Drug Development & Delivery

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Analytical Testing: A Critical Element

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

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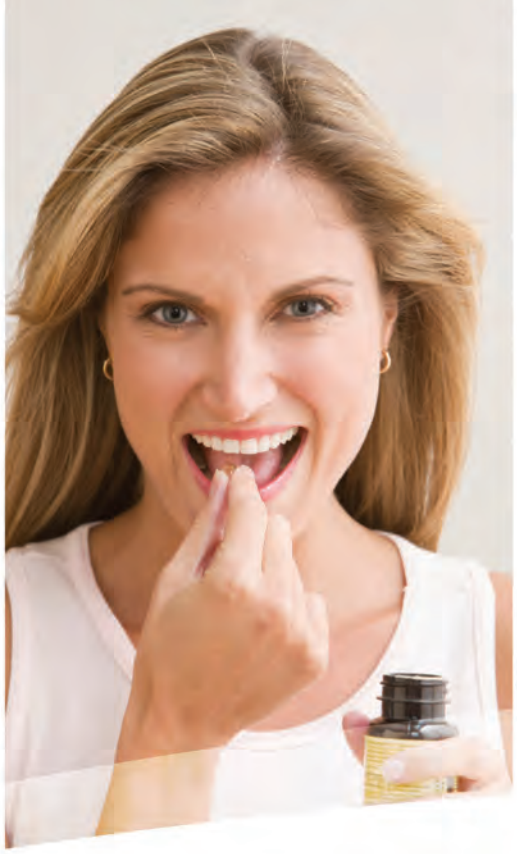

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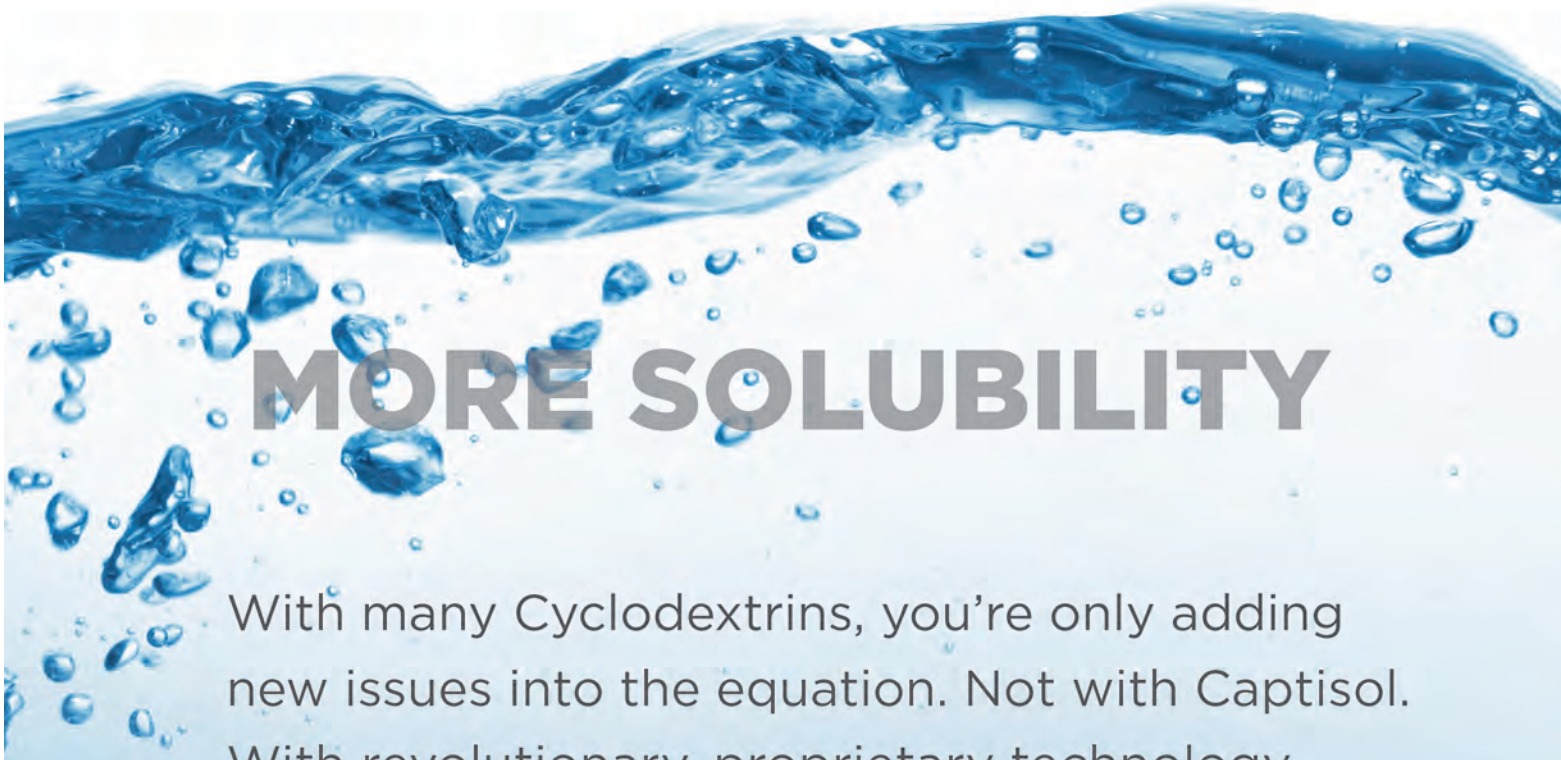

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A Critical Element

"The importance of analytical testing is evident by the growth of the CRO sector. ISR's report, 2014 CRO Market Size: 2012-2018, points out that the CRO market was projected to reach $23.6 billion in 2014. With a 7.9% CAGR from 2014 to 2018, CROs are benefiting from the increased rate of outsourcing and increasing R&D budgets from biotech and specialty/generics companies."

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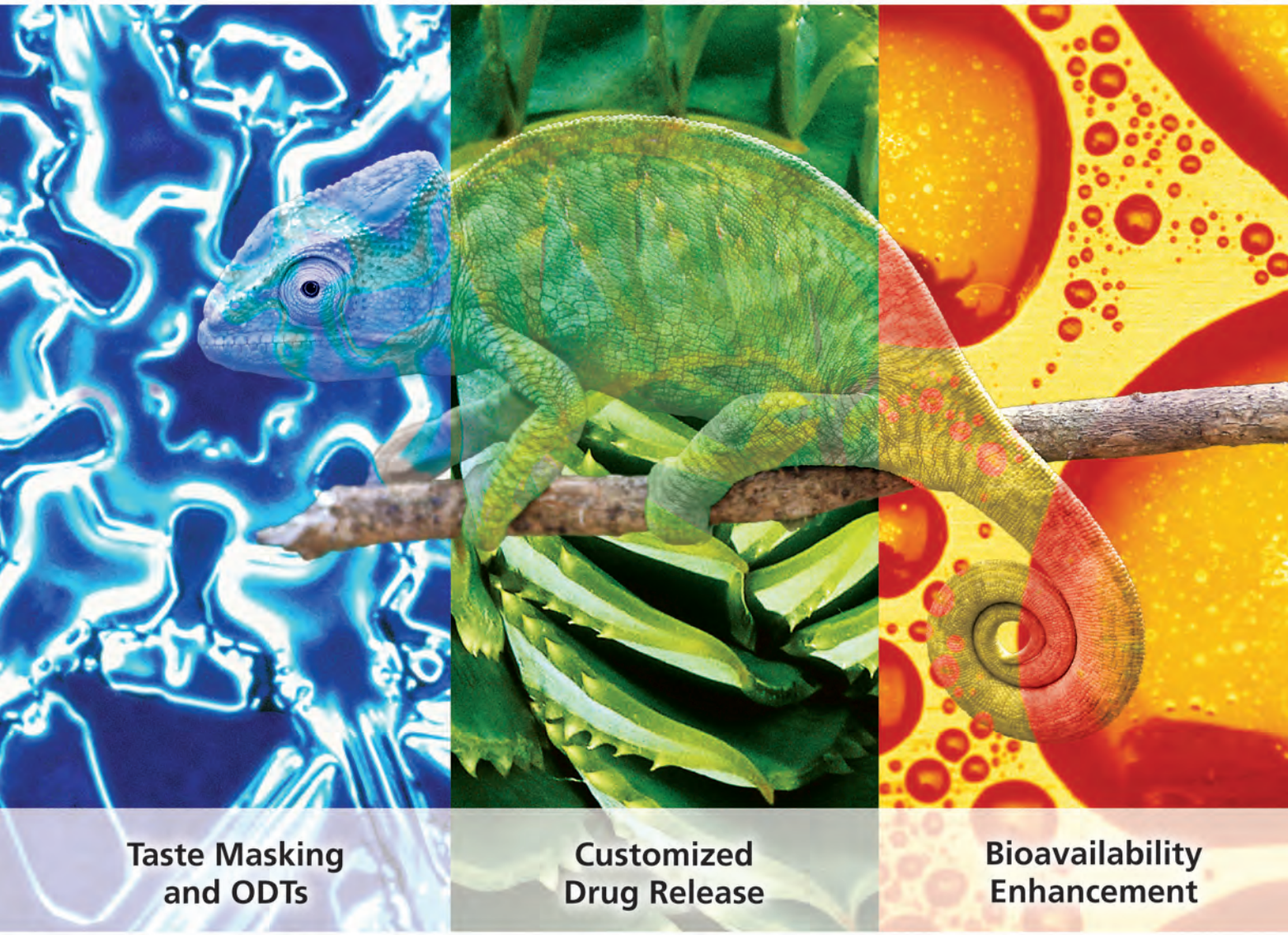

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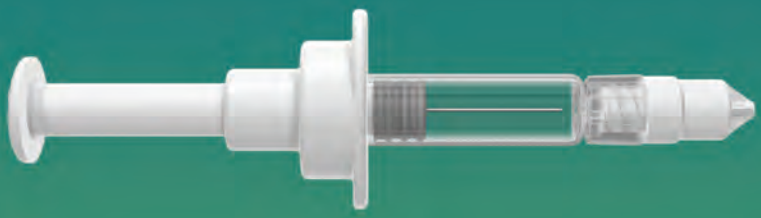

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Gilead Announces Amended Agreements With Janssen

Gilead Sciences, Inc. recently announced an expansion to its agreement with Janssen R&D Ireland for the development and commercialization of a new once-daily single tablet regimen containing Gilead's tenofovir alafenamide (TAF) and emtricitabine, and Janssen's rilpivirine. The original agreement was established in 2009 for the development and commercialization of Complera, marketed as Eviplera in the European Union, which combines tenofovir disoproxil fumarate, emtricitabine and rilpivirine in a once-daily tablet. Gilead will initiate Phase III studies of emtricitabine/rilpivirine/TAF in the coming months. Pending the product's approval, Gilead will be responsible for the manufacturing, registration, distribution, and commercialization of the regimen in most countries, while Janssen will distribute in approximately 17 markets.

