface will promote wetting of the mucosal surface for improved intimate contact leading to formulation polymer chain mobility into the mucus layer.

Drug release and permeation through the mucosa is influenced by the mucosa microenvironment. Therefore, drug delivery systems for the oral mucosa are designed with the help of mucoadhesive polymers that are generally formulated for optimum chain length (molecular weight) and chemical functionality.7 The physiological pH 5.8 to 7.4 of the oral cavity typically tracks with the variability of saliva pH. At physiological pH, the mucosal layer carries a net negative charge due to the sialic acid and sulfate groups originating from mucus.

Mucoadhesive properties are effectively evaluated by determining the adhesive strength between the polymer matrix and a substrate, in this case, the buccal mucosa.8 Several mucoadhesive tests have been explored in the literature, which typically measure the force required to detach a device from the substrate through the application of an external force. Testing of mucoadhesion properties measure how successfully a device will bond, and can help to predict how well this bond can withstand normal activities, such as the force applied by tongue abrasion, talking, swallowing, etc. within the oral cavity.

ARx has developed mucoadhesion testing methodologies similar to those reported in the literature, but has adapted these tests to meet the end-user's specific requirements. Synthetic membranes are selected to simulate similar responses to those of viable mucosal membranes in order to achieve comparable results between test and reference products. Testing is usually conducted at 37°C, pH 6.4 to 7.2 to be comparable to the physiological environment of the oral cavity.

The most relevant test parameters for measuring mucoadhesive performance include:

- **Compression Force** – This measurement mimics the forces present during application of the device to a substrate (buccal mucosa) and can also provide information on creep compliance of the device.
- **Dwell Time** – The duration of time the device is permitted to reside on the membrane prior to removal. Dwell times for testing purposes range from instantaneous to about 60 seconds.
- **Peeling Force** – The force required to remove the device from the membrane.
- **Ultimate Hydration of Device** –The amount of moisture present during device/membrane equilibration and prior removal. Hydration of the device is based on chemical composition, dwell time, and thickness/mass of the system. Hydration affects how well the device interacts and adheres to the membrane.

## APIS FOR BUCCAL DRUG DELIVERY

Dissolvable films that are employed in buccal drug delivery applications ideally contain APIs that are lipophilic due to the requirement for permeation through a stratified, lipid-rich oral epithelium. This epithelium layer is not as keratinized as the stratum corneum of skin, which is composed of lipid bilayers that form lamellae. The intercellular spaces of the oral epithelium, on the other hand, are relatively hydrophilic compared to skin. Various epithelial sites within the oral cavity vary in terms of the lipid concentration residing in the intercellular spaces because they do not contain the highly organized lipid lamellar layer that is found in the stratum corneum. The environment of the oral epithelium's intercellular spaces is

predominantly aqueous, containing varying degrees of lipid content that arise from the membrane-coating granules of the basal cells.

The lipophilicity limitation may eliminate some APIs from consideration; however, many drug compounds and corresponding salt forms can be formulated in a vehicle with a selected pH buffer to take advantage of the drug's pKa for promoting optimum absorption. Care must be exercised to avoid irritation to the mucosal tissue when pH buffering becomes significantly different from the physiological pH.

Researchers have some latitude in how much API can be incorporated into a dissolvable film formulation. API concentrations are typically limited to about 50% of the final unit mass; however, the size of the final product is adjustable to deliver the proper dose.[9] Thicker films can be produced to yield higher strengths. In the case of buccal applications, it is up to the product designer to determine at what point the thickness or overall size of the buccal drug delivery device becomes unacceptable to the patient. Because there is a limitation in the size of the final buccal product, typically 1 to 5 square centimeters, this limited surface area dictates that the APIs must be fairly potent.

As in transdermal drug delivery applications, the incorporation of chemical penetration enhancers can facilitate the transport of difficult APIs across the buccal mucosa and thereby allow for the delivery of compounds with a higher molecular weight. Some common penetration enhancers used to increase permeability, include sulfoxides, alkyl-azones, pyrrolidones, alcohols and alkanols, glycols, surfactants, and terpenes.10

Looking forward, the use of micronized and nano-particle APIs that form a dispersed phase within a film can open the door for potentially more effective drug delivery methods. Ultimately forming a solid-state solution of the API within the polymer matrix is the primary goal for improving bioavailability. With increased surface area of the API combined with a larger direct-contact surface area of film, there is the potential to improve bioavailability and to increase uptake from the mucosal surface. By modifying the residence time of the buccal delivery device while in contact with the mucosal tissue, early stage work suggests this type of system has the potential to effectively deliver drugs in a shorter timeframe.

## CONCLUSION

Two important considerations for the next generation of drug delivery technologies are overall cost and compliance to improve the patient experience and tailored drug delivery. The buccal and sublingual oral mucosa will continue to be an area of growing interest for drug delivery as researchers evaluate ways to improve bioavailability, patient compliance, and product lifecycle beyond tablet and injectable formats.

Formulators experienced in the art of designing with excipients and polymers enable the specialized delivery of a variety of APIs. The range of formulation flexibility available through dissolvable film platforms provides product developers a basis of proven experience through the success gained through the oral thin film format. This flexibility ranges from dissolution rates broad enough to create bioerodible mono- or multi-layer constructions, as well as non-eroding mono- or multi-layer systems. Combining dissolvable film technology with a tailored transmucosal adhesive ensures the desired dwell time for proper dosing, while opening the door to the possibility for controlled-release buccal applications. ◆

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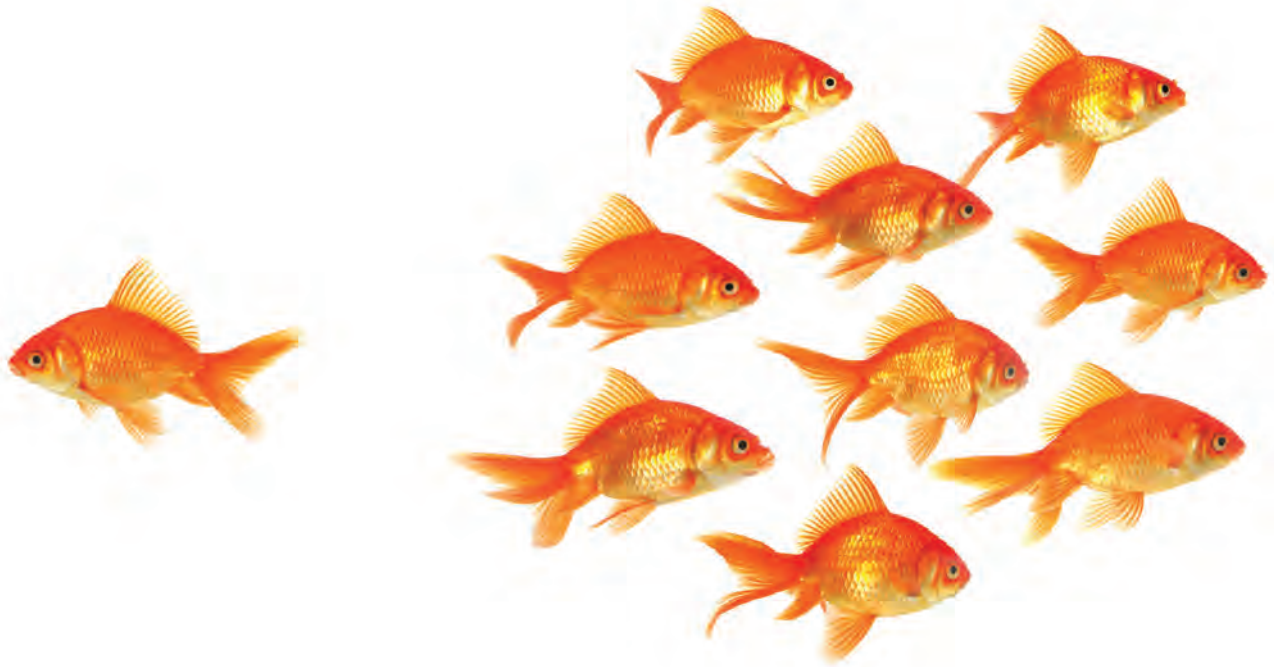
## BIOGRAPHY


**Scott D. Barnhart** is the Technical Director for ARx, LLC, a wholly owned subsidiary of Adhesives Research, Inc. With more than 25 years R&D experience, Mr. Barnhart's career has focused on drug matrix formulation and process capabilities for transdermal drug delivery systems and the development of the company's dissolvable film platform technologies. He earned his BS in Chemistry and Biology from The Pennsylvania State University and his MS in Organic Chemistry from Shippensburg University. Contact Mr. Barnhart at Adhesives Research, P.O. Box 100, Glen Rock, PA 17327; E-mail: sbarnhart@arglobal.com or phone: (717) 227-3206.



# Following QbD. Upstream.

QbD guidelines are broadly observed to achieve operational excellence for scale-up and manufacturing, and the same disciplined approach can be applied at the earliest stages of drug development. Agere's Quadrant 2™ platform adopts and extends these best practices for solubilization formulation.

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# SPECIAL FEATURE

## Outsourcing Formulation Development & Manufacturing: Early-Stage Partnerships Are On The Rise

By: Cindy H. Dubin, Contributor

The pharmaceutical industry likes to outsource. And that fact is blatantly obvious when one considers the outsourcing activity within the formulation development and manufacturing sector.

According to a 2013 report from Frost & Sullivan, on a global scale, pharma spent $13.43 billion on contract manufacturing services. That number is expected to reach $18.49 billion by 2017.

The Frost & Sullivan report indicates that injectable dose formulations will likely be the primary growth driver for outsourcing through 2017, primarily due to an increased pharmaceutical and biotechnological focus on complex disease areas.

However, in 2012, solid-dose formulations were the largest segment, constituting 49.8% of the total pharmaceutical contract manufacturing market, and is projected to grow at a CAGR of 3.4% through 2017. Generics are the key driver for growth in this segment. Liquid and semi-solid dose formulations are considered a mature market and its CAGR is expected to be only around 2.5% from 2012 to 2017. This is due to a decreasing demand for such formulations, primarily attributed to associated transportation, storage, and packaging issues.

Because of pharma's increased outsourcing practices, contract formulation and manufacturing providers are striving to provide a greater value proposition for clients by engaging earlier in projects and establishing longer-term relationships. According to Frost & Sullivan, many are focusing on pre-clinical development services and can transition from offering clinical services to commercial manufacturing to

**In Pharmatek's new packaging line, an operator is filling the hopper with capsules before entering the bottle filler.**

AAIPharma Services offers cGMP solid oral dose and parenteral dose manufacturing capabilities, including small and large molecules with the flexibility to support early product development through commercial supply.

integrate throughout the value chain of clients. *Drug Development & Delivery Magazine* recently asked leading CMOs and CDMOs to describe the value-added services they offer with respect to formulation and manufacturing. Solving challenges of insufficient solubility, poor stability, identifying excipient candidates, and particle design topped their list of offerings.

## AAIPHARMA SERVICES CORP. & CAMBRIDGE MAJOR LABORATORIES, INC.—LINKING DRUG SUBSTANCE & DRUG PRODUCT CAPABILITIES

AAIPharma Services Corp. and Cambridge Major Laboratories, Inc. recently joined to form a comprehensive pharmaceutical development and manufacturing services supplier. With nearly 800 employees operating out of 7 sites in the U.S. and Europe, the combined capabilities include API development and manufacturing, solid-state chemistry, formulation development, analytical development and testing services, clinical and commercial finished dosage form manufacturing (solid dose and parenteral), packaging, and stability services.

"Our family of companies delivers reliable partnership and superior value to pharmaceutical, biotechnology, medical device, and generics companies by providing access to comprehensive services – from early-phase studies to commercial production of APIs and finished dosage forms," says Paul Maffuid, PhD, Exceutive Vice President of Pharma Operations at AAIPharma Services Corp. "By linking drug substance and drug product capabilities, our family of companies provides a continuous process to establish the physical properties of the drug substance (e.g. salt forms and polymorphs, particle size distribution) early to achieve the target product profile. This also ensures a smooth transition from formulation development to manufacturing, as well as ensuring consistency through clinical development."

Pharmaceutical companies bear the challenge of delivering on simultaneous objectives related to profitability, to both advance a portfolio of pipeline candidates, and also reduce operational costs. "We see increased demand for contract dosage form development and manufacturing overall, both for programmatic and transactional work, because of the efficiency gains that outsourcing provides," says Dr. Maffuid. "Outsourcing transfers to suppliers the responsibility for fixed costs associated with operating and staffing manufacturing facilities, for costs associated with adherence to regulatory guidelines, and for capital investment in technology."

In January of 2014, AAIPharma Services Corp. completed a multi-million dollar expansion of its cGMP parenteral manufacturing facility in Charleston, SC. The expansion doubled the facility's sterile product development and production capacity and added state-of-the-art redundancies to major processing equipment. New facility features include low line loss and in-line weight check capabilities. In addition, the buildout was engineered to accommodate a pilot and production-scale SP Hull lyophilizer, which will more than triple the facility's lyophilization capacity by late 2014, and afford seamless lyophilization cycle optimization and scale-up, explains Dr. Maffuid.