TAF is a novel nucleotide reverse transcriptase inhibitor that has demonstrated high antiviral efficacy at a dose 10 times lower than Gilead's Viread (tenofovir disoproxil fumarate), as well as an improved renal and bone safety profile.

"We believe that TAF's efficacy and safety advantages may make it a strong backbone of new fixed-dose combinations and single tablet regimens," said Norbert Bischofberger, PhD, Executive Vice President, Research and Development and Chief Scientific Officer, Gilead Sciences. "Gilead is pleased to continue its collaboration with Janssen to bring improved treatment options to patients living with HIV."

Gilead and Janssen also have amended a licensing agreement for the development and commercialization of a once-daily single tablet regimen for HIV containing Gilead's TAF, emtricitabine and cobicistat, and Janssen's darunavir. Under the amended agreement, Janssen will be responsible for further development of the regimen and, subject to regulatory approval, the manufacturing, registration, distribution, and commercialization of the product worldwide.

Actavis Confirms Receipt of Complete Response Letter

Actavis plc recently confirmed it has received a complete response letter from the US FDA for its New Drug Application (NDA) for the fixed-dose combination (FDC) of nebivolol and valsartan for the treatment of hypertension.

"Although we are disappointed in the receipt of a complete response letter, Actavis remains committed to bringing treatments to market that address the significant public health issue of cardiovascular disease," said David Nicholson, Senior Vice President, Actavis Global Brands R&D. "Bystolic is a safe and effective option that is commonly used in combination with other antihypertensive medications to help patients reach blood pressure treatment goals. We will review the complete response and determine the appropriate next steps."

Data submitted to the FDA in support of approval of this NDA included a single Phase III randomized, controlled trial of approximately 4,100 patients. In this pivotal efficacy study, the FDC of nebivolol and valsartan met its primary and key secondary endpoints, demonstrating statistically significant reductions from baseline in diastolic and systolic blood pressure at 8 weeks in patients with hypertension, versus both nebivolol alone and valsartan alone, including either monotherapy agent at its highest doses. The rate of patients experiencing at least one treatment-emergent adverse event was similar across treatment groups and placebo. In addition, a 52-week open-label safety study was conducted to describe the long-term safety profile of the nebivolol/valsartan combination. As of 2014 data, the worldwide exposure of each component drug has been ~40 million patient-years for nebivolol and ~180 million patient-years for valsartan.

Angiochem Publishes Data for Treatment of Brain Metastases

Angiochem recently announced that ANG4043, a peptide-monoclonal antibody (mAb) conjugate, entered the brain at therapeutic concentrations, resulting in significantly prolonged survival in mice. The antibody is directed against HER2, which is the protein targeted by Herceptin. Because the mAb is conjugated to Angiopep-2, it is recognized by the LRP1 receptor and takes advantage of a receptor-mediated transcytosis mechanism to cross the BBB. This proprietary technology has been clinically validated with ANG1005, a peptide-paclitaxel conjugate currently in Phase II studies. The data published in Molecular Cancer Therapeutics shows that Angiochem's technology to cross the BBB is applicable to biologics such as mAbs.

In the published results, ANG4043, a Novel Brain-penetrant Peptide-mAb Conjugate, is Efficacious against HER2-positive Intracranial Tumors in Mice, Angiochem researchers show that ANG4043 binds LRP1 receptors while retaining the pharmacological properties of the native anti-HER2 mAb, including high affinity HER2 binding and anti-proliferative activity in HER2-expressing cells. In vivo, ANG4043 achieves therapeutic brain concentrations in healthy mice and in mice bearing intracranial HER2+ tumors, which are targeted by ANG4043. In this HER2+ intracranial tumor model, treatment with ANG4043 (15 mg/kg IV, twice-weekly) increased median survival time by 78% (80 days compared to 45 days for control).

ANG4043 was created by conjugating the Angiopep-2 to an anti-HER2 mAb to bring an effective anticancer therapy to treat HER2+ brain metastases from breast cancer. In a series of in vivo experiments, ANG4043 has demonstrated that it reaches the brain, targets HER2+ tumors, induces intracranial tumor shrinkage, and significantly increases survival in mice that have been intracranially implanted with HER2+ tumor cells. Overall study results of ANG4043 further validate the potential of the applicability of Angiochem technology to create brain-penetrant mAbs.

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ARIAD & Otsuka Announce Co-Development & Commercialization Agreement

ARIAD Pharmaceuticals, Inc. and Otsuka Pharmaceutical Co., Ltd. recently announced they have entered into an agreement for Otsuka to commercialize ARIAD's Iclusig (ponatinib) in Japan and nine other Asian countries and to fund future clinical trials in those countries. ARIAD will lead the completion of the Japanese New Drug Application (NDA) for Iclusig, and Otsuka will file the NDA on behalf of both companies for regulatory approval in resistant and intolerant chronic myeloid leukemia (CML) and Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ALL) in 2015. Iclusig is an approved BCR-ABL inhibitor in the United States, Europe, and Australia.

The agreement provides for Otsuka to receive exclusive rights to market Iclusig in Japan and nine other Asian countries in return for an upfront payment of $77.5 million to ARIAD, a milestone payment upon regulatory approval in Japan for patients with resistant and intolerant Philadelphia-positive leukemias, and additional milestone payments for approval in other indications.

Following approvals in the Territory, Otsuka will conduct sales activities and record sales. ARIAD will also receive a substantial share of net product sales.

ARIAD will continue to fund the completion of its ongoing pivotal trial of Iclusig that will form the basis of the filing for regulatory approval in Japan, while Otsuka will fund additional agreed-upon clinical studies in the Territory. For ARIAD-sponsored global studies that include sites in Japan, Otsuka has the option to contribute to the funding and gain access to the data for use in the Territory.

A joint development and commercialization committee will oversee clinical development and commercialization of Iclusig in the Territory, including approval of any development or commercialization plans. Otsuka will have exclusive commercial rights to Iclusig and will promote it as its sole tyrosine kinase inhibitor in the Territory. In addition to Japan, the other Asian countries that are included in this agreement are China, South Korea, Indonesia, Malaysia, the Philippines, Singapore, Taiwan, Thailand, and Vietnam.

Iclusig is a kinase inhibitor discovered by ARIAD. The primary target for Iclusig is BCR-ABL, an abnormal tyrosine kinase that is expressed in chronic myeloid leukemia (CML) and Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Iclusig was designed using ARIAD's computational and structure-based drug-design platform specifically to inhibit the activity of BCR-ABL. Iclusig targets not only native BCR-ABL but also its isoforms that carry mutations that confer resistance to treatment, including the T315I mutation, which has been associated with resistance to other approved TKIs.

Merck to Acquire Global Biopharmaceutical Company for Billions

Merck and Cubist Pharmaceuticals, Inc. recently announced the companies have entered into a definitive agreement under which Merck will acquire Cubist for $102 per share in cash, which represents a 35% premium to Cubist's average stock price for the most recent 5 trading days (at press time).

Unanimously approved by the boards of directors of both companies, the transaction has an equity valuation of $8.4 billion and will also include $1.1 billion in net debt (based on projected cash balances) and other considerations for a total transaction value of approximately $9.5 billion.

The acquisition of Cubist creates strong fundamental value with return on capital in excess of Merck's hurdle rate within a few years of closing. Merck expects the acquisition to add more than $1 billion of revenue to its 2015 base. While the transaction will be neutral to non-GAAP EPS in 2015, Merck expects it to be significantly accretive to non-GAAP EPS in 2016 and beyond. The acquisition will be accretive to both Merck's sales and earnings growth.

Cubist complements Merck's strategy and the global initiative Merck launched last year, particularly in the area of sharpening its commercial focus on key therapeutic areas that have the potential to deliver the greatest return on investment. With the company's long-standing leadership in anti-infectives as well as its customer-focused operating model, Merck identified the hospital acute care segment as one of the company's key priority areas in which it believes it can have the greatest impact in addressing significant unmet medical needs while delivering the greatest value to customers and society.

Under the terms of the agreement, Merck, through a subsidiary, will initiate a tender offer to acquire all outstanding shares of Cubist Pharmaceuticals, Inc. The closing of the tender offer will be subject to certain conditions, including the tender of shares representing at least a majority of the total number of Cubist's outstanding shares (assuming the exercise of all options), the expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act and other customary conditions. Upon the completion of the tender offer, Merck will acquire all remaining shares through a second-step merger without the need for a stockholder vote under Delaware law. The companies expect the transaction to close in the first quarter of 2015.

Cubist Pharmaceuticals, Inc. is a global biopharmaceutical company focused on the research, development, and commercialization of pharmaceutical products that address significant unmet medical needs in the acute care environment. Cubist's corporate headquarters is based in Lexington, Massachusetts, with international headquarters located in Zurich, Switzerland.

iTeos Therapeutics Announces License & Collaboration With Pfizer

iTeos Therapeutics SA recently announced a strategic collaboration with Pfizer Inc. pursuant to which iTeos will license to Pfizer rights to iTeos' preclinical compounds targeting Indoleamine 2,3-dioxygenase (IDO1) and Tryptophan 2,3-dioxygenase (TDO2). Pfizer will be responsible for the development and commercialization of IDO1 and TDO2 drug candidates. Additionally, the parties will collaborate to discover and validate new targets that play key roles in the ability of tumors to evade immune responses. These new targets will be shared by iTeos and Pfizer for further independent or collaborative development.

iTeos will receive from Pfizer an up-front payment of € 24 million, plus an equity investment, licensing fees and collaborative funding. Further, iTeos will be eligible to earn potential milestone payments from Pfizer based on the achievement of specific development, regulatory, and commercial milestones across the IDO1 and TDO2 programs, in addition to royalties on sales. iTeos also has the opportunity to earn additional milestone and royalty payments for any of the new target programs that are advanced by Pfizer.

Indoleamine 2,3-dioxygenase (IDO1) and Tryptophan 2,3-dioxygenase (TDO2) are enzymes that break down the amino acid tryptophan. They are expressed in many cancers. Their elevated expression in tumors locally degrades tryptophan, blunting tumor surveillance by the immune system and as such preventing tumor rejection. Specific inhibitors for each enzyme might permit the treatment of a wider variety of tumors, which often express only one of the two enzymes. In tumors that express both enzymes, the combined use of IDO1 and TDO2 inhibitors could reveal complementary benefit for personalized cancer therapy.

Juno Therapeutics Raises IPO Target to $191 Million

Seattle cancer-immunotherapy company Juno Therapeutics recently announced it has upped the target for its pending initial public offering of stock and gave the first indication of its intended pricing.

The company aims to sell up to 9.25 million shares at $15 to $18 each, it said in a filing with the Securities and Exchange Commission. If its underwriters exercise an option to sell another 1.3 million shares, the offering could raise as much as $191 million before costs. Juno would have about 76 million shares of common stock after the IPO, meaning that at the high end of the pricing range, its market capitalization would be roughly $1.4 billion. The offering is expected to price next week, according to IPO tracker Renaissance Capital.

The preliminary prospectus Juno filed in November 2014 outlined plans to raise a maximum of $150 million and gave no pricing details. Investor interest in biotechnology stocks has been strong recently. The Nasdaq Biotechnology Index of 117 companies is up more than 23% since mid-October 2014.

Juno is pursuing several techniques that use genetic engineering to help individual patients' immune-system cells attack cancer cells. It is building on clinical results and technology from its partnerships with the Fred Hutchinson Cancer Research Center, New York's Memorial Sloan Kettering Cancer Center, and Seattle Children's.

Results in small numbers of patients have been strong but the company has yet to begin large-scale trials. Its two most advanced product candidates target patients who have not responded to other treatments for B cell leukemias and lymphomas, which are cancers of the blood and the lymph nodes.

Unilife Signs Long-Term Commercial Supply Agreement

Unilife Corporation recently announced the signing of a worldwide 10-year Commercial Supply Agreement with a global pharmaceutical company for the use of the Depot-ject™ delivery system with an approved ocular injection therapy.

The identity of the pharmaceutical company and its target therapy, which is approved in the US and Europe for the treatment of a high prevalence disease of the retina, will remain confidential at this time to protect the commercial interests of the customer. The customer has entered into this arrangement to support the lifecycle management of this approved therapy, which is administered via intravitreal injection into the eye. Unilife anticipates the commercial availability of Depot-ject with this therapy after a 12- to 24-month process of customization and regulatory approval for the drug-device combination.

Compared to conventional practices, Depot-ject is designed to allow a clinician to precisely deliver the therapy into the eye through an injection to help protect a drug depot. Unilife will begin to generate revenue from the customer program this quarter via an upfront fee and customization payments. Unilife has granted the customer exclusive access to Depot-ject for use with the target drug in the relevant therapeutic area.

Mr. Alan Shortall, Chairman and Chief Executive Officer of Unilife, said "Unilife has created a broad portfolio of ocular delivery systems to enhance the intravitreal injection of ophthalmic therapies. The safety, simplicity, and convenience of our Depot-ject delivery system has significant potential to improve patient care in the delivery of sustained release drug depots, and allow customers to further differentiate their brands of therapy from current or future competition. We are pleased to have signed our first commercial supply agreement within this fast-growing market segment, and look forward to supporting the customer in the rapid conversion of its approved therapy into our Depot-ject delivery system."

The Depot-ject delivery system has been designed to enable the precise placement of a drug depot into the eye with the clinician having full control over the site of implantation. The drug depot implant is contained within the lumen of the needle enabling it to be supplied ready for implantation. Depot-ject has been designed to provide clinician-controlled implantation and needle retraction to help protect the therapy and the eye of the patient. An ergonomic design allows clinicians to implant a therapy using similar steps to an injection.

Insys Therapeutics Receives FDA Orphan Drug Designation

Insys Therapeutics, Inc. recently announced that the US FDA has granted orphan drug designation (ODD) to its Liposome Entrapped Paclitaxel Easy to Use (LEP-ETU) candidate for the treatment of gastric cancer. LEP-ETU is an improved formulation of paclitaxel, a widely used chemotherapeutic agent.

Insys acquired LEP-ETU during its merger in 2010 with NeoPharm. Orphan drug designation is granted by the FDA Office of Orphan Products Development to novel drugs or biologics that treat rare diseases or conditions affecting fewer than 200,000 patients in the US. The designation provides the drug developer with a 7-year period of US marketing exclusivity upon approval, as well as certain financial incentives that can help support its development.

Paclitaxel is an anti-microtubular network agent and is active in a broad spectrum of malignancies. To enhance its poor solubility, paclitaxel is formulated with or bound to a delivery vehicle. Taxol is formulated with ethanol and Cremophor EL, a polyethoxylated castor oil that leads to infusion-related hypersensitivity reactions. In Abraxane, paclitaxel is bound to albumin nanoparticles.

Gastric cancer is the fifth most common cancer in the world, and the third-leading cause of cancer death. In the US, it is estimated that approximately 22,000 people will be diagnosed with gastric cancer in 2014.

Insys Therapeutics is a specialty pharmaceutical company that develops and commercializes innovative drugs and novel drug delivery systems of therapeutic molecules that improve the quality of life of patients. Using its proprietary sublingual spray technology and its capability to develop pharmaceutical cannabinoids, Insys addresses the clinical shortcomings of existing commercial products. Insys currently markets two products, Subsys, which is sublingual Fentanyl spray for breakthrough cancer pain, and a generic version of Dronabinol (THC) capsules. The company's lead product candidate is Dronabinol Oral Solution, a proprietary orally administered liquid formulation of dronabinol. Insys is also developing a pipeline of sublingual sprays, as well as pharmaceutical cannabidiol.

Achillion Shows Potential for Best-in-Disease Regimen

Achillion Pharmaceuticals, Inc. recently announced positive interim results from two studies supporting a short duration, potentially best-in-disease regimen of its proprietary NS5A and nucleotide inhibitors, ACH-3102 and ACH-3422.

"We believe that achievement of 100% SVR4 in 6 weeks in the ACH-3102 proxy study, combined with the high potency and safety demonstrated by ACH-3422, highlights the ability of our exceptional, fully owned portfolio to excel in the HCV market," said Milind Deshpande, PhD, President and Chief Executive Officer of Achillion. "We look forward to initiating in 2015 short duration, pan-genotypic Phase II therapeutic trials to evaluate the doublet of ACH-3102 and ACH-3422, with the ultimate goal of improving patient care and access to treatment."

Achillion announced 100% SVR4 results from the ongoing 6-week trial. This study is an interferon-free, ribavirin-free, Phase II open-label, randomized study to evaluate the efficacy, safety, and tolerability of 6 weeks of 50 mg of ACH-3102 and 400 mg of sofosbuvir, a marketed nucleotide polymerase inhibitor, once daily, in treatment-naïve genotype 1 HCV-infected patients. The primary objective of the study is determination of sustained viral response 12 weeks (SVR12) after completion of therapy.

Eighteen patients were enrolled, including 12 active and six observational patients. Mean baseline HCV RNA viral load was 10 million (7 log10) IU/ml, range 2 million (6.23 log10) - 97 million (7.99 log10) IU/ml, including seven patients with baseline HCV RNA viral load exceeding 6 million (6.78 log10) IU/ml. Of the 12 active patients enrolled, 10 patients were genotype 1a and two were genotype 1b.

Four weeks after the completion of therapy, 100% (n=12/12) achieved SVR4, independent of baseline viral load, gender, and IL28B status. No post-treatment viral relapse has been observed to date. SVR12 results will be reported during the first half of 2015. The combination of ACH-3102 and sofosbuvir was well-tolerated with no serious adverse events, no discontinuations due to adverse events, and no clinically significant laboratory or ECG abnormalities.

Dr. Deshpande further commented "The ACH-3102 Phase II results continue to support the best-in-class profile of our second-generation NS5A inhibitor. Despite the presence of high baseline viral loads in patients, including one patient with nearly 8 log10 HCV RNA at baseline, ACH-3102 in combination with a nucleotide demonstrated rapid suppression of viral replication. We believe the ability to achieve 100% SVR4 after only 6 weeks of therapy highlights the role ACH-3102 could play in unleashing the full potential of a NS5A-nuc combination regimen."