In 2013, AAIPharma Services added a multi-layer tablet press, the Korsch XL 400 MFP, with a flexible design platform that permits production of all tablet formats (single-layer, bi-layer, tri-layer and core-coating) on a single tablet press.

"Many of our early-phase pharma clients are challenged with the need to meet aggressive timelines and/or overcome challenging molecular properties," he says. As an example, one client required an injectable dosage form for a Phase I study on a fast track timeline. The aggressive timeline dictated that route optimization for active pharmaceutical ingredient (API) production would occur concurrently with dosage form development activities. Before initiating formulation development, the analytical methods were evaluated and deemed stability indicating. Formulation development work was initiated with experimental material, and optimization work was required to address insufficient solubility, poor stability, and excipient restrictions specific to the target patient population. "Using available developmental grade API, AAIPharma Services developed a strategy for dissolution, pH adjustment, and oxidation protection enabling sterilization by filtration and filling prior to lyophilization," explains Dr. Maffuid.

"The ability to conduct real-time analysis using stage-appropriate validated stability indicating methods in our analytical development group was essential to this effort, and within one month of release of the first lot of cGMP compliant API, AAIPharma Services was able to manufacture the first lot of Phase I product for clinical evaluation."

In another early-phase challenge, a client requested three strengths of immediate-release capsules for a blinded study using a drug development candidate with extremely poor solubility across the desired pH range, and poor wettability that resulted in processability and uniformity issues with the existing manufacturing method. AAIPharma addressed the wettability issue by incorporating a GRAS surfactant into the dry blend process, resulting in an improved dissolution rate to the target amount and ensured that the target immediate release profile was achieved.

A third early-phase scenario illustrates how AAIPharma developed a feasible clinical approach for human evaluation of a client compound within acceptable limits for co-solvents and surfactants. In this case, the client requested the development of an injectable vehicle with a high-dose target, short lifetime, and rapid clearance rate. "While the client was able to achieve some improvement in solubility by increasing pH, it was not enough improvement to deliver a feasible dosage form, and the increased solubility came at the expense of stability," says Dr. Maffuid. "The AAIPharma solution was to develop a two-component formulation – the active pharmaceutical ingredient (API) was dissolved in a non-aqueous vehicle consisting of GRAS solvents and surfactants, and the aqueous vehicle enabled safe IV administration with a solution that was physically and chemically stable."

The AAIPharma Services team is also adept at expedited technology transfer for clinical and commercial projects. For instance, a client requested a study to understand why it was seeing low antioxidant levels in a commercial product. AAIPharma put together a plan to understand the impact of excipients on antioxidant stability. "We conducted a controlled study using materials from manufacturing inventory, replicated manufacturing conditions, and conducted support analysis for antioxidant levels at time points ranging from hours to weeks at controlled temperatures. Results were obtained within two hours of prototype vial preparation, and we demonstrated that one excipient in the formulation was responsible for the reduction in antioxidant level."

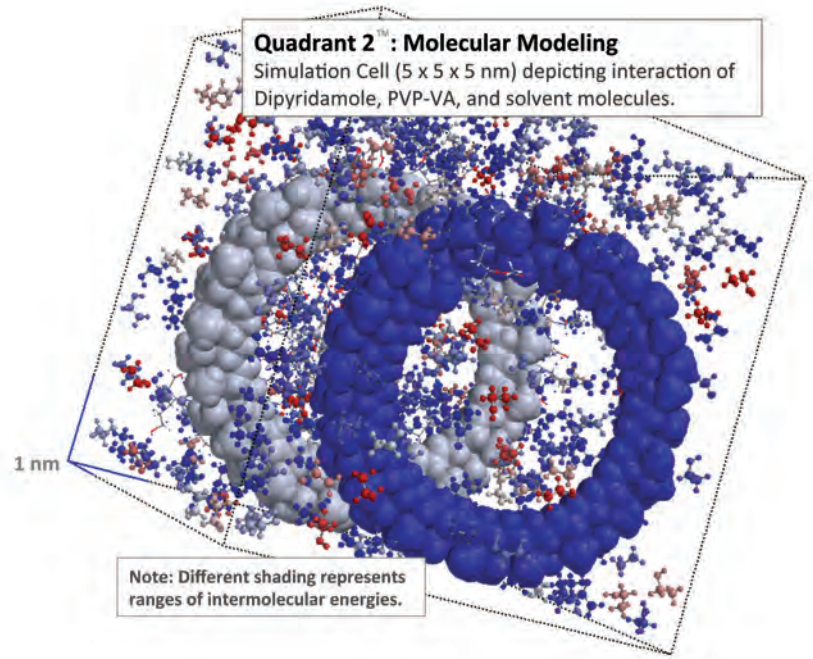
Dr. Maffuid goes on to explain how AAIPharma has successfully leveraged technology for dosage form development and for extending patent life on existing branded products. In this scenario, AAIPharma investigated the feasibility of formulating a highly flexible drug delivery system using mini-tablets in hard gelatin capsules to deliver one or more drugs in a variety of release profiles. The feasibility of delivering a drug or multiple drug combinations in a biphasic immediate/extended release manner was demonstrated by combining mini-tablets of various release profiles in a hard gelatin capsule. In the end, the team demonstrated that a pulsatile release pattern is feasible with the combination of immediate-, delayed-, and extended-release mini-tablets.

Based on these various scenarios, Dr. Maffuid is convinced that outsourcing formulation development and manufacturing will continue to increase, driven by the overall trend to offset fixed costs and capital expenditure, with faster-than-market growth expected in biopharmaceutical manufacturing, biosimilars, targeted therapies, high potency drugs, and injectable dosage forms.

## AGERE—A BEST-PRACTICES APPROACH TO FORMULATION & MANUFACTURING

Agere is a CDMO specializing in solubilization formulation through amorphous solid dispersions to enhance oral bioavailability. The company offers solubilization formulation services through Phase II clinical trials materials manufacturing. Agere's global client base ranges from virtual and small-size companies to mid-size and Top-

**In 2013, Agere introduced the Quadrant 2™ solubilization platform, a technology that encapsulates the QbD approach to design formulations and improve oral bioavailability.**



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It's no coincidence that Agere's service offerings are based on trends the CDMO sees in the marketplace. According to Casey Jones, Vice President, Corporate Development, the company is experiencing an increase in demand for assistance in solubilization formulation, as the types of drugs in development that are poorly soluble is growing. "We performed an analysis that shows that approximately 10% of all drugs that have been approved in the last decade had relied on solubilization technologies; we expect that this represents a sort of "tip of the iceberg" as a greater number of compounds in development face solubility issues."

QbD is being embraced broadly in the industry for scale-up and manufacturing, which delivers increasing advantages and lowers the cost of drug development. "We believe adopting a QbD approach even earlier, at the formulation design stage, will become essential," says Ms. Jones. "The benefits of bringing this discipline to formulation include greater efficiencies as iterations toward the client goal are minimized and overall risk to the project is reduced."

In 2013, Agere introduced the Quadrant 2™ solubilization platform, a technology that encapsulates QbD principles and is guided by the client's API and QTPP (Quality Target Product Profile) to design formulations that not only improve oral bioavailability, but also meet the overall goals for the drug product.

"For CDMOs, it's a balancing act to meet the client's requirements for a formulation that is optimal for their API and at the same time delivers an efficient path to the clinic," says Ms. Jones. "The Quadrant 2 QbD-based platform facilitates the process by providing a rigorous up-front "set-up" of the problem." This defines the ultimate solution space for the desired drug product. Two major benefits accrue. "By focusing on the targeted solution space, we eliminate the least-likely excipient candidates and invest program effort on optimization of the most probable to achieve stability, performance, and manufacturability requirements. And by relying on the agnostic analyses enabled through experimentation and modeling, the excipient candidates that emerge are not limited to ones that could have been predicted had we solely relied on experience."

And Agere continues to meet the needs of its clients. Through early integration of the formulation and process development, Agere operations utilize a detailed technical transfer plan, bringing on new equipment capabilities, as required, and ensuring plant availability to deliver when requested.

"As standards are adopted throughout the development process from formulation through commercial manufacturing, the ability of clients to choose the best-in-class at each stage becomes a reality," says Ms. Jones. "With a streamlined and standardized interface between each phase, our clients will be empowered by the best quality option for each part of a program. Since the desire for a one-stop-shop approach remains strong, there will be increasing pressure on CDMOs to deliver competitive quality and value at every stage."

## BEND RESEARCH/CAPSUGEL'S DFS—SCIENCE & ENGINEERING TO MEET TOUGH FORMULATION CHALLENGES

Capsugel is a global leader in delivering high-quality, innovative dosage forms, and solutions to its customers in the health care industry. The company sells nearly 60% of the world's hard capsules, with a broad portfolio of gelatin, vegetarian, and other specialized capsule technologies. Capsugel's Dosage Form Solutions (DFS) business unit was formed in 2013 with the addition of Bend Research (acquired in October 2013); Encap Drug Delivery (acquired in March 2013); and Capsugel's pre-existing research and manufacturing operations. Now combined under a single banner, Capsugel's DFS is a leader in drug delivery technologies and formulation development. Formulation offerings include technologies for oral bioavailability enhancement, modified release, taste-masking, and other specialized areas including pulmonary drug delivery, abuse deterrence, and biotherapeutic formulation and production.

"Capsugel's DFS business unit accelerates and improves product development through an array of proprietary technologies including lipids and liquids, spray-dried dispersions, hot-melt extrusions, and through specialized manufacturing, including FDA/MHRA-accredited finished dosage sites that can handle highly potent, controlled substance, hormonal and oncology compounds," describes Doug Lorenz, Vice President, Applied Technology at Bend Research.

"In the area of bioavailability enhancement, our comprehensive technology offering includes amorphous dispersions (produced by spray-drying or hot melt extrusion), lipid formulations, micronizing and nanotechnologies, and formulations based on conventional and lipidic salt forms," says Mr. Lorenz. "Our clients include small biotech companies to large pharma. We support programs from early-stage discovery through commercial manufacture."

Capsugel's DFS provides clients with a science-based approach to select the optimum solution to bioavailability enhancement based on molecular properties and target product profiles, as well as customer preferences. Growth areas for Capsugel's DFS include development and manufacture of formulations for inhalation, and formulation and manufacturing support for biotherapeutic molecules.

Based on the company's formulation experience, Mr. Lorenz says a key trend in the pharmaceutical industry is the advancement of increasing numbers of compounds with low solubility. It is estimated that more than half of all new chemical entities have poor bioavailability because of low solubility. Capsugel's DFS offers technologies that enable the delivery of low-bioavailability compounds, including amorphous formulations prepared by spray-drying and hot-melt extrusion, nanocrystalline formulations, and lipid-based/self-emulsifying formulations.

In the past year, Mr. Lorenz explains how Capsugel's DFS helped a small biotech client that was encountering low bioavailability for a compound in a preclinical development program and how Capsugel's DFS helped seek out a solution that could be implemented rapidly, using small quantities of API at a modest cost. "From the properties of the molecule, we were able to use our formulation models and bulk-sparing methods to identify a spray-dried amorphous formulation using less than 200 mg of API," he explains. "After achieving positive in vitro test results, we rapidly manufactured 20 grams of spray-dried dispersion (SDD) for use in range−finding toxicology studies. This body of work was completed in less than 3 weeks from the initial evaluation to shipment of study supplies. Based on successful results and the high bioavailability obtained in these studies, the client requested larger-scale manufacture of SDD to support regulatory safety studies."

As this example illustrates, Capsugel's DFS establishes a long-term, alliance-based relationship as a development-team partner. "This close relationship with our clients enables optimal scientific interaction, provides for efficient communication, and facilitates rapid progression toward program goals. Our clients tell us that our broad, full-service capabilities make us the ideal development partner," says Mr. Lorenz.

## GATEWAY ANALYTICAL—A NICHE IN INVESTIGATIONS & PARTICLE SIZING

Gateway Analytical is a multi-faceted analytical testing laboratory focusing on niche areas of pharmaceutical testing and investigations. Its client base spans the entire gamut of the pharmaceutical drug market from development to manufacturing. Its chemically specific particle sizing services have been focused on supporting the generic drug industry by providing detailed analysis to help developers establish bioavailability and prove bioequivalence, with Raman Chemical Imaging, which has proven to be a game changer when dealing with identifying the chemical makeup agglomerates, aggregates, and polymorphs, explains David Exline, Vice President of Gateway Analytical.

Over the past year, Gateway Analytical has offered new services in the areas of glass delamination testing, automated particle identification with combined Raman/LIBS analysis to characterize overall populations of foreign particulate, and expanded services in the area of chemically specific particle sizing.

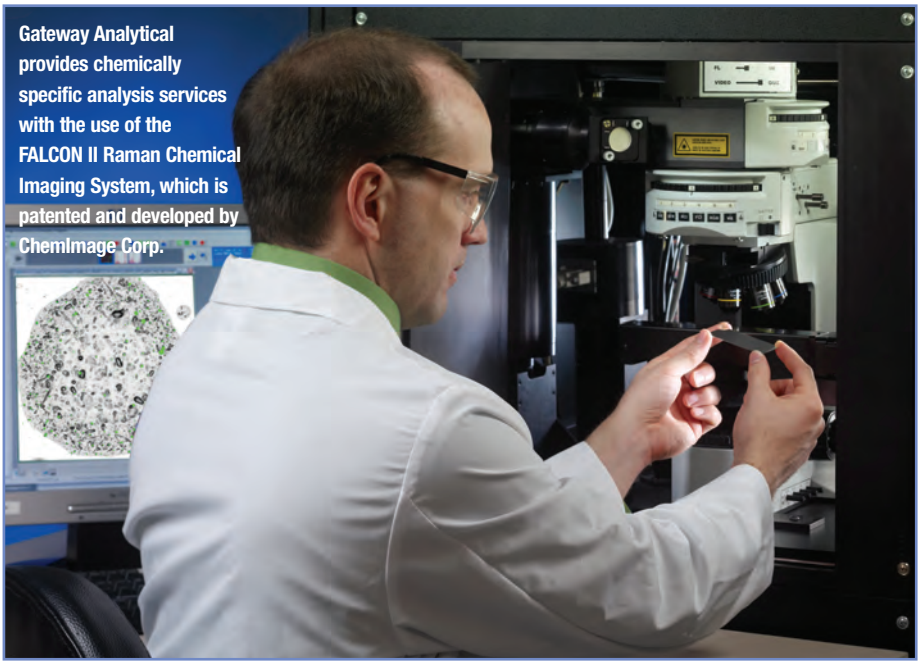
"Pharmaceutical investigations revolving around foreign particulate appears to be a major trend within the market," explains Mr. Exline. There are many challenges associated with the characterization of foreign particulate in the pharmaceutical industry. The main reason for this is the combination of materials that make up an end product. "Whether the goal is to identify a material, determine failures and product defects, perform reverse engineering investigations, identify foreign materials, or maintain quality of the product, the understanding of mixtures is critical in this analysis."

Within its chemically specific particle sizing group, Gateway has seen growth in the need to size and characterize agglomerations in drug products as this issue has significant impact on the drug quality and provides significantly more information about a product compared to conventional particle sizing methods.

One example would be the application of chemically specific particle sizing to a generic formulation compared to an innovator product. "A client can utilize this method to address the FDA critical path opportunity for generic nasal suspensions formulations by providing the accurate and precise drug particle size measurement to demonstrate bioequivalence and save a considerable amount of time and money by being able to potentially wave the in vivo biostudies," he describes.

Mr. Exline believes that the trend for future formulation and manufacturing outsourcing will involve the need for detailed information of foreign particulate and API/excipient components on a particle

by particle basis. “Historically, many bulk analytical methods have been satisfactory for characterization of materials,” he says. “With the increasing scrutiny in the areas of foreign particulate investigations and the need to better understand API-excipient and API-API agglomerations, the need for highly specific single-particle characterization methods will become increasingly important.”



Gateway Analytical provides chemically specific analysis services with the use of the FALCON II Raman Chemical Imaging System, which is patented and developed by ChemImage Corp.

## MAINE BIOTECHNOLOGY SERVICES—SPECIALIZING IN ANTI-ID SCREENING

MBS provides monoclonal and polyclonal antibody services, from design and development to production, characterization, and assay development. MBS works with both pharmaceutical and diagnostic companies to develop antibodies against their targets of interest, which may include small molecules, recombinant antigens, peptides, and anti-idiotypes. Tools such as MultiPure technology and Octet Red kinetic analysis are used to allow customers the opportunity to refine their clone selection earlier in the process. The antibodies developed by MBS are used by customers to support therapeutic product release and clinical trials, as well as within their 510K approved diagnostic kits.

As Carrie Rice, Sales Director at MBS, explains, “Our pharmaceutical customers increasingly have a need to develop anti-idiotypic antibodies for antibody neutralization assays. Anti-Id antibody candidates are screened for the ability to neutralize or block specific ligand binding of a therapeutic antibody. Monitoring therapeutic antibodies in clinical samples requires the ability to differentiate between administered antibody and naturally-occurring endogenous antibodies. This has become increasingly difficult as antibody biotherapeutics more closely resemble circulating human immunoglobulins. Anti-idiotypic antibodies specific for the unique variable region of the therapeutic antibody are ideal for this purpose.”

The most common end applications for anti-id antibodies developed at MBS are in the space of preclinical research for therapeutic antibodies. They can be used as reagents in pharmacokinetic studies, immune response immunogenicity assays, in ligand binding or neutralizing studies, or in antibody blocking assays.

In the past year, MBS has built on 25 years experience in hybridoma development to offer anti-idiotypic antibody development. “For some of our pharmaceutical customers, developing the research use assays required for drug monitoring is a challenge or distraction that they do not want to divert their internal R&D resources to. In order to respond to that customer need, MBS has added assay development services to our offerings so that we may assist the customer one step further in the process,” explains Ms. Rice. “We are now regularly evaluating antibody performance in sandwich ELISAs and bridging assays for customers. Pharma customers can now take clones with known performance and supporting data straight to their CRO for clinical assay development.”

Ms. Rice describes one client’s antibody development program. “One of our customers was faced with a challenge that we hear from so many: Get a companion assay up and running as soon as possible so that we can get our clinical trials going. As MBS had been part of the original antibody development program, we went back to our inventory and revived antibodies that had already been developed. We optimized assays that had already been used in the development program and made them robust and repeatable enough to be transferred to a clinical lab for assay development work. Had our customer gone back to square one, developing an assay could have added 9-12 months and tens of thousands of dollars to their program.”

MBS finds itself in an evolving market and that could affect the service pharma customers can expect from providers. “The industry is experiencing a wave of acquisitions and outsourced manufacturing by antibody service providers to overseas providers. Sometimes that outsourcing is obvious and sometimes it is not made clear to the customer. Often, the pricing for projects undercuts the service providers that have longevity here in the United States.

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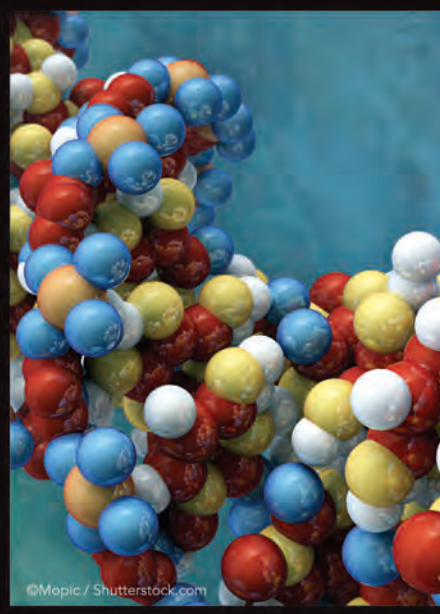


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The risk, in our view, is that as the industry trends toward needing more and complex hybridoma developments in the anti-idiotypic space," she says. "Base model providers with canned approaches will likely not be able to meet the growing challenges that anti-idiotypic developments present."

## METRICS, INC.—TACKLING BIOAVAILABILITY

Metrics Inc. provides solid oral dose pharmaceutical development and manufacturing services to pharmaceutical industry clients worldwide. Areas of expertise include formulation development, first-time-in-man formulations, and clinical trial materials manufacturing for Phase I, II, and III trials leading to commercial-scale manufacturing, and analytical method development and validation services. Formulation development services include handling insoluble and unstable actives, potent and toxic actives, and small molecule delivery. Instant-release and controlled-release tableting, capsule filling, over-encapsulation, milling, micronizing, and enteric coating are also offered.

The CDMO is finding that the formulation development market has been faced with an increasing proportion of drug substances that are BCS II (Biopharmaceutics Classification System, category II) that need enhanced bioavailability techniques. These techniques run the gamut from IP-based spray drying and new excipients to requests to use common practice equipment, including milling, sieving, and the addition of polymeric materials, explains Jeff Basham, Vice President of Business Development at Metrics. Drug substance salt or polymorph manipulations also can be used to help this process.

Metrics Inc. has begun offering a novel drug delivery technology called SUBA®

**Scientists at Metrics, Inc. are working for enhancement of bioavailability techniques to respond to market demand.**

(Super Bioavailability) that involves co-processing of the poorly water-soluble active pharmaceutical ingredient (API) with a cellulosic enteric polymer. Co-processing is the means by which the particle size is reduced and further re-crystallization of the active ingredient is hindered by the presence of the enteric cellulosic polymer. The smaller particle size of the water-insoluble API allows for a higher level of bioavailability in the small intestine.

"The benefit of SUBA is the development of an affiliated technology that uses an *in vitro* analytical technique to test whether we've successfully achieved a sub-micron particle size distribution of the poorly soluble API," says Mr. Basham. "A Big Pharma sponsor wants to know right away whether SUBA technology is even applicable to the API, so the use of *in vitro* testing allows us to determine pretty quickly whether SUBA is applicable to that particular product."

When applied successfully, SUBA can deliver therapeutic and convenience benefits that include reduced dosing frequency, increased patient compliance, improved side effect profile, and a more constant therapeutic effect.

Mr. Basham explains that SUBA was successfully used in the reformulation of itraconazole, an anti-fungal drug that has been available on the market in 100 mg dosage form. At that dosage form, itraconazole had been known to cause several side effects that are not beneficial to patient compliance. By employing SUBA technology, itraconazole has been re-formulated such that patients are exposed to just half the amount of itraconazole per dosage form as before, he says.

"Anytime you can reduce the amount of API and still deliver the same amount of effective use of it, you mitigate the possibility of side effects. The U.S. Food and Drug Administration is always looking for a reduction in side effects or an increased level of safety and potential patient compliance."

## NORWICH PHARMA SERVICES—ONE SITE DOES IT ALL

The Norwich Pharma Services manufacturing facility located in Norwich, NY offers contract development and manufacturing services with a focus on synchronized outsourced solutions from a single provider. Norwich offers services that

Norwich has expanded bin blending technology to match pilot-unit capabilities.

cover the complete lifespan of its customers' products, which makes bringing those products to market faster and more cost-effective, claims Stephanie Ferrell, Senior Manager, Marketing Communications at Norwich. "This single-destination facility offers customers, from large pharmaceutical companies to virtual organizations, a full range of services along the supply chain. From buying API to product distribution, Norwich has the capabilities for Phase I to III product development within the walls of the facility."

While the company's predominant focus is in developing and manufacturing solid oral dose, tablets, and capsules, Norwich also provides liquid dose services. Unit operations range from blending, encapsulation and coating to fluid bed, blister packing, and liquid fill packaging.

According to Ms. Ferrell, customers are looking for service providers that will be long-term partners. "The opportunity to work with a provider starting in early Phase I through commercial manufacturing gives customers a continuity of service while saving them time and money from having to move their project to other facilities for different phases. Thus, service providers need to be able to offer a wide breadth of services while having the flexibility and scalability to make sure that customer needs are met," she says.

On the commercial manufacturing side, Norwich has expanded its blending technology options by adding bin blending to match pilot-unit capabilities. "Many newer products are being processed using bin-blenders because they offer the potential for better uniformity and to overcome obstacles in product robustness," explains Ms. Ferrell.

Norwich strives to offer flexibility with new technologies while maintaining legacy v-blending capabilities for customers not interested in moving their products to a new technology. Additionally, low humidity capabilities have been expanded to handle products down to a 30% humidity environment, and packaging capabilities have been expanded to provide an increase in packaging speed from 25-50%, depending on bottle size.

Norwich's depth of project management experience was highlighted when a customer presented a controlled-release tablet that required technical development and scale-up manufacturing, explains Ms. Ferrell. Key challenges for the drug formulation included temperature control, coating sensitivity, and clarity. In addition, the sensitive tablet coating process could impact the release profile of the drug through one or more laser-drilled holes. "Norwich immediately focused the project to design process parameters that control the quality of coating as well as its final clarity," she says.

The Norwich team learned how to operate and perfect the innovative laser drill process technology used for the complicated potent compound. Equipment installation was performed in a room designed to meet stringent Class 1 Division 1 standards and minimize potential risks to personnel and environment.

"In collaboration with the customer, the Norwich team emerged as specialists on how to operate the new equipment but also optimized the design of the laser drill technology because of the focus of the project team. There were no regulatory issues to report and the tech transfer was on time, as defined in the project plan, despite the need to cross over from the pilot plant equipment to commercial operations. Norwich also successfully filed two registration batches – both completed 100% right the first time in support of an FDA filing."

## PARTICLE SCIENCES, INC.—A VARIETY OF FORMULATION APPROACHES

Particle Sciences, Inc. is an integrated provider of drug development services. Particle Sciences focuses on BCS II/III/IV molecules, biologics, and highly potent compounds through a variety of technologies, including emulsions, gels, micro- and nano-particulates, drug/device combination products, and solid solutions. Through a full range of formulation, analytic, and manufacturing services, Particle Sciences provides pharmaceutical companies with a development solution that minimizes the time and risk between discovery and the clinic.