Achillion also announced interim study results demonstrating that ACH-3422 achieved proof-of-concept in a Phase I trial for patients with treatment-naïve genotype 1 HCV. In the 700-mg dose group, mean maximal reduction in HCV viral RNA load of 4.8 log10 IU/ml was observed within 14 days with 3 out of 6 patients achieving undetectable HCV RNA (< 10 IU/mL, target not detected). The pharmacodynamic characteristics of ACH-3422 provided sustained antiviral activity resulting in an additional 1.4 log10 reduction in HCV RNA between day 7 and day 14 of dosing.

"The safety profile, potent antiviral activity, and high barrier to resistance observed with ACH-3422 in this Phase I trial exhibit the important characteristics a nucleotide inhibitor provides in HCV treatment regimens," commented Dr. David Apelian, Executive Vice President of Clinical Development and Chief Medical Officer at Achillion. "The data, combined with the Phase II proxy study results, lead us to believe that the doublet regimen of ACH-3102 and ACH-3422 can be a highly competitive, regimen to cure HCV. Furthermore, the ability to explore a triplet regimen with sovaprevir, our protease inhibitor, may allow for shorter treatment durations especially in harder-to-treat patient populations."

This adaptive design Phase I trial is a randomized, double-blind, placebo-controlled trial investigating the safety, tolerability, pharmacokinetics, and antiviral activity of ACH-3422. The trial has evaluated escalating doses ranging from 50 mg to 700 mg of ACH-3422 in healthy volunteers in single ascending dose cohorts followed by 14-day multiple ascending dose cohorts. All doses were well-tolerated with no significant adverse events, ECG, or laboratory abnormalities noted. Cohorts of treatment-naïve genotype 1 HCV-infected patients were enrolled and received once-daily treatment with ACH-3422. Patients in the 50-mg, 150-mg, and 300-mg cohorts received 7 days of treatment; patients in the 500-mg and 700-mg cohorts were treated for 14 days. All doses of ACH-3422 were well-tolerated with no treatment-related SAEs, no discontinuations due to adverse events, and no clinically significant laboratory or ECG abnormalities.

Phylogica Enters Research & Licensing Agreement With Genentech

Phylogica Ltd. recently announced it has extended its collaboration with Genentech, a member of the Roche Group, by entering into a Research and Licensing agreement to discover novel antibiotics. Phylogica will employ its Phylomer drug discovery platform, including its proprietary cell-penetrating peptide discovery technology to identify Phylomer peptides suitable for further evaluation. Under the terms of the agreement, Phylogica will receive an upfront payment of $500,000. In addition, Phylogica is eligible to receive research, development, and commercialization milestone payments totaling up to US$142 million.

Phylogica's CEO Dr. Richard Hopkins commented "We are delighted to continue building upon on the success of our initial collaboration with Genentech. This alliance has the potential to address an unmet need for novel antimicrobials to treat bacterial infections, including drug-resistant superbugs."

Roche to Acquire Dutalys to Augment Development Pipeline

Roche recently announced it has agreed to acquire Dutalys GmbH, which specializes in the discovery and development of fully human, bi-specific antibodies based on its proprietary DutaMab technology. The bi-specific antibodies developed with this platform are designed to provide novel, best-in-class molecules for several therapeutic areas. This deal further highlights Roche's leadership in the development of therapeutic antibodies.

"The platform developed by Dutalys is a breakthrough technology, and we are excited about integrating it within Roche," said John C. Reed, Head of Pharma Research and Early Development. "It strengthens our R&D capabilities in delivering bi-specific antibodies, which have the potential to create transformational new medicines."

"We are delighted to have found a partner who has the capability to fully leverage our technology for maximum patient benefit," added Roland Beckmann, Co-founder and CSO of Dutalys. "DutaMabs are suitable for the treatment of numerous disease mechanisms and therapeutic targets, and we are very much looking forward to developing diverse novel therapeutics within the Roche R&D team."

Under the terms of the agreement, Roche will make an upfront cash payment of $133.75 million to shareholders and make additional contingent payments of up to $355 million based on the achievement of certain predetermined milestones.

A conventional bi-specific monoclonal antibody is a biotechnologically engineered artificial protein that is composed of fragments of two different monoclonal antibodies and consequently can bind to two different antigens. The DutaMab technology platform differs by enabling the development of fully human bi-specific antibodies where each arm of the antibody shows high affinity and simultaneous binding against both targets, excellent stability, and good manufacturing properties. This enables the treatment of disease mechanisms that could not be addressed with conventional bi-specific antibodies.

EXCIPIENT UPDATE

Soluplus®: An Understanding of Supersaturation From Amorphous Solid Dispersions

By: Oksana Tsinman, Konstantin Tsinman, PhD; and Shaukat Ali, PhD

Amorphous Solid Dispersions (ASDs) have been widely accepted as a desired solution for enhancing solubility and bioavailability of poorly soluble drugs.[1] With a trend in increased number of poorly soluble new chemical entities (NCEs), the industry is adapting non-conventional formulation technologies, exploiting the existing polymers, and exploring innovative ones to expedite drug development.[2] However, the applicability of those polymers in such technologies has also created new challenges associated with processing and manufacturing or thermal instability, such as hot melt extrusion and Kinetisol®, or residual solvents, such as spray drying and co-precipitation.[3-6]

A number of polymers, including polyvinylpyrrolidone (PVP), copovidone (PVP-VA), hydroxypropylmethylcellulose (HPMC), hydropropylmethylcellulose acetate succinate (HPMCAS), amino methacrylate copolymer among others have been used in ASD formulations.[1c] However, a clear understanding of factors responsible for maintaining supersaturation and stability of drug molecules to overcome precipitation and retardation of dissolution in the gastrointestinal milieu, and their impacts on the bioavailability of APIs from polymeric ASDs, is still lacking and thus highly warranted.[7-10]

Soluplus®, a polyethylene glycol, polyvinyl acetate and polyvinylcaprolactame-based graft copolymer (PVAc-PVCap-PEG), has been studied extensively in ASDs of several investigational, and model drugs in hot melt extrusion,[11-21] spray drying,[22-24] high shear dispersions, Kinetisol,[25] electrospinning/electrospraying,[26-27] microwave radiation,[28-29] solvent casting,[30] solvent evaporation,[31-33] ball milling,[34] physical/co-milling blends,[35-36] and thermal heating[38] amongst others.

This article is aimed at understanding the in vitro solubilization of a model drug CBZ, more specifically, at the interplay between achieved supersaturation and flux of a model drug from Soluplus amorphous dispersions. The mechanisms underlying the supersaturation and diffusive flux of drug across membrane from ASDs will also be discussed and postulated.

MATERIALS & METHODS

Soluplus (BASF, Florham Park, NJ) was used as received. Carbamazepine was extruded with Soluplus on a 16-mm twin screw extruder (Thermo Fisher) under the processing conditions as reported previously.[38] A miniature device µFLUX™ together with in situ fiber optic dissolution monitoring system µDISS Profiler™ (Pion, MA, Figure 1) were used to measure flux of free drug in receiver compartment separated from the donor by the artificial membrane.[39]

RESULTS

Solubilization of CBZ & CBZ-Soluplus Extrudates: Dissolution of CBZ & CBZ Soluplus Dispersions in SGF & FaSSIF

Figures 2A and 2C illustrate the dissolution and solubility of pure crystalline CBZ in SGF (pH 1.2) and FaSSIF (pH 6.5) buffers. It is clear that as the dissolution progressed, the CBZ concentration peaked in the first 30 min reaching approx. 200 µg/ml. As the dissolution continued, the solubility of CBZ declined due to re-crystallization equilibrating at ~150 µg/ml, and stayed constant for > 16 hours.[40] With Soluplus dispersions, on the other hand, CBZ solubility increased and peaked at >300 µg/ml, and stayed in supersaturation for over 16 hours without precipitation in both SGF and FaSSIF media (Figures 2B and 2D). The solubility of CBZ in ASDs was at least 2-fold higher than that in pure CBZ and was also independent of pH changes. Because the ASD of CBZ was fully dissolved in this experiment, the solubility enhancement ratio could not be determined.

Dissolution & Flux of CBZ at pH 7.4

To further explore the supersaturation, the solubility of CBZ was investigated using 2-chamber µFLUX system. The donor compartment contained pure drug or ASD formulation (1mg/mL CBZ load in pH 7.4 Prisma HT buffer), while the receiver chamber contained pH 7.4 buffer and a surfactant to simulate the sink conditions.[39] Figures 3A and 3B show the concentration – time profile of CBZ in donor and receiver chambers, respectively. The CBZ concentration continued to increase in the receiver with flux changing slightly depending on the concentration level in the donor.

In Soluplus dispersion, CBZ peaked to maximum concentration of 1 mg/ml, maintaining the supersaturation over 4 hours (240 min) as illustrated in Figure 4A. It ultimately followed a gradual precipitation, but the CBZ flux in the receiver chamber continued to stay nearly constant despite precipitation of CBZ in the donor (Figure 4B).