In the past year, Particle Sciences increased its offerings around GMP nanomilling, hot-melt extrusion, and spray

drying to address formulation of BCS II molecules, explains Robert. W. Lee, PhD, Vice President, Pharmaceutical Development Services, Particle Sciences, Inc. In the second quarter of this year, the company will be offering a proprietary pro-drug approach that drastically increases the solubility of BCS II molecules. This will offer an alternative to nanoparticles for parenteral delivery of insoluble compounds, claims Dr. Lee.

Throughout the formulation process, Particle Sciences incorporates a Quality by Design (QBD) approach using modeling and Design of Experiments (DoE) to arrive at the best product with the strongest regulatory package. "One of our clients had a sterile emulsion that it wanted us to manufacture under GMPs using our M110EH Basic Biopharma Microfluidizer. At the requested scale of 120 L, the number of passes was prohibitive and by using a DoE approach, we were able to reduce the number of passes sufficiently to allow for an acceptable manufacturing process," explains Dr. Lee.

As this example demonstrates, CDMOs are no longer simply a set of hands. "Clients expect a high level of basic science competency and sophisticated processing capabilities. A well-positioned CDMO needs to be able to lead a development effort."

## PATHEON—SOLVING SOLUBILITY & FLOWABILITY PROBLEMS

Patheon Inc. is the pharmaceutical services business owned by DPx Holdings. The company is a leading provider of CDMO services, pharmaceutical products, and products for other industries. With global headquarters in Durham, NC, DPx has a footprint of 24 locations across North America, Europe, Latin America, and Australia. Patheon provides preclinical, clinical formulation development (Phase I to III), scale up, and process development of solid oral and sterile dosage forms. In addition, Patheon provides registration batch manufacturing, process validation, QbD, and small- and large-scale commercial manufacturing.

"We undertake formulation and process development of a variety of dosage forms – simple solid oral forms in early-stage clinical development and late-stage clinical development such as powders, granulates, capsules, tablets, softgels, sterile liquids, lyophilized powder in vials, and prefilled syringes," describes Anil Kane, PhD, Executive Director, Global Formulation Sciences, PDS, Patheon.

The dosage forms developed are immediate release as well as controlled release forms in a variety of technologies to meet the dosage profile for clinical therapeutic efficacy. Patheon also offers formulation development and manufacturing services in life cycle management for pediatric dosage forms, fixed-dose combinations as multi-layer tablets, multiparticulates, beads, minitablets, etc.

Because of its support of clinical and commercial development and manufacturing services, Patheon has a keen sense of formulation trends. For instance, Dr. Kane says that an increasing number of new chemical entities being created out of drug discovery in the preclinical stage exhibit poor aqueous solubility and poor bioavailability. "These compounds pose significant challenges in solubilization, absorption, and permeation on oral administration. The efficient formulation of these compounds requires expertise in the techniques and technologies that can deliver the drugs into the systemic circulation by improvement in bioavailability."

He also points out a rising number of products being developed as line extensions or as part of a life cycle management strategy. "Development of modified release, controlled-release dosage forms, and active drug layering are on the rise," he says.

And, due to the regulatory changes in Europe and North America, Patheon also sees an increase in demand for pediatric formulation development of many new clinical drug candidates. "A significant number of fixed-dose combinations of two or more new chemical entities, or a combination of NCIs plus an off-patent for existing drugs are being developed and tested in clinical trials for existing or newer indications," Dr. Anil explains. "Based on the drug dosage profile required, its site of absorption, maximum therapeutic efficacy, and its stability with other active ingredients, a multi-layer tablet, bi or trilayer, a tablet in a tablet, multi-particulates in a capsule are being developed to address the need of the clinical studies and for marketing approval."

In the past year, Patheon launched the "Early Development" service in Cincinnati and at its Milton Park site near Oxford, UK, to address API characterization, formulation screening, clinical formulation manufacture, and stability studies. The company also launched development and commercial manufacturing services of softgels as standard softgels, and using its patented technologies to target the drug at various regions of the gastro-intestinal tract. Patheon has invested in Phase II scale manufacturing capabilities at the Milton Park site. In addition, Patheon is also investing in equipment and capability of handling high potent compounds at these early-development centers.

Through formulation development, Patheon has solved low-solubility problems and developed formulations with significantly higher exposure in animal model or first-in-man clinical studies. The increase in bioavailability was achieved using one or the other techniques from the tool kit – micronization, micro fluidization, lipid-based solubilization, or by solid dispersion techniques such as spray drying or hot-melt extrusion.

Patheon has also addressed problems of poor flowability of active drug substance

Patheon undertakes formulation and process development of a variety of dosage forms.

powders and developed manufacturing and scalable processes that can support commercial large-scale manufacturing. In the area of sterile dosage forms, several projects have been successfully completed where a formulation was developed to stabilize the drug in a sterile solution and monitor the physical and chemical stability over a period of time.

## PHARMATEK—MEETING FORMULATION CHALLENGES

Pharmaek is a full-service dosage form development and GMP manufacturing services organization. Services include preformulation testing, analytical and formulation development, GMP manufacturing, clinical packaging, labeling and distribution, and stability testing and storage. With 15 years of experience developing small molecules and peptides for oral and injectable delivery, Pharmatek specializes in the development and manufacture of challenging compounds and complex formulations, including poorly soluble NCEs and controlled-release formulations.

According to Elizabeth Hickman, Associate Director, Marketing, Pharmatek, the need for formulation and manufacturing technologies that address poor solubility continues to increase.

At the same time, companies want the most efficient and cost-effective route to the clinic to establish compound efficacy. "Technologies such as API-in-Capsule and simple blend formulations in Phase I are an attractive solution for companies that want to reduce investments in the early stages," Ms. Hickman says. "Previously, we had only seen this strategy used by virtual and small pharmas, but now see this strategy being utilized more and more by our large pharma clients."

When a phase-appropriate strategy makes sense for the compound and the client's objectives, Pharmatek's objective is to select the least complex formulation approach that provides acceptable in-vivo performance. "In some cases, this cannot be achieved without the use of more complex formulation technologies," says Ms. Hickman. "In those cases we will utilize our broad experience with the development of amorphous dispersion, lipid delivery, fluid bed processing or melt granulation."

To determine the best route forward, Pharmatek will screen the compound against several formulation strategies in parallel, while using a minimum quantity of API. As Ms. Hickman explains, because the data is only as good as the method used to generate it, Pharmatek first starts with a solid stability-indicating analytical method, develops a thorough understanding of the compound's physiochemical properties, and develops a discriminating dissolution method for the evaluation of prototypes. Lead prototypes are then tested *in vivo* before selecting a clinical formulation. "From bioavailability enhancement technologies for insoluble compounds to API-in-a-capsule, we match the best solution with the physiochemical characteristics of the compound and the company's corporate goals, clinical timelines, and development budget."

Pharmatek recently purchased an automated bottling and labeling line. The addition of the line is part of the company's ongoing investment to support increasing demand for larger scale productions. "Automatic bottling improves the efficiency and accuracy of clinical packaging, resulting in a reduction in overall costs and time-to-clinic. Additionally, the new bottling line significantly increases Pharmatek's overall capacity, allowing higher throughput and larger GMP manufacturing runs," says Ms. Hickman.

To complement its toolkit of solutions for poorly soluble compounds, Pharmatek recently invested in particle size reduction technology with the addition of a Jet-O-Mizer Jetmill for the micronization of API. The company also recently added a Niro Mobile Minor Spray Dryer. The new spray dryer will complement current spray drying capabilities and enable the production of larger batches for early-phase clinical trials.

Pharmatek has seen a growth in the number of peptide compounds being developed in recent years. In the past year, the company has worked on seven peptides for early-phase development. Formulation strategies include suspensions, liquids, frozen liquids and lyophilized products.

Each formulation strategy requires a thorough understanding of peptide chemistry and injectable development.

Because peptides are easily susceptible to degradation, well-developed orthogonal analytical methods are essential to successful formulation development. "We've dealt with diverse peptides and successfully implemented analytical methods to characterize the product and develop formulations designed to mitigate the risk of degradation."

An operator at Xcelience inputs parameters for roller compaction.

## XCELIENCE—OVERCOMING QBD CHALLENGES

Xcelience is a full-service CDMO that can manage the progression of a pre-IND API through the development process. A client's API can be fully characterized (salt and polymorph screens, intrinsic solubility, etc.) before formulation development. Xcelience can develop a range of formulations, including capsules, tablets, oral solutions/suspensions, and topical products, using technologies such as roller compaction, extrusion/spheronization, wet granulation, and self-emulsifying systems for liquid products. The formulations are then moved into GMP manufacturing.

According to Paul Skultety, PhD, Vice President, Pharmaceutical Development Services & Project Management at Xcelience, one of the biggest trends in formulation development is the incorporation of QbD principles in the development process. Formulation development must be performed such that critical quality attributes can be identified. This, in turn, will allow for critical process parameters to be evaluated and a risk assessment performed using tools such as Failure Modes and Effect Analysis to help determine which parameters might impact the process. The parameters that have an impact on the critical quality attributes can be evaluated using appropriate statistical study designs. "The data from these studies can be used to develop the design space (ranges for these parameters) for each critical process parameter," describes Dr. Skultety. "By identifying and controlling these parameters, the product will have the desired quality characteristics. The design spaces will assist in determining in-process testing limits and the finished product specifications." The data can further be applied to help justify the validation plan that will be used once the product moves to commercial scale.

In addition to QbD, another trend that Xcelience has identified is the need to develop pediatric dosage formulations sooner in the life cycle of a new compound. "In a number of cases, we have been asked to develop a pediatric formulation with an acceptable flavor (taste) before filing the adult dosage formulation," says Dr. Skultety. "We have developed several pediatric formulations including chewable tablets, sachets, and oral liquids. Because these were new molecules, the taste properties of the formulations were evaluated using a model compound. This allowed for refinement of the formulation and the development of an acceptable-tasting final formulation."

While reformulating taste can be a challenge, Xcelience was also faced with the challenge of an extremely adhesive compound. "It was a fairly high-dose compound, which further exacerbated the problem," he explains. "No matter how much lubricant was used, the compound would always stick to the punches. Our scientists were able to develop a processing technique that allowed for the tablets to be compressed on the high-speed tablet press with no build up on the punches."

Going forward, Dr. Skultety expects that more companies will be outsourcing their formulation development. "It is difficult for small and mid-size companies to have the needed breadth of expertise and equipment in-house to handle all that is involved in this area. It is a tremendous expense to build a GMP facility, purchase the needed equipment to handle the various batch sizes, and then maintain the facility," he says. "If a company does have a larger portfolio of compounds, it is more cost effective and faster for it to outsource the formulation development, the analytical work, and stability studies." ◆

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# Technology & Services Showcase

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## Solid Oral Dosage Forms


Agere Pharmaceuticals' services include solubilization formulation design and development, cGMP analytical, and solid oral dosage forms. Solid dosage forms supported include tablets, capsules, powder for inhalation, and alternative dosage forms. Our capabilities include excipients selection, drug excipient ratios, and process development. We also support clients by preparing 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. Formulation development leverages our Quadrant 2™ solubilization platform, and all Agere services follow QbD guidelines. For more information, contact Agere at (541) 318-7115. or visit **www.agerepharma.com**.

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There are lots of analytical laboratories that do routine testing, but who do you call when you need a highly complex problem solved? From developing and validating complicated methods, to the identification of a complex degradation product, our team can solve your pharmaceutical development problem. One-third of our staff is composed of PhD-level chemists who will develop a customized solution for you. Our laboratory is FDA-Registered, DEA-Licensed, cGMP-Compliant, ISO/IEC 17025-Accredited, and can work within your tight deadlines. Our specialties include method development & validation, preformulation & formulation, extractables & leachables, stability & release testing, degradation analysis, Phase I-IIa clinical trial product manufacturing, chemical characterization, and litigation support services, including patent infringement & counterfeit analysis. For more information, contact Avomeen at (800) 930-5450 for a free initial consultation with a PhD Chemist, email scientist@avomeen.com, or visit **www.avomeen.com**.

## Gum Base Supplier

Health in Gum
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www.healthingum.com

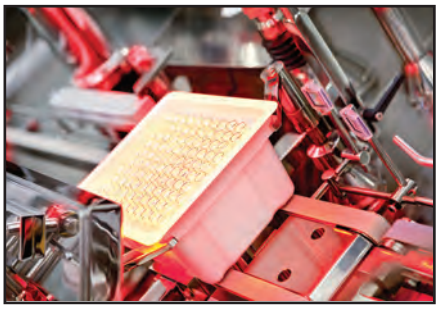
Cafosa, part of the Wrigley/Mars group of companies leading the chewing gum market, is the world's leading Gum Base supplier for confectionery, nutraceutical, and pharmaceutical applications. Gum Base is the main ingredient used to produce chewing gum, a combination of polymers, resins, and softeners plus an inorganic filler that gives different textures and chewing properties to chewing gum depending on its composition. Cafosa has developed an innovative concept for the pharmaceutical industry: Health in Gum is an excipient, a directly compressible powder gum containing a mix of Gum Base and polyols to which you can add your API, so you can create medicated chewing gum by adding your APIs to Health in Gum powder. Health in Gum offers an innovative drug delivery system for your products. There is no need for specific chewing gum production equipment. For more information visit, Cafosa at **www.healthingum.com**.

# Technology & Services Showcase

## 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**.

## 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.**

## Full-Service CDMO

CordenPharma is the pharmaceutical brand of International Chemical Investors Group. Formed in 2006, CordenPharma is a full-service partner for cGMP Contract Development & Manufacturing (CDMO) of oral, sterile, highly potent, and antibiotic pharmaceutical Drug Products and associated Packaging Services. In APIs, CordenPharma is a leading CDMO service provider in chiral synthesis and other advanced APIs. They additionally produce specialized pharmaceutical ingredients, such as peptides, synthetic lipids, carbohydrates, and highly potent APIs. For more information, visit CordenPharma at **www.cordenpharma.com**.

## Super Refined® Excipients

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

# Technology & Services Showcase

## Development & Manufacturing

DPT

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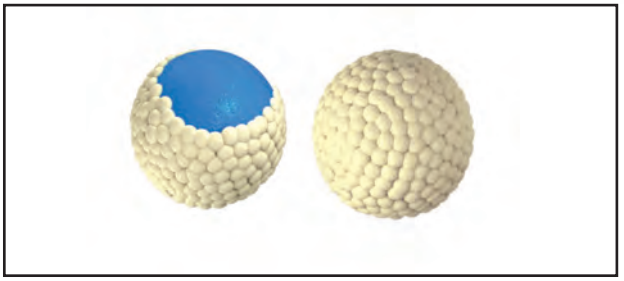
DPT is a contract development and manufacturing organization (CDMO), specializing in semi-solids and liquids for biopharmaceutical and pharmaceutical products since 1938. From virtual to large pharma, from concept to commercialization, from sterile to non-sterile - DPT offers the broadest range of capabilities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

## Solvent-Free Hot Melt Coating



Applicable to taste-masking, modified-release, or protective barrier formation, this solvent-free process is ideal for treating difficult or moisture-sensitive drugs. Developed by Gattefossé, the process entails depositing a fine mist of molten lipid onto drug particles when suspended in a fluid bed coater. Upon the solidification of the lipid mist on the substrate surface, a uniform coating is formed. The coating performance may be controlled by adjusting process parameters and or selecting a different lipid. The resulting solid particles may be directly filled into capsules or compressed into tablets. Unlike the conventional coatings, the process helps eliminate the risks and costs associated with addition/removal of solvents. For more information, please contact your local Gattefossé representative or visit **www.gattefosse.com**.

## Innovative Syringe Systems

The Gerresheimer Group is a leading global partner for the pharma and healthcare industries with expertise in both glass and plastic. Our product offering ranges from standard pharmaceutical containers to customized drug delivery systems, such as syringe systems, insulin pens, and inhalers for safe medication dosage and application. Gerresheimer Bünde is known for its excellence in the area of RTF® syringes (Ready-to-Fill), which are supplied completely washed, siliconized, assembled, nested, packed in tubs, and sterilized to the customers. A range of proprietary accessories, such as the rigid needle shield with thermoplastic elastomer (TERNS) and the tamper-evident Luerlock 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 about prefillable syringes, contact Dr. Arno Fries at +49 5223 164-401 or visit **www.gerresheimer.com**.

## Insulin Management System

# Technology & Services Showcase

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Ligand is a biopharmaceutical company that develops and acquires technology and royalty revenue generating assets that are coupled to a lean cost structure. Ligand's Captisol® platform technology is a patent protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol® has enabled five FDA-approved products, including Pfizer's VFEND® IV and Baxter's Nexterone®. For licensing opportunities, call Captisol Services at (877) 575-5593 or visit **www.captisol.com.**

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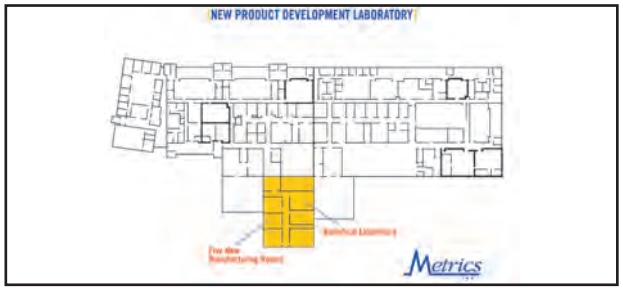
## Product Development Lab




Metrics is making significant investments in facilities and equipment for the benefit of contract services clients with a new laboratory to better support fast-track development of pharmaceutical products. The $1.6-million, 4,524-sq-ft facility provides maximum flexibility for early formulation and analytical method development. The facility is designed for preclinical development of early formulation prototypes and related analytical methods. In this laboratory setting, formulators and chemists will have significant autonomy to conduct development activities more quickly. Segregated from the main Metrics operations and containing fully dedicated equipment, these new processing suites have independent HVAC systems and state-of-the-art engineering controls, such as interlocking airlock doors, room air pressure differentials, high-volume room air turnover, and 100% HEPA air filtration. For more information, visit Metrics Inc. at **www.metricsinc.com.**

## Development & Manufacturing

Norwich
PHARMA SERVICES

Norwich Pharma Services is a recognized leader in full-service contract pharmaceutical development and manufacturing. Through its Synchronized Outsourced Solutions, Norwich offers customers a single source with the highest level of quality and reliability from product development to scale-up and commercial manufacturing through clinical services. By offering complete services for a product's entire lifespan, Norwich provides your project with an efficiency and consistency of service that helps bring it to market faster and more cost-effectively. For over 126 years, Norwich has built a reputation for dependable product supply and established an unparalleled history of regulatory compliance. For more information, visit **www.norwichpharma.com.**

# Technology & Services Showcase

## Child-Resistant Closure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DRUG DEVELOPMENT Executive
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# BioCellChallenge: Optimizing the Potential of Intracellular Therapeutic Antibodies

**Laurent Meuier, PhD**
**CEO**
**BioCellChallenge**

*In many human diseases, such as cancers, proteins are mutated or over-expressed, which results in aberrant physiological processes. These proteins can be cell membrane receptors, proteins involved in cell signalling or intracellular routing, proteins involved in transcription regulation, or others. Protein-protein interactions are a key component of these processes. The use of antibodies that are able to interact with specific domains of the proteins involved in these interactions is particularly important to developing future treatments against diseases. Drug Development & Delivery recently spoke with Dr. Laurent Meunier, CEO of BioCellChallenge, to discuss the development of a new liposomal formulation allowing the use of intracellular therapeutic antibodies.*

**"Recently, BioCellChallenge has worked on the development of an antibody intracellular delivery reagent based on a liposomal formulation. The result is a very efficient and non-toxic antibody intracellular delivery system that is very easy to use with any antibody on the market. This system, named ImmunoCellin, functions by encapsulating the antibodies through non-covalent interactions. Because no organic chemical coupling occurs, the delivered antibodies retain their structure and function."**

## Q: Why did BioCellChallenge decide to create a solution to deliver antibodies into live cells?

**A:** Forty years ago, Alan F. Williams showed that monoclonal antibodies could be raised against biologically interesting molecules with a very high specificity. Since then, monoclonal antibodies have become a very useful tool, not only for immunotherapies, but also as in vitro tools for diagnostic and research purposes. Antibodies are not able to pass naturally through the membranes of live cells toward potential intracellular targets. Today, all of the therapeutic antibodies used in treatment are targeting proteins located on the surface of the cell membrane, such as receptors. The market for therapeutic antibodies reached $44 billion worldwide in 2011.

The concept of therapeutic antibodies has, however, led to the recent development of intrabodies. These intracellular antibodies,

produced directly into the cytosol, were designed to interfere with a range of protein targets inside cells, in order to modify their functionality and fight against viral infections, cancer diseases, or other targets.

However, even if a lot of progress has been made in such immunotherapies, used against intracellular targets, this approach still necessitates overcoming a number of challenges in order to envisage using it as a therapy option.

An alternative approach is to directly deliver antibodies into live cells. The advantage of this is that thousands of existing monoclonal antibodies could be used and no specific engineering or selection of a specific intracellular antibody is needed. In addition, this alternative approach does not require gene therapy steps in order to express an intracellular antibody. Therefore, all the problems associated with gene therapy and the modification of our genetic material is overcome. For this reason, BioCellChallenge developed a system allowing for the intracellular delivery of antibodies.

## Q: How is the drug delivery marketplace evolving, and why is it becoming more important in the fight against diseases?

**A:** In the past 15 years, there has been a considerable evolution in the intracellular drug delivery market. However, most of our studies were focused on gene therapy, and the delivery of nucleic acids, such as genes or siRNAs, into cells. Only a few projects that were not gene therapy related were undertaken in order to deliver non-nucleic acid molecules, including proteins, into living cells. Today, finding the way to deliver drugs efficiently, without secondary effects in the human body, is even more of a challenge than drug discovery. This is especially relevant in cancer, where very efficient molecules have been developed but have not yet been used because they couldn't be delivered properly into the organism. If we can find the way for the drug to reach its target, there could already be efficient systems that could treat or have an effect on various pathologies.

Protein transduction domains (PTDs), small membrane-permeable peptide carriers, were proposed in the mid 1990s to deliver different cargoes into the cells, including proteins and antibodies. However, their poor interaction with cargoes has necessitated chemical engineering in order to covalently link them together. Recently, several liposomal formulations have also been developed. Their main advantages are that they can interact directly with different cargoes by electrostatic and hydrophobic interactions and that chemistry preparatory steps are not needed. However, although some of these formulations are accessible on the market, their efficiency is still limited, and some new developments and optimizations have been necessary to increase their efficiency.

Recently, BioCellChallenge has worked on the development of an antibody intracellular delivery reagent based on a liposomal formulation. The result is a very efficient and non-toxic antibody intracellular delivery system that is very easy to use with any antibody on the market. This system, named ImmunoCellin, functions by encapsulating the antibodies through non-covalent interactions. Because no organic chemical coupling occurs, the delivered antibodies retain their structure and function.

## Q: How does ImmunoCellin function and why is it unique?

**A:** The antibodies are delivered into the cells in 4- to 24-hour periods, depending on cell types. They are able to find and bind their targets inside the cytosol of living cells. For example, antibodies directed against a protein of the nuclear pore complex localize to the nuclear envelope a few hours after their intracellular delivery.

ImmunoCellin is very quick and simple to use. It works in the same way as a nucleic acid transfection reagent. As it is a liposomal formulation in water, adding a few microliters of the liposomes to a few micrograms of the antibody with 15 minutes of incubation will create the encapsulation of the antibodies within the liposomes. No chemical coupling is required, and both antibodies and liposomes interact together through non-covalent interactions. These complexes are then added directly into the cells.

Critically, there is no inhibition due to the presence of the serum added in tissue culture media. This is particularly important for both in vivo and therapeutic approaches. Another important result we have obtained is that additives, such as BSA, which may be present in commercially available antibodies, do not interfere with ImmunoCellin and do not inhibit its activity. This allows the use of the reagent with any antibody on the market without any further purification process.

## Q: What type of diseases can ImmunoCellin target? How could it contribute to the battle against these diseases?

**A:** Because there are antibodies against all identified proteins, ImmunoCellin can target many diseases involving the malfunction of proteins or "infectious" proteins in cells. The malfunction of proteins is responsible for a wide number of diseases, including cancers, neurodegenerative disorders (Alzheimer's, Parkinson's), and some infectious diseases.

ImmunoCellin has been designed to block intracellular protein functions for immunotherapy purposes, but it can also be used in more "fundamental" studies. For example, siRNA intracellular delivery enables the shutting down of the expression and all the functions of the targeted protein. However, if this protein has several different functions inside cells, it is more advisable to inhibit only one function by using a specific monoclonal antibody directed against a specific domain of the protein. As it will interfere with a single cellular mechanism, a specific function of the protein can be determined with certainty. ImmunoCellin is also particularly suitable for use in kinetic studies of intracellular protein localization in response to different stimuli. It can also directly interfere with protein traffic in the cytosol or the nucleus; by targeting a localization signal, for example. ImmunoCellin is therefore a powerful tool for developing a broader understanding of the protein-protein interactions, which form the basis of cell functions.

## Q: What are the future plans for BioCellChallenge?

**A:** This new system is aimed particularly at pharmaceutical and biotechnology industry R&D teams working on therapeutic antibodies. As a result, BioCellChallenge is keen to develop partnerships with other companies in the pharmaceutical and biotechnology industry. The ImmunoCellin system is also particularly relevant to cellular and molecular research biologists worldwide.