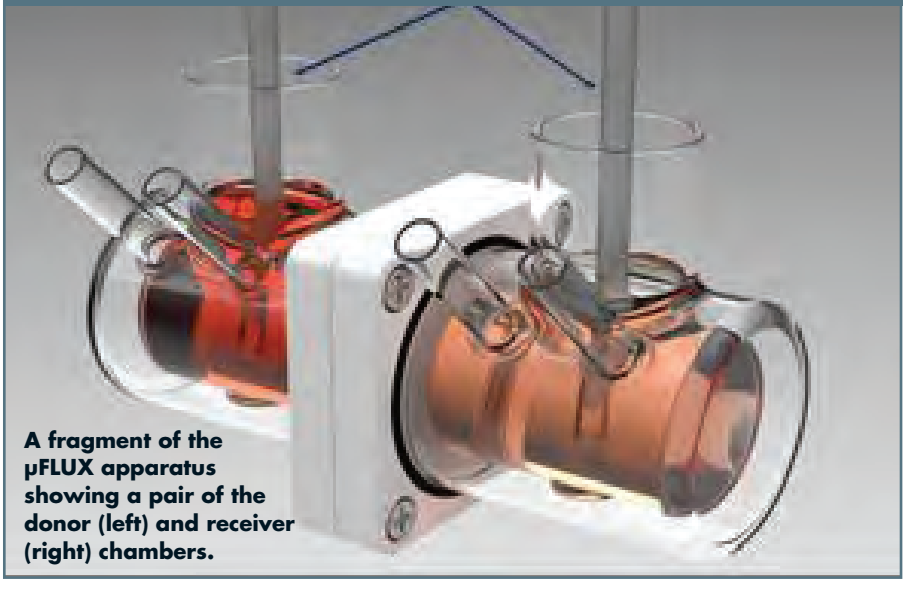
The data suggests that flux of free CBZ in the receiver from Soluplus dispersions was about 3-fold higher than that from pure CBZ at pH 7.4 in over 4 hours. The higher concentration of CBZ in donor resulted in higher flux of CBZ across the membrane in receiver during all phases; dissolution, supersaturation, and precipitation of drug.

Figure 5 illustrates curves from dissolution, supersaturation, and precipitation processes during the first 200 min from pure CBZ (Figure 3B) and Soluplus dispersions (Figure 4B) at pH 7.4 ASB buffer. Figure 5 illustrates that despite quick re-precipitation of CBZ, it was possible to detect differences between the initial flux of 1.2 $\mu g \cdot min^{-1} \cdot cm^{-2}$ (supersaturation region), the flux during precipitation (0.92 $\mu g \cdot min^{-1} \cdot cm^{-2}$), and the flux when the concentration of CBZ reached equilibrium concentration (0.85 $\mu g \cdot min^{-1} \cdot cm^{-2}$). The flux from CBZ-Soluplus remained nearly constant within a 0.5- to 3-hour period and was ~3 times higher than for pure CBZ. Following the onset of re-precipitation, it decreased only slightly from 2.7 to 2.4 $\mu g \cdot min^{-1} \cdot cm^{-2}$.

DISCUSSION

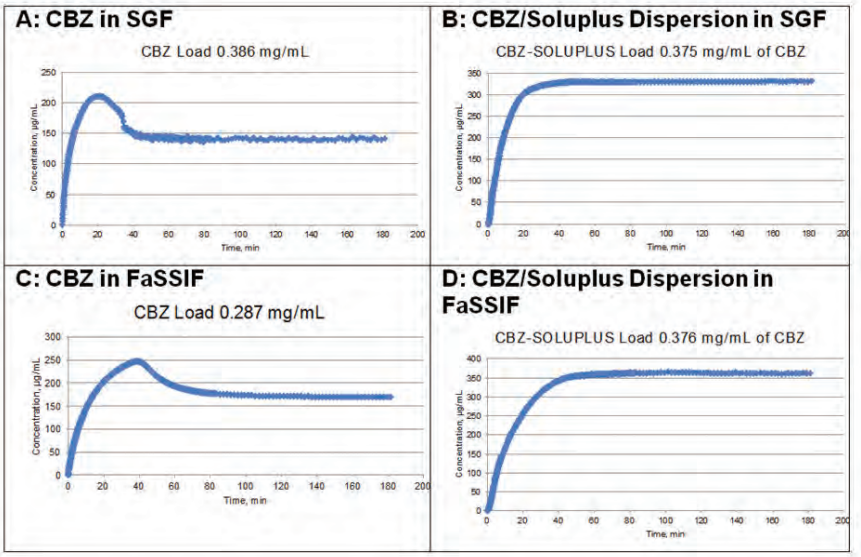
This study describes the application of Soluplus, a hydrophilic polymeric solubilizer, in solid dispersions of a model drug carbamazepine. The scope of this study is limited to understanding of hydrophilic polymers and their behaviors on amorphous dispersions. Therefore, the studies from other hydrophilic polymers have been examined in the context of drug's solubility, loading, precipitation, dissolution, and supersaturation, and also compared with Soluplus dispersions. Such comparisons are necessary to help

FIGURE 1



A fragment of the µFLUX apparatus showing a pair of the donor (left) and receiver (right) chambers.

FIGURE 2



Concentration (µg/mL) versus time (minutes) of CBZ from pure (A and C) and Soluplus dispersions (B and D) in SGF (pH 1.2) and FaSSIF (pH 6.5).

identify the polymers based on a postulated model for achieving the desired supersaturation.

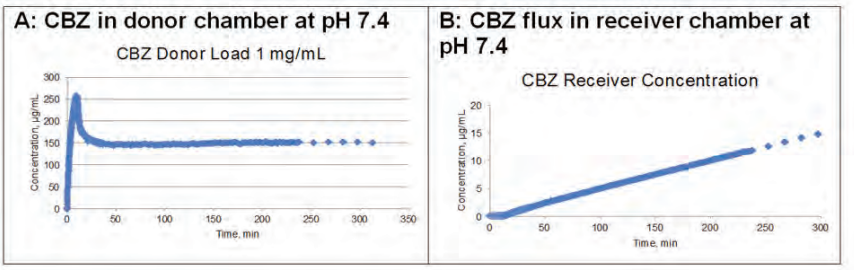
Amorphous Solid Dispersions With Hydrophilic Polymers

Sun and Lee studied the effects of infusion of a hydrophilic polymer (PVP K-90) on supersaturation of model drugs in amorphous dispersions.[41] The gradual infusion of the crystalline inhibitor PVP increased the maximum indomethacin concentration and attained the supersaturation much longer as opposed to a faster infusion, suggesting that the hydration of PVP was critical for achieving and maintaining a higher kinetic solubility. Like PVP, hydrophilic polymers, such as HPMC, were also effective and maintained the supersaturation of felodipine and nifedipine from amorphous dispersions.[42]

Verreck and Brewster observed that the addition of hydrophilic polymers PVP (K-30) and PEG 400 did not help maintain the supersaturation of an investigation compound (m.p. 300°C), but the addition of polyoxyl hydrogenated 40 castor oil (Kolliphor® RH40) with PVP K-30 (1:3), resulted in maintaining the supersaturation.[43] Addition of Poloxamer 407 in Soluplus dispersions with carbamazepine not only helped facilitate the extrusion process but also improved the loading and miscibility of drug in the polymer, and hence, increased the dissolution rate.[12] In a recent study, vitamin E TPGS (Kolliphor® TPGS) when used in copovidone (PVP-VA) extrudates inhibited the precipitation and increased the miscibility and loading of carbamazepine and fenofibrate (unpublished).

Intermolecular interactions and complexation originating from H-bonding, ionic, and/or van der Waal's interactions of hydrophilic polymers with drugs play an important role in solubilization, stability, and maintaining supersaturation.[44] For example, Soluplus with multiple interaction sites increased the solubility of albendazole as high as 50% in amorphous dispersions also maintaining the supersaturation, while, HPMCAS neither enhanced solubility nor resulted in supersaturation. With other model drugs, such as fenofibrate, the HPMCAS performed better than Soluplus and/or HPMCE5 and maintained supersaturation, and significantly improved the bioavailability in rats.[45] In other cases, HPMCAS performed relatively better than copovidone with itraconazole dispersions, presumably due interactions between an alkaline drug and an acidic polymer,[46] while it performed sluggish as compared with Soluplus dispersion.[23] In cases where drugs are sensitive to acidic or alkaline, changing the microenvironment pH or counter-ions of ASD might be equally important for preventing re-crystallization and achieving the supersaturation, and increasing the kinetic solubility in

FIGURE 3

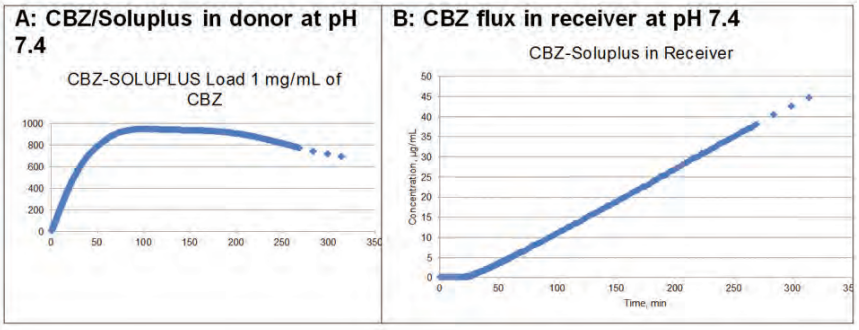


Dissolution, supersaturation, and re-precipitation of CBZ in the pH 7.4 buffer in the donor compartment (A); and appearance of CBZ in the receiver compartment (B).

solution.[21] In a recent study, inclusion of Soluplus in atorvastatin calcium dispersions also prevented re-crystallization, and achieved 3.6-fold higher bioavailability in rats from amorphous dispersions as compared to physical mixtures.[22] In our study, solubilization of CBZ from a physical mixture was identical to Soluplus amorphous dispersion, suggesting that drug was likely solubilized in the polymeric micelles, which prevented re-crystallization and maintained the supersaturation (data not shown). Thus, the lipophilic and solubilizing characteristics of Soluplus are crucial for complexing with drugs to help not only for maintaining supersaturation in vitro but also increasing the bioavailability.[15,47]