With these future partnerships in mind, BioCellChallenge is working on some additional improvements of immunoCellin. For example, we are currently working on a specific ImmunoCellin formulation adapted for in vivo approaches. We are also working on the GMP compliance of several of our molecules. ◆

# INTRAORAL DELIVERY

# Utilization of Intraoral Administration for Enablement & Enhancement of Drug Delivery – Highlights of Recent Commercial Products

**By:** Zhen Yang, PhD, Yunhui Wu, PhD

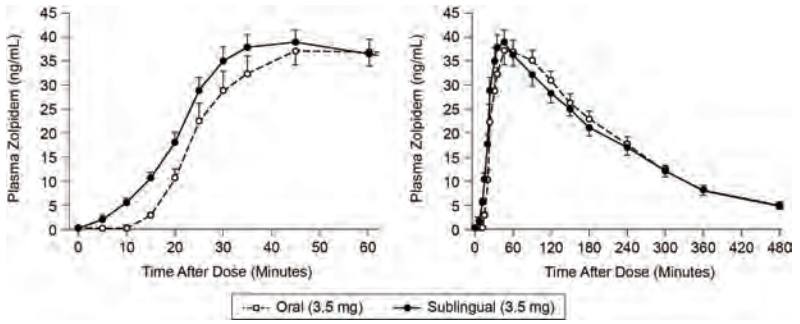
## INTRODUCTION

Intraoral administration of therapeutics through the mucosal linings of the oral cavity is one of the alternative delivery approaches. Alternative routes of drug delivery have enabled drugs that cannot be delivered via the oral route due to poor oral bioavailability.[1] Traditionally, such drugs have been administrated through the parenteral route, which is often not a preferred approach for patient compliance. This challenge has presented an opportunity for utilizing the intraoral route as a viable option in the pharmaceutical industry. Many classes of drugs could benefit from intraoral administration by avoidance of first-pass metabolism and other unfavorable factors (eg, degradation, food/pH effect) in the GI tract. In addition, as the oral mucosa is highly vascularized, transmucosal absorption could access to systemic circulation directly and provide the potential for fast onset of action. This advantage could be a desirable development requirement for certain medical needs, such as pain management, cardiovascular treatment, insomnia, and migraine treatment. Patient adherence and preference for intraoral administration are also favored compared to other alternative routes (eg, nasal, pulmonary, transdermal) as intraoral administration shares similar dosage forms with traditional oral delivery but with a more convenient and discreet manner. There are several good recent review papers covering intraoral formulation development and therapeutic applications.[2-4] The purpose of this article is to highlight several commercialized intraoral formulations from a clinical pharmacokinetic perspective and reveal its mechanism for enablement or enhancement of drug delivery via intraoral administration.

## HIGHLIGHTS OF RECENT COMMERCIAL EXAMPLES

Clinical pharmacokinetics associated with intraoral delivery is intriguing, considering it combines the unique characteristics of initial intraoral absorption and subsequent intestinal absorption. Although pharmacokinetic profiles vary among different drugs via intraoral administration, three categories could be classified when compared to conventional oral delivery based on current commercial products. For the first category, intraoral formulations enable the delivery of drugs that cannot be achieved by the conventional oral route (eg, due to extensive first-pass

**FIGURE 1**




**Mean plasma zolpidem concentration vs. time profiles after sublingual and oral zolpidem tablets at a dose of 3.5 mg in human (left: 0-60 minutes; right: 0-480 minutes) (Data were obtained from Intermezzo NDA file[9])**

metabolism). For the second category, enhancement of pharmacokinetic (PK) and pharmacodynamic (PD) performance is achieved by intraoral administration in comparison to the existing oral delivery formulation (eg, faster onset of action). In the last category, intraoral dosage forms are aimed to differentiate with existing oral products by further improving patient convenience and/or compliance, eg, orally disintegrating tablet (ODT) or film (ODF), for patients with difficulty in swallowing conventional tablets. Three recent approved commercial products delivered via intraoral administration are presented herein to reflect the aforementioned general categories. These examples represent three scenarios for various levels of modulation of clinical pharmacokinetics by applying the intraoral route in comparison to the conventional oral delivery. The relevant pharmacokinetic parameters are summarized in Table 1 for each case.

**TABLE 1**

| Drug | Route/Dosage/Dose | $C_{max}$ (μg/L) | $T_{max}$ (h) | $AUC_{0\text{-}inf}$ (μg*h/L) | $AUC_{0\text{-}20\ min}$ (μg*h/L) |
|---|---|---|---|---|---|
| Asenapine | PO/Tablet/5 mg | 0.14 | 0.53 | 0.87 | N/A |
| | Sublingual/Tablet/5 mg | 2.58 | 3.0 | 16.2 | N/A |
| Zolpidem | PO/Tablet/3.5 mg | 46.0 | N/A | 161.5 | 0.74 |
| | Sublingual/ Tablet/3.5 mg | 43.8 | N/A | 170.0 | 2.27 |
| Vardenafil | PO/Tablet/10 mg | 10.78 | 0.75 | 30.48 | N/A |
| | Supralingual/ODT/10 mg | 12.15 | 1.5 | 42.37 | N/A |

Note: N/A means data were not listed in the NDA file.

**Pharmacokinetic parameters of asenapine, zolpidem, and vardenafil after PO and IO administrations in human. (Data were obtained from various NDA files published by FDA)[9,12,13]**

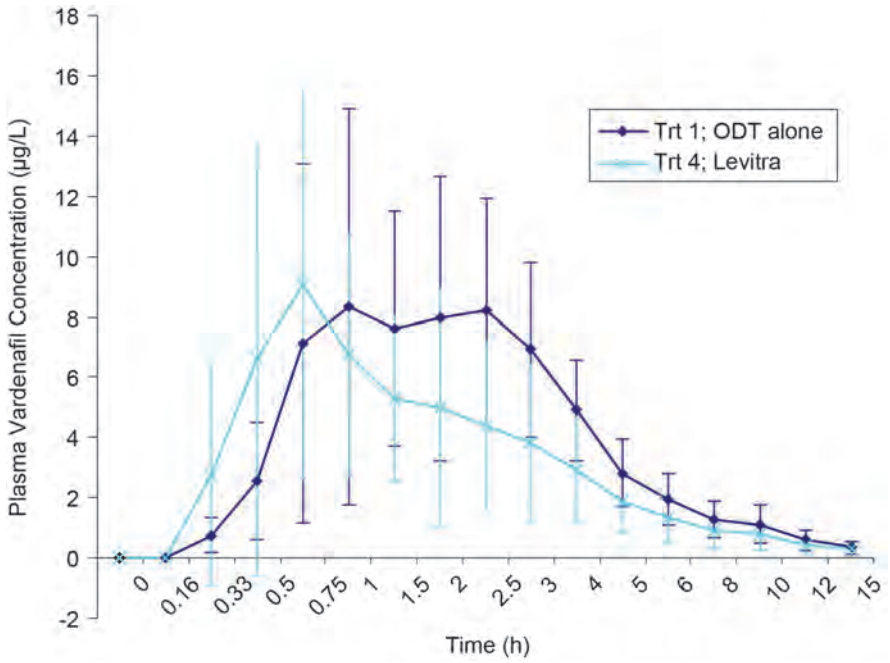
## Enablement of Drug Delivery - Asenapine Sublingual Tablets (Saphris®)

Asenapine is indicated for the treatment of acute schizophrenia and bipolar disorder. According to Biopharmaceutics Classification System (BCS), asenapine maleate is classified as a BCS Class 2 compound (low solubility, high permeability). In early Phase I studies in healthy volunteers, asenapine was administered orally, but this route of administration was abandoned soon due to only 2% of oral bioavailability caused by extensive and rapid first-pass metabolism. Based on the human study using [$^{14}$C] asenapine sublingually, >70% of circulating radioactivity was associated with conjugated metabolites, and the major metabolic routes were direct glucuronidation and N-demethylation.[5] In addition, this study suggested that at least 50% of the dose administered sublingually was absorbed as 50% radioactivity was recovered from urine, which supported the explanation that first-pass metabolism caused the poor oral bioavailability. The sublingual tablet was subsequently developed, and the absolute bioavailability was increased to 35% at a dose of 5 mg.[6] The increased bioavailability after sublingual administration of asenapine is primarily attributed to sublingual absorption as the contribution from intestinal absorption is minimal. The commercialization of Saphris clearly demonstrated the enablement of intraoral delivery for drugs that have failed in development as conventional oral dosage forms.

In addition to the relative bioavailability between the two delivery systems, several biopharmaceutical studies were performed to assess the safety and efficacy of the sublingual tablet under various dosing scenarios, including the effects of drinking water, administration sites, and food intake. Compared to a relatively longer and constant transit time in the GI tract for oral delivery, the residence time in the oral cavity is short, variable, and controlled by saliva swallowing and water intake. In general, water intake after sublingual administration is expected to reduce the residence time of the intraoral dosage form in the oral cavity. Interestingly, the clinical results showed that the exposure and $T_{max}$ of asenapine were highly independent of the residence time of the drug in the oral cavity beyond 2 minutes.[6] Specifically, drinking water after 2 minutes post-sublingual administration has a minor impact on the pharmacokinetic profiles of asenapine. And, water intake at 5 minutes post-sublingual administration showed only 10% reduction of AUC, and there was no change in exposure after longer time. Furthermore, drinking water at only 2 minutes post-sublingual administration had no visible effect on $T_{max}$.[6] The possible reason for these rather unexpected observations is that fast partition was achieved between drug in solution and mucosal membrane, so no further absorption occurred even the residence time was longer. Because of these results, patients are only instructed to not eat or drink for 10 minutes after administration of asenapine sublingual tablets.

Although patients are instructed to place the tablet under the tongue when taking

## FIGURE 2




**Plasma concentration-time profiles comparing human PK of vardenafil for the 10-mg ODT (without water intake) vs. 10-mg Levitra (with water intake). (Data were obtained from Staxyn NDA file[13])**

sublingual tablets, deviation from this instruction could occur in practice. Some patients may allow the tablet to dissolve on the top of the tongue or place the tablet buccally. Such deviations from the instruction could theoretically alter the pharmacokinetics considering different permeability and thickness across various mucosal tissues in oral cavity. Hence, it is important to understand the effect of different absorption sites (sublingual, supralingual, or buccal) on clinical pharmacokinetics of an intraoral dosage form. The in vivo results showed that asenapine exposure was the highest with buccal administration, followed by sublingual, and the lowest from the supralingual route.[7] However, the differences in the pharmacokinetics between buccal and sublingual administration were minor (<20%) and were considered to be of limited clinical relevance. Similarly, supralingual administration was bioequivalent to sublingual administration based on AUC. Tolerability and safety studies were also performed and not affected by variability of placing tablet on different mucosal tissues. These results demonstrated that although sublingual administration is the recommended dosing route, administration at different intraoral sites has no clinically relevant impact on asenapine pharmacokinetics.[7]

The effect of food on pharmacokinetics was also assessed for the sublingual tablets of asenapine. Because asenapine is primarily absorbed in the oral cavity, food intake is not expected to affect its absorption phase when dosed sublingually. However, asenapine is a high-clearance compound, and its pharmacokinetics may be affected by elevated liver blood flow due to the intake of a high-fat meal. The clinical results showed that mean asenapine exposure was approximately 20% lower after intake of a high-fat meal prior to dosing. As the food effect on asenapine exposure was small, it was not considered as clinically relevant. Therefore, no additional food restrictions are required during asenapine dosing except for avoidance of eating and drinking for 10 minutes post-administration to ensure optimal absorption in the oral cavity.[8]

### Enhancement of Drug Delivery - Zolpidem Sublingual Tablets (Intermezzo®)

Zolpidem is a nonbenzodiazepine hypnotic agent for the short-term treatment of insomnia. Zolpidem has rapid and good oral absorption, and the absolute oral bioavailability is 70% in human with moderate first-pass metabolism. Oral tablets of zolpidem tartrate are available on the market under the trade name of Ambien®. Considering fewer disturbances were preferred for insomnia patients when taking medicines, several intraoral dosage forms (no need to dose with water) were developed and approved in recent years. Oral spray of zolpidem tartrate, Zolpimist®, was approved by the FDA in 2008. Later, Edluar® (zolpidem tartrate sublingual tablet, 5 mg and 10 mg), received FDA approval in 2009. In 2011, lower doses of zolpidem tartrate sublingual tablets (1.75 mg and 3.5 mg), Intermezzo®, received FDA approval as well. Both Zolpimist and Edluar were developed for the treatment of insomnia with sleep initiation difficulties while Intermezzo was developed for the treatment of insomnia when middle-of-the-night awakening is followed by difficulty returning to sleep.

In addition to the advantage in patient convenience and/or minimal disturbance to sleep, intraoral dosage forms of zolpidem also provide desirable pharmacokinetic and pharmacodynamic benefits in comparison to

the conventional oral tablet. The latest FDA-approved zolpidem tartrate sublingual tablets (Intermezzo) are a good example. A relative bioavailability study was conducted to compare bioperformance between the sublingual tablets and the conventional immediate-release oral tablets. Although both $C_{max}$ and $AUC_{0\text{-}inf}$ values were similar between the two dosage forms, a faster rise of PK profile was observed after sublingual administration compared to the normal oral dosing (Figure 1). The partial area under the curve up to 20 minutes ($AUC_{0\text{-}20min}$) was three-fold greater for sublingual administration compared to oral administration (Table 1). The greater $AUC_{0\text{-}20min}$ value indicated the contribution from rapid transmucosal absorption in the oral cavity for the sublingual tablet compared to Ambien.[9] It is worth to note that although sublingual administration provides intraoral absorption, bioequivalence is achieved between oral and sublingual administration of zolpidem. This outcome is largely due to good intestinal absorption of zolpidem and high bioavailability achieved from the oral route.

Most importantly, several PD studies demonstrated that sublingually administrated zolpidem has a significant earlier sleep initiation as compared to oral zolpidem in both healthy and insomnia patients.[10,11] The sublingual formulation significantly shortened latency to persistent sleep (LPS), sleep onset latency (SOL), and latency to stage 1 (ST1L) in comparison to oral zolpidem. It indicated that transmucosal absorption of zolpidem in the oral cavity could translate into faster onset of action compared to the conventional oral tablet. Regarding next-day residual effect, sublingual administration showed similar or less side effect in the Digit-Symbol Substitution Test (DSST) compared to the oral tablet. Both favorable efficacy and safety profiles showed benefits of Intermezzo to differentiate from the previously approved oral product.[9] Similarly, Zolpimist (oral spray of zolpidem), also showed faster intraoral absorption and early onset of action compared to Ambien.[12]

Because sublingual administration of zolpidem resulted in significant transmucosal absorption, the effect of residence time was evaluated in clinical study using different swallowing times. Patients were separated into three groups, which swallowed every 2 minutes, every 5 minutes, or swallowed once at 10 minutes post-administration. As expected, the extent of absorption from swallowing every 2 minutes appears to be less than that from swallowing every 5 minutes. Interestingly, the PK results of swallowing every 5 minutes were comparable to that of swallowing once after 10 minutes.[9]

Regarding food effect, food significantly lowers bioavailability of Intermezzo compared to that under fasting conditions. $C_{max}$ is decreased by approximately 38%, and $AUC_{0\text{-}t}$ is decreased by 19% following administration with food, while $T_{max}$ is increased from 1 hour in the fasted state to around 3 hours in the fed state.[9] The observed food effect for Intermezzo is similar to oral products (Ambien). Based on this result, Intermezzo is instructed not to be administered with or immediately after a meal.[9]

The example of Intermezzo illustrates that intraoral delivery can enhance both pharmacokinetic and pharmacodynamic profiles of a drug, while bioequivalence is demonstrated between the conventional oral tablet and the sublingual tablet. As a matter of fact, this approach has been served as an effective way for product life cycle management.

## Improvement of Patient Convenience - Vardenafil Orally Disintegrating Tablets (Staxyn®)

Vardenafil hydrochloride is a phosphodiesterase type-5 (PDE5) inhibitor for the treatment of erectile dysfunction (ED). Its oral dosage formulation, film-coated immediate-release tablets (Levitra) was approved by the FDA in 2003. Vardenafil showed rapid oral absorption with >90% drug almost entirely recovered in feces using [$^{14}$C] vardenafil. Due to extensive first-pass metabolism, most radioactivity was from its metabolites, and the absolute oral bioavailability of Levitra is 15%.[13] A 10-mg orally disintegrating tablet of vardenafil (Staxyn®) was developed and subsequently approved by the FDA in 2010. In general, ODTs are intended for placement on the tongue where they disintegrate and dissolve in saliva, and then swallowed. The GI tract is usually considered as the major absorption site for most ODT formulations; however, there are a few exceptions where transmucosal absorption plays a dominant role for drugs that have extensive first-pass metabolism, for instance Zelapar® ODT.[14] The objective of vardenafil ODT development was to develop a formulation that allows patients to take it in a discreet manner (without water), thus potentially improving convenience to the patients.

As usual, the initial development strategy was to demonstrate bioequivalence of the ODT with the already approved film-coated tablets as this approach potentially allows the fastest regulatory approval under the 505(b)(2) application. However, compared to Levitra, the $C_{max}$ and AUC of vardenafil after administration of the ODT formulation (without water intake) increased by 15% and 44%, respectively, in healthy male volunteers (Figure 2). For ED patients, the $C_{max}$ was somewhat lower (8%), but AUC was still greater by 29% relative to Levitra.[13] Possibly due to a slower intraoral absorption compared to GI absorption, the $T_{max}$ of vardenafil ODT right shifted from 0.75 hours to 1.5 hours (Table 1). The increased bioavailability of the ODT was attributed to transmucosal absorption in the oral cavity that bypasses the first-pass metabolism. In order to gain mechanistic understanding of the absorption process, a clinical study was conducted to measure the absolute amount of vardenafil absorbed in the oral cavity. Healthy subjects were asked to hold a 10-mg vardenafil solution in their mouths for 15 minutes without swallowing. Subsequently, they expelled the solution and rinsed their mouths with 20 mL of water five times. The mouth rinses were collected and analyzed to estimate intraoral absorption.[15] The relative bioavailability (ratio of AUC values) after sublingual administration was 24.6 % compared to the oral administration (control group) of vardenafil solution. After subtracting the amount of drug recovered in saliva and rinsing water, 8% of the 10-mg dose of vardenafil was absorbed in the oral cavity.[15] Considering only 15% of vardenafil was orally bioavailable at the same dose, the amount of intraoral absorption (0.8 mg) led to an increase of bioavailability via bypassing of first-pass metabolism to some extent.[15] Because Staxyn is not bioequivalent to Levitra, the two dosage forms are not interchangeable.

As the ODT formulation showed suprabioavailability, clinical studies to demonstrate its efficacy and safety were performed in two Phase III studies. Staxyn was significantly superior to placebo in all efficacy parameters assessed, and a retrospective analysis showed it has a rapid onset of action comparable with that of Levitra.[16] Furthermore, the safety data were in line with that already known for Levitra, indicating a similar safety profile.

The effect of dosing with and without water was also evaluated as part of vardenafil ODT development. The results indicated that dosing without water could result in a significantly higher exposure than that of dosing with water. The systemic exposure (AUC) of vardenafil ODT formulation was decreased by 29 % when the ODT was swallowed with water. This is primarily due to less intraoral absorption occurring after dosing with water, thus the labeling indicates that the dose should be administered without water. For the ODT formulation, food intake (high fat, high calorie) reduced the $C_{max}$ of vardenafil by ~ 35%, while the AUC of vardenafil was not significantly affected. Therefore, it is concluded that the ODT formulation can be administrated regardless of food intake.[15]

Vardenafil ODT is a unique formulation that differentiates from the existing film-coated tablet by providing a favorable PK profile (suprabioavailability), similar PD effect, and preferred patient convenience. In addition to benefit patients that have difficulty in swallowing tablets, the small ODT size and the award-winning burgopak slider pack made it discreet to carry and take vardenafil compared to the conventional oral tablet.

## CONCLUSIONS

In summary, a selective review of recently approved intraoral-associated products highlighted the importance and opportunities of utilizing the intraoral route to enable or enhance drug delivery through modulation of pharmacokinetic profiles, which results in an improved efficacy or patient convenience. Increased bioavailability, faster onset of action, and improved patient convenience represented three major scenarios that intraoral delivery is superior to conventional oral delivery from a clinical pharmacokinetic perspective. Furthermore, compared to oral delivery, intraoral administration showed some unique biopharmaceutical features, such as effects of water intake and saliva swallowing, administration site within oral cavity, and food intake. The examples described in this review have showcased that intraoral delivery can be effectively used for the development of a new chemical entity (NCE), as well as be creatively applied to product life cycle management to differentiate from the existing products. ◆

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**Dr. Zhen Yang** is a Senior Scientist at Merck. As a member of the Biopharmaceutics group, he supports biopharmaceutical evaluation of oral formulations at various clinical development stages. His areas of interest focus on oral, intraoral, and intranasal delivery development and pharmacokinetics. Prior to Joining Merck, Dr. Yang worked at USA Medical Toxicology as a Laboratory Supervisor. He earned his BS in Pharmaceutics from China Pharmaceutical University, his MS from Shanghai Institute of Pharmaceutical Industry, and his PhD in Pharmaceutical Science from University of Houston.

**Dr. Yunhui (Henry) Wu** is currently a Director of Biopharmaceutics in Pharmaceutical Sciences & Clinical Supply in Merck Research Laboratories (MRL). Dr. Wu's research activities have spanned from drug discovery, preclinical and clinical formulation development, and life-cycle management. Dr. Wu joined MRL at West Point, PA, in 1996. He leads a group of scientists who evaluate biopharmaceutical performance of clinical IR/CR formulations of global development candidates using various in vivo, in vitro, and in silico models. His group also conducts rapid feasibility assessment of alternative drug delivey, including intraoral, intranasal, topical, transdermal, ocular, and injectable routes. Dr. Wu earned his BS in Chemistry from University of Science & Technology of China, his MS in Medicinal Chemistry from Shanghai Institute of Pharmaceutical Industry, and his PhD in Organic Analytical Chemistry from New York University.

# Executive Summary

**Ron Squarer**
*Chief Executive Officer*
*Array BioPharma Inc.*

# Array BioPharma: Steadily Moving to Late-Stage Development, Preparing for Commercialization

Array BioPharma Inc. is a biopharmaceutical company focused on the discovery, development, and commercialization of targeted small molecule drugs to treat patients afflicted with cancer. Seven Phase 3 or pivotal studies are already in progress, or are planned to begin within the coming months. These programs include Array's wholly-owned hematology drug, filanesib (ARRY-520) for multiple myeloma (MM), and two cancer drugs, selumetinib partnered with AstraZeneca and binimetinib (MEK162) partnered with Novartis.

First, Array is developing filanesib in combination with the novel proteasome inhibitor Kyprolis (carfilzomib). To support this, Array is already advancing a Phase 2 trial of Kyprolis plus filanesib. This study will be followed later this year with a Phase 3 registration trial with this same combination. Array is also investigating the activity of single-agent filanesib in a global Phase 2 trial, which should start enrolling patients over the next couple of months.

Second, Array's binimetinib team continues to enroll patients in a Phase 3 trial in low-grade serous ovarian cancer. Array is also supporting Novartis with its two Phase 3 trials in NRAS-mutant melanoma and BRAF-mutant melanoma. NRAS-mutant melanoma represents the first potential marketed indication for binimetinib, with a projected regulatory filing from the NRAS-mutant melanoma study estimated by Novartis to be in 2015. And AstraZeneca is rapidly advancing three pivotal trials with selumetinib in KRAS-mutant non-small cell lung cancer, differentiated thyroid cancer and metastatic uveal melanoma. Uveal melanoma represents the first potential marketed indication for selumetinib, with an estimated primary completion date for the trial of mid-2015.

Finally, Array and its partners continue to develop a rich pipeline of earlier-stage assets across therapeutic areas, including most notably, ARRY-614, a Phase 1 p38/Tie2 inhibitor designed to treat myelodysplastic syndrome (MDS) patients, and ARRY-797, a Phase 2 p38 inhibitor advancing in a small study in patients with LMNA-related dilated cardiomyopathy (DCM), a serious, genetic cardiovascular disease, believed to be caused by a mutation of the lamin A/C gene which leads to cardiovascular death, heart transplant or major cardiac event. Array anticipates having preliminary results from this study by the end of 2014.

With a deep pipeline of clinical and preclinical candidates, Array is focused on two strategic objectives: First, Array will selectively develop and commercialize drugs that address an unmet medical need for patients fighting cancer. As filanesib advances into pivotal studies, Array will begin to build a hematology-focused sales and marketing organization to prepare for product launch and commercialization. Second, Array will identify best-in-class development and commercialization partners for its non-core assets to fully maximize the potential of those drugs. As evidenced by its existing collaborations with AstraZeneca, Celgene, Genentech, InterMune/Roche, and Novartis, among others, Array's drugs draw interest from the most successful pharmaceutical companies in the world. Drug Development & Delivery recently interviewed Chief Executive Officer Ron Squarer about the company's pipeline and evolution into a fully integrated, commercial-stage biopharmaceutical company.

## Q: What makes Array's business model unique? How have you been able to be so successful in the drug development arena?

**A:** Array was founded in 1998 as a discovery phase, small molecule-focused company. Its platform was designed to accelerate the discovery of novel chemical entities by integrating protein structure-based design, target-driven combinatorial chemistry and using proprietary software to predict drug properties that would decrease attrition rates in drug development.

Array's business model emphasized the design and creation of proprietary screening libraries and other uniquely designed collections of compounds that would speed the drug discovery process. Collaborative and wholly-owned discovery programs focused on novel therapeutic targets. These targets were chosen based on the linkage to human clinical data (i.e., genetic mutations) that drive certain disease conditions and novel targets within signaling pathways that have been validated by injectable protein therapeutics.

Funding from partners, proprietary tools, and expertise gained through multiple discovery programs allowed Array to build a fully integrated pharmaceutical company over time. This approach has proven successful. In Array's 15-year history, 18 molecules have advanced into human testing and development. Of these, 15 remain in development, ten are currently in Phase 2 or 3 trials, having stood the test of early clinical evaluations. Most importantly, the non-dilutive fundraising from our strategic partnerships has allowed Array to retain full global ownership of important clinical-stage assets we believe show great promise in addressing significant unmet medical need in diseases like MM and MDS.