Qian et al observed that the solubility and loading of an investigation compound (BMS-A) was significantly higher in PVP-VA, which led to faster re-crystallization and slower dissolution and lower bioavailability compared to HPMCAS.[48] In a study with Soluplus containing 15% itraconazole, the extrudates were stable over 3 months under accelerated conditions and did not show any signs of surface re-crystallization or retardation of dissolution (unpublished). The stability of ASDs was also dependent upon the processes used in manufacturing. For example, when Soluplus, HPMCAS and PVP were used in spray drying and melt extrusion of felodipine, the dissolution rates were comparable for both spray dried powders and melt extrudates, but the physical stability of the extrudates was better than the spray dried powders due, in part, to stronger interactions of drug and polymer caused by intimate

FIGURE 4

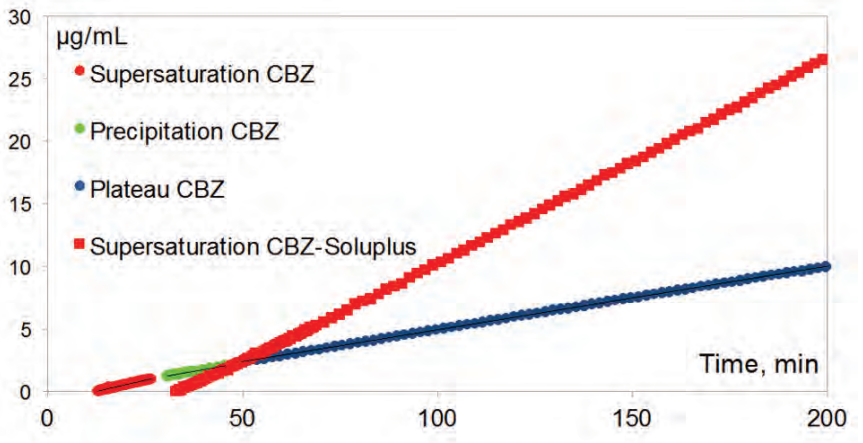


Solubility (in donor) and flux (receiver) of CBZ from ASD, with showing "parachute" supersaturation behavior of CBZ in Figure 4A.

mixing at higher processing temperatures.[11] The presence of residual solvents in ASD powders caused phase separation and formation of local drug domains. Soluplus dispersions with 15% itraconazole prepared by melt extrusion, and spray dried also behaved identically. Both formulations maintained supersaturation for an extended period before re-crystallization.[23]

Solubilizers also play an important role in influencing the permeation of drugs across the membranes from solid dispersions. Kanzer et al examined the effects of sorbitan monolaurate, polyoxyl 40 hydrogenated castor oil and propylene glycol laurate on permeation of calcein through phospholipid barrier from the melt extrudates composed of copovidone (PVA-VA) copolymer as a placebo and with two HIV drugs.[49] The surfactants with lower HLB values, for example, propylene glycol and sorbitan monolaurate (ca. HLB 4-6) did not show any change in permeability and electrical resistance, and hence, were both compatible with lipid barrier. In contrast, polyoxyl 40 hydrogenated castor oil (HLB 16) in both API free and API containing melt extrudates increased permeation of calcein primarily attributed to leakage of the membrane. This is consistent with an earlier study wherein polyoxyl 35 castor oil (HLB 12-14) was also incompatible, and caused the leakage of lipid membrane.[50] When

FIGURE 5



Comparison of drug flux from ASD (red squares) and crystalline CBZ (circles) for the first 200 min.

FIGURE 6

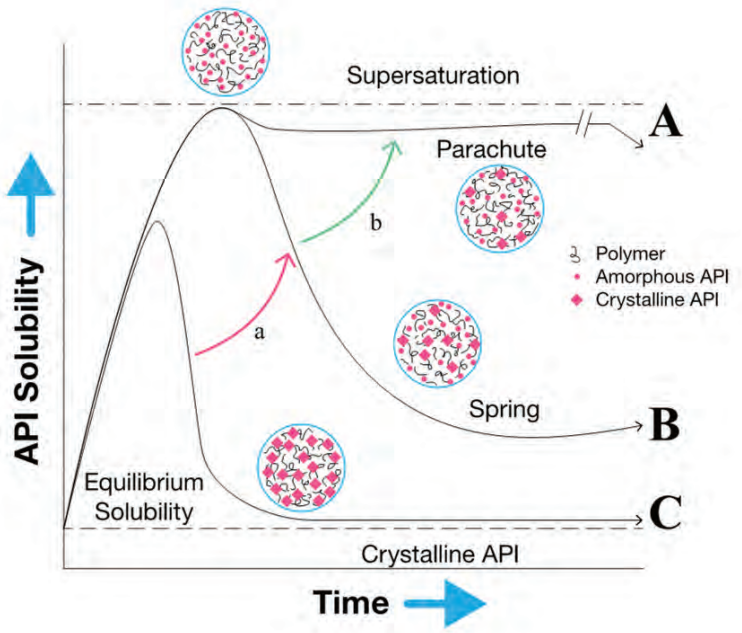


Illustration of API solubility with time from a polymeric solid dispersion; equilibrium solubility of crystalline API is shown by the dashed line, supersaturation solubility is shown by the dash-dotted line; a parachute (Curve A) represents the API maintains in a nearly amorphous state over an extended period showing the sign of only a few (or none) APIs crystals. Curve B represents that API attains supersaturation quickly "spring" before crashing into solution due to increased nucleation or precipitation of API; whereas, the API is kinetically unstable and crashes within minutes of exposure in aqueous solution (Curve C) without achieving the supersaturation. Arrow a represents the prevention of API nucleation to achieve a spring profile; whereas, arrow b represents the transformation of spring to parachute curve by preventing the re-crystallization of API from an amorphous dispersion.

tested with CaCo2 cells, the PVP-VA/drug dispersions containing sorbitan monolaurate, the flux of drugs was much higher as compared to lipid barrier, suggesting that active and passive transports both interplayed for such increase.[53]

Raina et al examined the flux of felodipine and nifedipine through a cellulosic membrane (MWCO of 6-8 K) with HPMC as a crystalline inhibitor in aqueous solution. The flux of drugs increased linearly in relation to donor concentration as long as drugs remained in the supersaturation.[42] The data from our studies also suggests that the flux of CBZ through PAMPA membrane from Soluplus dispersions was 2.5- to 3-fold higher than flux from untreated CBZ.[51]

Mechanisms Underlying the Supersaturation

The data from the Soluplus and carbamazepine study, and the examples cited in this article from the literature with hydrophilic polymers, shed light on understanding of supersaturation from amorphous solid dispersions. It also highlights the factors responsible for drug and polymer interactions and stability of amorphous dispersions, to help identify the physico-chemical characteristics of polymers relevant to supersaturation. Hence, three possible scenarios are proposed to further simplify the supersaturation phenomenon, and are illustrated in Figure 6.

1. Curve 6A may arise from polymers possessing good solubilization and crystalline inhibitory properties. The combination of both attributes could lead to increased kinetic solubility and maintaining supersaturation, and will appear as a parachute before precipitation. Maintaining such behavior could lead to significantly higher in vitro trans-membrane flux and meet narrow therapeutic windows for the absorption and bioavailability of drugs.

2. Curve 6B may arise from polymers possessing some degrees of solubilization but probably lacking a significantly larger lipophilic characteristic, thereby, limiting the complexation with drugs. In such cases, the desired solubility of drugs can be achieved, but supersaturation will be maintained briefly yielding a limited kinetic solubility and exhibiting a "spring" behavior, before the precipitation begins. This trend could be reversed to a parachute Curve A by the addition of a surfactant or solubilizer with higher HLB values, and/or a hydrophilic polymer with desired crystalline inhibitory properties.

3. Curve 6C may arise from polymers possessing moderate to poor solubilization and complexation abilities, wherein, the supersaturation could hardly be achieved due to precipitation (limited kinetic solubility), leading to an immediate

drop in the dissolution upon exposure to aqueous solutions. This trend could be reversed by the addition of an appropriate solubilizer and/or polymers with desired crystalline inhibitory properties, and in such cases, Curve C could follow the same trend as Curve B with limited kinetic solubility, or in a rare case, will follow the Curve A, allowing to maintain the supersaturation for an extended period.

CONCLUSIONS

Soluplus offers an advantage over many other polymers to study the supersaturation phenomenon due, in part, to its inherent amphiphilic characteristics derived from lipophilic and hydrophilic polymeric components. The data from this study clearly demonstrates that Soluplus possesses all the physico-chemical attributes for improving solubilization, maintaining supersaturation, and preventing the re-crystallization of drugs. Our data demonstrates that Soluplus dispersions maintains carbamazepine concentrations at least 3-fold higher than pure crystalline drug and also maintains the supersaturation like the Curve A (Figure 6). The outstanding in vitro performance of Soluplus dispersions could also help understand the increased in vivo performances of the extrudates of other model drugs in rats and beagle dogs.[15, 22]

The study showed that the increase of flux of CBZ in the receiver compartment is lower than the increase in apparent kinetic solubility of the drug from CBZ-Soluplus ASD, suggesting that the dissolved CBZ is present in both un-bound form (free drug) and CBZ-Soluplus complex (bound form) in donor compartment. Thus, the dissolution-permeability µFLUX™ device can be used to simultaneously monitor the flux of free drugs in solutions from a complex solid dispersion system. Additional studies are necessary at molecular levels to understand the supersaturation and its correlation with thermodynamic and kinetic stability and flux of drugs in the aqueous and biorelevant solutions. ◆

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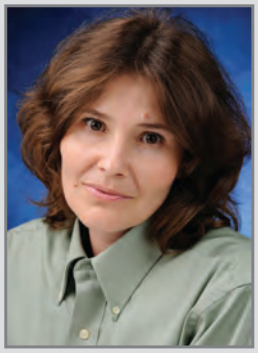

Ms. Oksana Tsinman is a Senior Scientist and a Manager of the Research and Analytical Laboratory at Pion Inc. She earned her Master's in Biochemistry in the Ukraine in 1990. Ms. Tsinman joined Pion in 2002 and quickly became an integral part of Pion's research team working on R&D projects that included among others optimization of high throughput solubility-permeability measurements, developing early stage formulation screening techniques and applying in situ UV fiber-optic measurements to preformulation screening. Her research in artificial membrane permeability measurements that would predict blood-brain-barrier transport was a basis for Pion receiving Phase I and II grant from the NIH. Her experimental skills and attention to the details made her a key part of multiple collaborative research projects with scientists from the pharmaceutical industry and academic institutions. She has co-authored more than 15 articles presented at international conferences and published in primary scientific journals.