## Q: Which of Array's drugs are advancing in Phase 3 and pivotal trials?

**A:** Three programs are advancing in Phase 3 trials: our wholly-owned hematology drug, filanesib for multiple myeloma, and two partnered cancer drugs, selumetinib and binimetinib. Filanesib is a highly selective, targeted KSP inhibitor with a mechanism of action distinct from currently available drugs to treat MM such as immunomodulatory drugs (IMiDs) and proteasome inhibitors. Across multiple studies, filanesib has demonstrated activity in heavily pre-treated MM patients, with a consistent safety profile including no drug-induced peripheral neuropathy and limited non-hematologic toxicity. Adverse events are generally limited to transient, non-cumulative and predominantly asymptomatic myelosuppression (decreases in blood counts) when supportive measures are used. We have further shown that alpha-1 acid glycoprotein (AAG) is a potential patient selection marker for filanesib. AAG is being further investigated in our pivotal trials, and could represent the first patient selection marker for a drug in myeloma.

Based on the strength of data from ongoing or completed clinical trials, and recent discussions with the Food and Drug Administration (FDA), Array is developing filanesib in combination with the novel proteasome inhibitor Kyprolis. To support the potential approval of filanesib, our development plan includes three current or future trials:

1. The FACTOR trial, which is expected to initiate in mid-2014, will be a global Phase 3 study comparing Kyprolis plus filanesib to Kyprolis alone in several hundred patients with relapsed and refractory multiple myeloma (RRMM). The primary endpoint of this trial is Progression Free Survival (PFS). There are more than 70,000 patients with RRMM in developed countries, and if successful, this would represent the first new drug to be combined with Kyprolis in patients who have previously been treated with Revlimid (lenalidomide) andVelcade (bortezomib).

2. A randomized Phase 2 trial comparing Kyprolis plus filanesib versus Kyprolis alone in 75 RRMM patients with PFS as the primary endpoint. This trial, which initiated in November 2013, is designed to confirm the dose and schedule of the combination of Kyprolis and filanesib observed in the Phase 1 Kyprolis plus filanesib trial at MD Anderson. This trial will further provide important safety and activity data to support the Phase 3 trial, including data to support AAG as a marker for patient selection in the combination of Kyprolis plus filanesib. In addition, published results from this trial should support Phase 3 enrollment.
3. The AfFIRM trial, a global Phase 2 study with single agent filanesib in 160 patients with RRMM, including both low- and high-AAG patients. Trial initiation is planned for mid-2014. The primary endpoint will be ORR in patients with low levels of AAG. This trial is also designed to support future regulatory submissions, will include important safety and pharmacology data, and will also validate the use of AAG.

Binimetinib, our MEK inhibitor partnered with Novartis, is advancing in three Phase 3 trials: NRAS-mutant melanoma, low-grade serous ovarian cancer and BRAF-mutant melanoma. NRAS-mutant melanoma represents the first potential indication for binimetinib, with a projected regulatory filing from the NRAS-mutant melanoma study estimated to be in 2015. The Novartis partnership is particularly important for Array, given the economics of the agreement, which includes double-digit royalties and co-detailing opportunities.

Selumetinib, our MEK inhibitor partnered with AstraZeneca, is advancing in three pivotal trials: KRAS-mutant advanced or metastatic NSCLC, differentiated thyroid cancer and metastatic uveal melanoma. Patients with KRAS NSCLC, which is approximately 25% of the NSCLC population, or 400,000 patients globally, represent the most significant area with unmet medical need. Uveal melanoma represents the first indication for selumetinib, and the estimated primary completion date for the trial is mid-2015.

## Q: Why do you believe these drugs represent significant revenue opportunities?

**A:** For every drug in our development pipeline, we believe we have identified an unmet need in healthcare: either a patient population that has few or no additional alternative options to current treatments, or an entirely new mechanism of action that represents a significant benefit over current therapies.

Our proprietary pipeline is focused on targeted drugs that treat cancer. We believe there is a substantial opportunity in creating drugs for these diseases to meet demand from the medical community for targeted therapies that not only treat the underlying disease and control symptoms, but do so more effectively and/or more safely than drugs that are currently available. We believe future patient care will improve with the use of screening to select targeted therapies for more effective disease treatment. Also, clinical trials aimed at well-defined patient populations may show improved response rates and may thereby increase the chances for approval with regulatory agencies, such as the FDA. This approach may result in a greater number of marketed drugs each aimed at a smaller subset of patients.

Filanesib, a highly selective, targeted KSP inhibitor with a mechanism of action distinct from existing therapies, is being developed to treat patients with multiple myeloma. Multiple myeloma is a cancer of the plasma cells in the bone marrow. For patients with multiple myeloma, as the number of malignant plasma cells increases and dominates the bone marrow, normal blood cell production is disrupted. The growth of malignant plasma cells also destroys normal bone tissue and causes pain and weakness in the bones. Frequently, multiple myeloma cells also produce a monoclonal antibody also called “paraprotein” or “M-protein” which can cause kidney problems and weaken the immune system.

Multiple myeloma is the second most common hematology malignancy in the US with over 24,000 newly diagnosed patients annually, and over 125,000 patients living with the disease in the US, EU, and Japan. Despite

advancements with new treatments, the vast majority of patients progress and die from multiple myeloma leaving an unmet need for novel agents which can provide benefit in combination with, and after existing therapies have failed.

Our partnered programs likewise target high-potential markets, such as lung cancer, melanoma, and thyroid cancer.

## Q: What other drugs in your longer term pipeline are you excited about?

**A:** ARRY-797 is an exciting compound with the potential to be an effective treatment for patients with a serious cardiovascular disease called LMNA-related dilated cardiomyopathy (DCM). Currently, there are no effective specific treatment options to alter the course of this rare degenerative genetic disease. By age 45, patients with LMNA-related DCM have an event free survival of only 31% despite conventional heart failure therapies (events defined as cardiovascular death, transplant or major cardiac event). In vivo studies of ARRY-797 in models of LMNA-related DCM demonstrated significant improvements in heart function, reversal of cardiac remodeling, general well-being and survival. Under a physician-sponsored, single-patient IND, a patient has been receiving ARRY-797 for one year. The patient has had echocardiographic improvements and the drug has been well-tolerated. Based on these encouraging data and discussions with the FDA, Array is enrolling a 12-patient Phase 2 study to explore the effectiveness and safety of ARRY-797 in patients with LMNA-related DCM. The primary endpoint is the change from baseline in a 6-minute walk test at 12 weeks. We anticipate having preliminary results from this study by the end of 2014.

## Q: What is your vision for the company?

**A:** All of Array's resources are focused right now on bringing our current development programs to commercialization. We believe our wholly-owned programs could represent significant revenue opportunities, as filanesib addresses a patient population struggling with significant unmet medical need and no good alternative treatments. Likewise, for the partnered portfolio, we have favorable economic agreements that will provide additional milestone payments over the coming years, as well as royalties once commercialization is achieved. With all of that, we can build a self-sustaining pharmaceutical development company once key drugs in our pipeline come to market.

## Q: How will you build a sales force to bring your wholly owned portfolio to market?

**A:** Our internal resources are focused on hematology indications, which is a very discrete market opportunity that can be served without the need to build a big pharma-sized sales force. Additionally, we feel confident about the benefit our drugs will provide to patients and physicians, so there will be compelling reasons to use our products. For these reasons, we believe strongly that we have the ability to quickly build out our team to successfully commercialize our drugs. The other drugs in our portfolio would be partnered with a company that has a sales force in place, so that would enable us to conserve resources. ■

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# Traffic Light Decision-Making

By: John A. Bermingham

All of us have faced decisions in which, if we make the right decision, we are a hero, and if we make the wrong one, we are a bum. This is particularly distressing when it comes to making a business decision with a result that can either make you a hero or get you fired.

There are three positions that you can take in making a business decision: 1) make no decision (worst); 2) make the wrong decision (better than No. 1 but still not that great); and 3) make the right decision (best). This is when traffic light decision-making comes into play.

A red traffic light means STOP. Don't do anything and remain in place. When this is your position on making a decision, you are not going anywhere. With every decision, there is an element of risk, and your responsibility is to minimize that risk. But freezing in place means you are automatically wrong, not making any progress, and worse, it will most probably come back to haunt you at a later date. Sometimes a no-go decision is the right decision, but this is different from freezing in place.

A green traffic light means GO. This means you motor ahead with a go decision regardless of the risks. The danger is that you have not weighed all of the risks relative to the rewards. This type of decision without checking the "cross traffic" can mean a real problem for you. It pays to check both ways before proceeding.

A yellow traffic light means CAUTION - be prepared to STOP or get ready to GO. Caution is a good thing, but not when it causes you to freeze in place. Assessing the risks and rewards is very wise when you are making a business decision, but you must be working toward the right decision, be it a go or no-go.

I believe sound business decisions should begin with the yellow caution light. Careful assessment of all of the factors surrounding what will become your final decision is a must. Soliciting the opinions of others is very helpful as long as you can separate the objective thinking and opinions from the political ones. Most important is communicating openly with your boss.

What often freezes people into place when having to make a risky decision is the fear of being fired if the wrong decision is made. However, if you make your boss part of that decision, or make he or she very aware of what your decision is and why, then you minimize the risk to yourself if things go south. This is part of the yellow caution light approach.

Remember, if you take the red light approach, then you freeze in place and are automatically wrong. If you take the green light approach, then you increase the odds of you being wrong. Either way, you are at higher risk to do yourself and your career damage.

The yellow caution light approach allows you to take responsible risk, which is what a good decision-maker always does. ◆



## BIOGRAPHY

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


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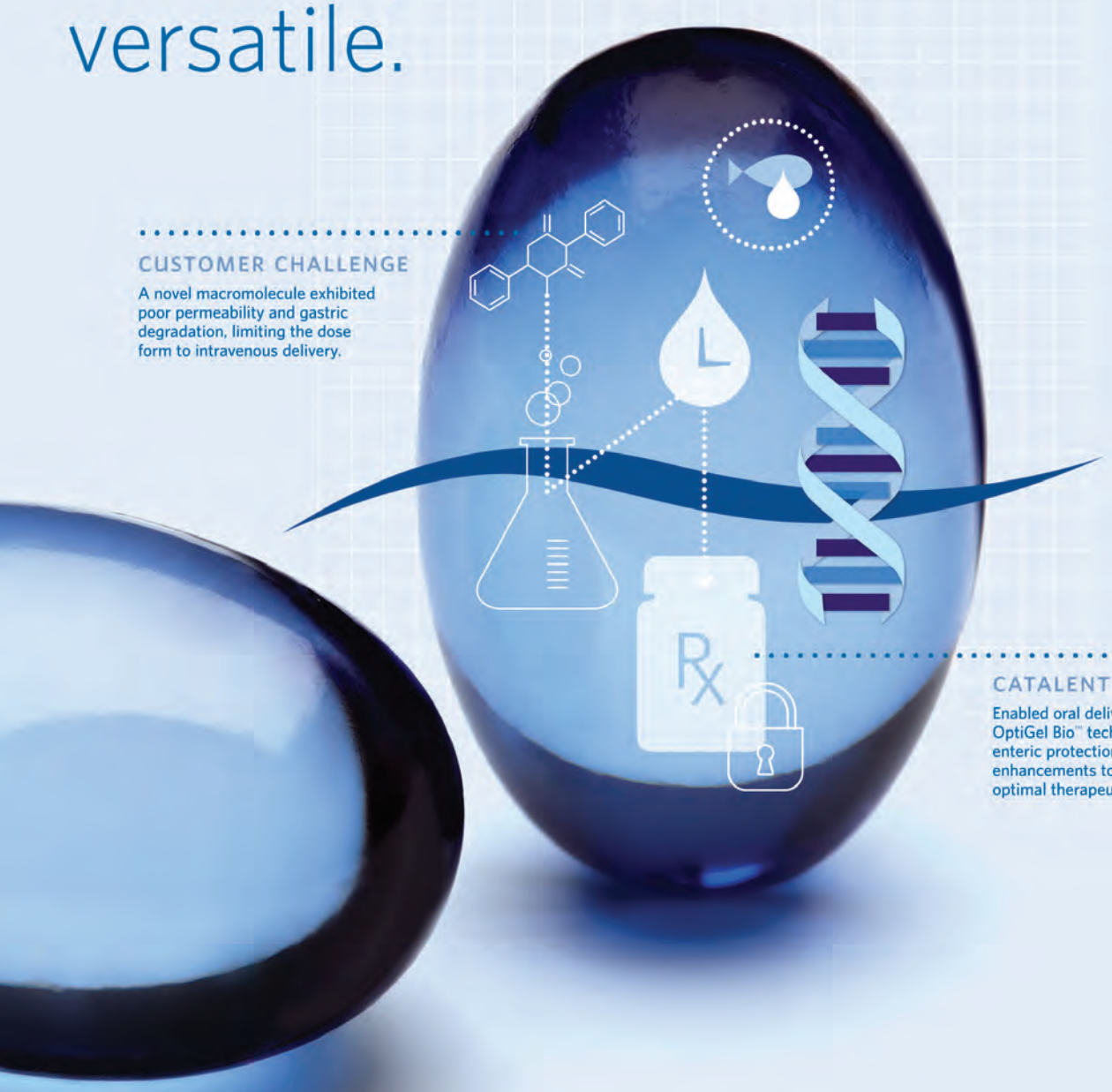


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