Dr. Konstantin Tsinman is the Director of Science and Research at Pion Inc. He joined the company in 1998 as principal developer of the very first commercial Parallel Artificial Membrane Permeability Assay (PAMPA) instrument and subsequently the high-throughput method for measuring solubility - pH profiles. He has been participating in numerous studies expanding the scope of applications for in situ UV fiber-optic instrumentation and utilization of derivative spectroscopy techniques for real-time concentration analysis of complex formulations in turbid solutions. Dr. Tsinman has been involved in multiple collaborative research projects with scientists from the pharmaceutical industry and academic institutions. He has co-authored more than 25 articles published in primary scientific journals and holds several patents. He earned his PhD in Physics in 1994 from the Institute for Metal Physics, Kiev, Ukraine.

Dr. Shaukat Ali has over 20 years of experience in the pharmaceutical industry, including 10 years at BASF, where he supports the solubilization platform and APIs. He serves the USP panel of experts for General Chapters-Physical Analysis. He is also a member of the editorial boards of American Pharmaceutical reviews, Contract Pharma, Drug Development & Delivery, Biopharma Asia (UK), and International Journal of Pharmaceutical Investigation. He has authored over 25 scientific articles and is inventor/co-inventor in 14 US patents. He earned his PhD in Chemistry from the City University of New York and pursued his postdoctoral interest at the University of Minnesota and Cornell University. Dr. Ali's areas of expertise include drug solubilization, liposome drug delivery, controlled release, and film development technologies.

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Management Insight

Pharmaceutical Innovation in the Second Machine Age

By: Derek Hennecke, CEO & President, Xcelience LLC

It was the best of times. It was the worst of times. It was the age of innovation. It was the age of stagnation. On the one side, we have those who argue that technology is advancing so fast we have achieved a second-derivative rate of change - the acceleration of acceleration. On the other side are those who claim we haven't seen true innovation since the 1970s; we are simply getting better at using the innovations we have. We are either powering forward, or barely moving at all. Which is it?

THE BEST OF TIMES: THE SECOND MACHINE AGE

Erik Brynjolfsson and Andrew McAfee argue persuasively in *The Second Machine Age* that about 30 years since the proliferation of computers, we are on the cusp of an unprecedented period of rapid advancement.

The second industrial revolution came with the invention of electricity. Change didn't follow immediately then either. Factory owners just replaced their steam engines with electrical ones. It was 30 years - a whole generation - before factory owners began to redesign their factories to take advantage of the flexibility electricity offered, and to combine this new invention with other related innovations, like the light bulb, to see productivity leap forward.

So it is with the new machine age. Computers proliferated in the 70s and 80s, and we thought our world had changed dramatically because we could create a document on a computer without White Out, or race a Pacman around a screen eating little green dots. The generation that invented

"Where, then, does our industry fall within the scope of innovation? Are we racing ahead, or just plugging along? Thiel argues that investing in large pharma is a bet against technology, since most of what pharmaceutical companies are doing is figuring out ways to extend the lifetime of patents and block smaller companies."

the computer couldn't yet see its true potential.

It took the next generation to realize the computer's digital, exponential, and combinatorial potential, according to Brynjolfsson and McAfee. Digital, because computers give access to more data than ever before. Exponential, because a child's play station today is more powerful than a military super computer in 1996. And combinatorial, because each innovation can be combined with other innovations to make even more innovations. Today, you can write an app and reach a million users just by putting it on the Facebook platform, which in turn is built on the Internet, which is built on the Web. When we put these advances together we see an explosion of innovation, unlike anything seen before.

One of the most exciting developments is computers that can learn. Computers like Watson, the famous computer that beat the world Jeopardy champion in 2010. Now, learning computers are working in call centers, in legal and banking industries. They are even transforming the medical profession as computers advance in diagnostics and surgery.

Yet the book - and if you can't make time for the book, I recommend the Ted Talk - is not a lament for the end of the labor force in a world where computers do everything from taxes to translation. Rather, it's an upbeat treatise embracing the boundless possibilities of a new world, while proposing policies to maximize innovations and collaborations that emphasize what Brynjolfsson and McAfee call the race with (not against) machines. In their view, a team of computers and humans can beat any humans, or any computers working alone.

THE WORST OF TIMES: ZERO TO ONE (TECHNOLOGICAL-STAGNATION SINCE THE 70S)

On the other side, we have Peter Thiel, co-founder of PayPal and Palantir, the first outside investor in Facebook, and an early investor in SpaceX and LinkedIn. In *Zero to One: Notes on Startups, or How to Build the Future*, Thiel argues that we are in an age of stagnation, but we're too dazzled by our shiny mobile toys to notice. Progress should go beyond what's happening in Silicon Valley, he says. As the slogan of his venture capital firm the Founders Fund admonishes, "We wanted flying cars; instead we got 140 characters." Twitter is a great company, but it's not advancing society.

If you want to see stagnation, argues Thiel, look to Microsoft, Oracle, or Hewlett Packard. These companies were once innovators, but now they just churn out marginally improved browsers and operating systems. To put your money in these companies is to place a bet on a future of incremental, and essentially inconsequential, advancements.

This line of thinking, too, can be persuasive. In fact, at times, I felt he was too generous in praising innovation over the last half century. Thiel advances the Manhattan project

and the interstate highway systems as the sort of innovation he'd like to see more of today. These projects were advancements, to be sure, but innovations? We already knew how to build roads. The interstate highway system just built more of them, and standardized the exits. The Manhattan Project culminated in the atomic bomb, but Einstein's theory of relativity was published in 1905. In fact, both projects were essentially just very, very expensive system upgrades.

THE STAGNATION OF PHARMACEUTICAL INNOVATION

Where, then, does our industry fall within the scope of innovation? Are we racing ahead, or just plugging along? Thiel argues that investing in large pharma is a bet against technology, since most of what pharmaceutical companies are doing is figuring out ways to extend the lifetime of patents and block smaller companies. They could be spending time looking for cures to Alzheimer's, he says, instead of recycling old ideas and milking profits.

Pity the Eli Lilly employee who reads that passage. Lilly has been betting the farm on a cure for Alzheimer's, exhausting avenue upon avenue of possibilities. What Thiel is missing is that we're still making huge innovative leaps and bounds in biochemistry and molecular biology. There is no existing knowledge base - such as roads, atomic science, or computers - that will, with fine-tuning, eventually lead to a cure. It's not as simple as sifting through the available molecules in the universe until we find the one that, in pill form, will yield what we seek. That could happen, but more likely when the answer comes it will be another "Who knew?" moment that brings an innovative combination of ingredients, such as technology, biochemistry, and perhaps diagnostics together.

If innovation is slow to come in our industry, it may be that we've not yet grasped the possibilities of the technologies available to us. We are still struggling to overcome the empirical nature of our work. It can take a decade from the time we identify a promising pathway till the time we prove it. Mother Nature sets some very strict limits on the rate at which cells reproduce, for example, and a controlled study to prove that a certain compound increases longevity can, by its very nature, never be completed in a matter of days or weeks. By contrast, electrical and mechanical models can be tested, revised, and retested in rapid, sometimes near instantaneous, succession.

The other drag on our acceleration is the rigors of government regulation. While necessary and important, it cannot be denied that the constant checks and double checks, filings and audits, hamper and add significant cost to any given process, and thereby reduce the number of potential cures any given company can choose to pursue.

THE ACCELERATION OF PHARMACEUTICAL INNOVATION

The machine age has undoubtedly touched our industry, from inventory management systems to HPLCs. But I'm not sure we can yet see a ground up revolution in drug development, such as, for example, the medical profession may foresee in light of recent innovations in medical diagnostics and laser surgery. Still, there are changes out there that may be the beginnings of something larger:

The Human Genome Project - The Human Genome Project (made possible by computers and the Internet) was completed in 2003, and it may take a generation for us to see how this stunning new information can be combined with other technologies and methods to transform drug development.

Virtual Research Companies:
Pop Test - Imagine a company that has no salaried employees. Led by CEO Randi Altschul, the Pop Test companies partner with a team of world-class scientists, MDs, PhDs, and clinicians who share ownership of the company. Altschul comes up with a visionary idea, honed by her years of experience in startups. The Pop Test

scientists then develop it, their legal team protects it, and their clinical team proves it, after which they sell it to someone else for commercialization. Their first breakthrough was the saliva diabetes (glucose) test, now in its last phase before FDA approval. The company owns four patents for saliva- based detection systems and clinical data showing sensitivity and specificity for different molecules in the 95th percentile. They have already expanded the Pop Test saliva platform to provide a saliva test for cholesterol, uric acid, and liver tests such as ALT and AST. All this, among other innovative process and technology products in the company pipeline, and all realized on a shoe-string budget (visit www.diabetespoptest.com).

Mass-Produced Diagnostics:
The Foldscope - Imagine an optical microscope that can be assembled from a punched sheet of cardstock, a spherical lens, a light emitting diode, a diffuser panel, and a watch battery to power the LED. It magnifies up to 2000 times and weighs 8g: enough magnification to spot *Leishmania donovani* and *Escherichia coli*, as well as malarial parasites. Developed by a team lead by Manu Prakash, an Assistant Professor of Bioengineering at the Stanford School of Medicine and funded by Bill and Melinda Gates, the Foldscope can be printed on a standard A4 sheet of paper and assembled in 7 minutes. Suitable for student and field research and basic diagnostics in the third-world (or any country), it costs less than a dollar.

Targeted Drug Regimens:
Theranostics - Theranostics brings two schools of thought together to create new value. It works in both directions: either a diagnostic that distinguishes patients or disease types, allowing for selection of the most appropriate therapy, or the opposite, whereby a drug shows efficacy but not for all, and diagnostics are used to identify those patients for whom it would work.

Shorter Clinical Trials:
Surrogate Endpoints - While not as flashy as a folding $1 microscope, sometimes a little process tweak can have a huge impact. I mentioned earlier that you couldn't prove a biological pathway with the lightening speed that is possible for an electrical pathway. And yet, we can shorten the process significantly by adopting surrogate endpoints that may correlate to a real clinical endpoint. For example, in the case of Alzheimer's, it may be possible to adopt the removal of arterial plaque as a surrogate endpoint for a clinical trial, in place of the actual endpoint, which would be curing the disease. This shortens the clinical process considerably, and over time, the true endpoint may be proven.

There is a school of thought that says that cures are like fruit on a tree, and the low-hanging fruit has already been picked. I don't subscribe to that theory. I believe ideas are limitless, and the tree is forever growing new fruit. From computers and the Internet to the Human Genome Project and the Foldscope, our generation has inherited a tree more heavily laden than any tree before it. We need only harvest it. It is the best of times. ◆

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Derek G. Hennecke
President & CEO
Xcelience

The Second Quadrant

Outsourcing Solubilization: Making Bioavailability More Broadly Available

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

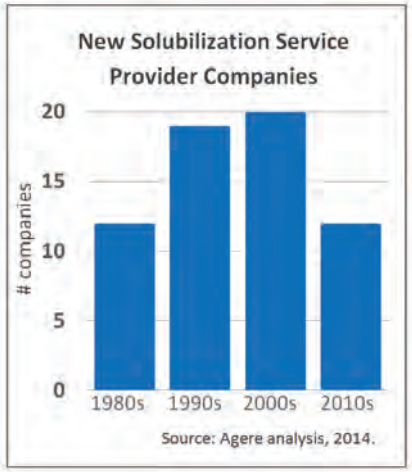
In 2014, *The Second Quadrant* examined how the solubilization market has evolved from the perspective of growth in the number of approved drugs utilizing solubilizing technologies and the diffusion of knowledge and innovation. In this 1st column of 2015, we explore how the contract services and manufacturing market has responded to the opportunity presented by the rising numbers of BCS Type II/IV clinical compounds and solubilized commercial products.

INNOVATION-BY-OUTSOURCING: IMPACT ON SOLUBILIZATION SERVICES

In 2008, research utilizing data from the Business Dynamics Statistics of the US Census Bureau challenged conventional wisdom relating to job creation and small companies. This relatively recent research revealed that new and young businesses – not just small ones – are the primary source of job growth that fuels the economy. Even more pertinent to our discussion, a recent report from The Brookings Institution noted that the drugs and pharmaceutical sector of the US economy is differentiated by a steadily increasing rate of new firm formation and net job growth for startups. Impressively, 44 new pharmaceutical-sector companies were created in 2011, representing a gain of 53% when compared with 1990. These results are even more striking when compared with the total US private sector that experienced a decline of 15% during this same period.[1]

Notably, the Brookings report attributes the "innovation-by-outsourcing" model of research and development as a contributing factor to job growth and new company formation. It's widely known that the pharmaceutical industry's reliance on service providers for research, development and manufacturing services in has been on a growth trajectory for many years. According to a 2013 report by Frost & Sullivan and as published in Drug Development & Delivery last April, the worldwide spend on contract manufacturing services in 2013 totaled $13.43 billion and is forecast to reach $18.49 billion by 2017.[2]

FIGURE 1



climate lends itself to divestitures, consolidations and acquisitions, as the market sorts out synergies and individual players refine their strategies.

A recent Agere analysis of dynamics experienced by this outsourcing sub-segment corroborates these expectations. Our study shows that since 1980, the industry has added nearly 70 new entrants into the solubilization services market space, with nearly 50% of those occurring since 2000, and 20% forming over the last 5 years[6] (Figure 1).

INSOLUBLE MOLECULES DRIVE MARKET DYNAMICS

The shift to promising and permeable but poorly soluble drugs – estimated to account for between 2,300 and 3,200 molecules in development worldwide[3] - has created an opportunity for service providers specializing in solubilization formulation development and manufacturing. The growing demand for services requiring a high degree of specialization is a recognized driver for a fragmented market, one in which numerous players offer critical and varied solutions to meet an expanding opportunity.[4] This type of market environment also fosters innovation, as older technologies are applied and new technologies and technological combinations emerge to keep up with the evolving market demand. The relative "newness" of the increasing number of insoluble molecules can also be seen to have catalyzed a marketplace where the frequently more agile small and medium players react quickly to offer services in high demand.[5] In addition, this market

CHANGES AND TRENDS IN THE SOLUBILIZATION SERVICES SPACE

Approved solubilized drugs over the last thirty-five years are evidence that there is a growing adoption of diverse solubilization technologies[7]. A historic analysis of marketed drugs can be used to predict trends in the acceptance and utilization of these different platforms. Another approach is to analyze the changes in the business environment of service providers that support solubilization projects.

In our effort to gain additional insights into shifts underway today, Agere conducted an analysis of the service providers offering solubilization solutions from formulation development through commercial manufacturing since the 1970s. Our study looked at market entry, market exit and consolidations of companies offering services in the following platforms: lipid/softgels, microparticles, nanoparticles, solid dispersions, and other miscellaneous technologies. This analysis utilized publically available information to compile all known companies involved in research, development and manufacturing in support of solubilization of 3rd party molecules as a service.[8]

OVERALL GROWTH IN NUMBER OF SOLUBILIZATION SERVICE PROVIDERS

There has been a significant increase in the number of companies offering services to meet the solubilization needs of pharmaceutical and biotechnology companies over the last 35 years. A summary of some of our findings are presented in Figure 2. While a few companies such as RP Scherer were started many decades ago (1933), the majority of players emerged after the 1970s. In fact, between 1980 and today, the number of service providers in this market sub-segment has grown nearly 10 fold. This growth is striking when taking into account the consolidation resulting from 40 acquisitions and mergers during this same period. These activities both

FIGURE 2

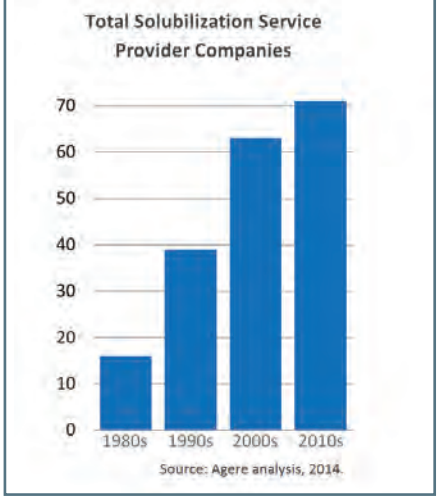
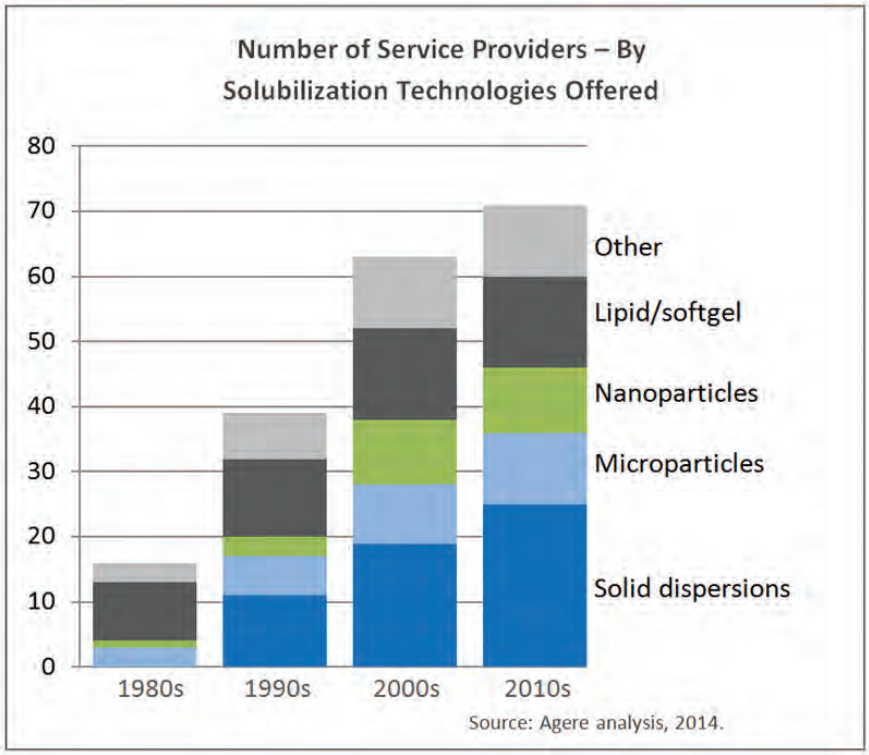


FIGURE 3



aggregated companies and also took some companies captive, removing them from our count of specialized service providers.

When looking at the number of companies offering services by solubilization platform, we see trends that correlate with the findings from our prior studies on marketed drugs and literature citations. Not surprisingly, softgel providers dominated in the two earliest decades in our analysis, and the number of companies has stayed relatively constant in this market segment. Starting in the first decade of this century, however, the number of service providers in the solid dispersion sub-segment exceeded that of lipid/softgel providers. And service providers utilizing solid dispersion platforms continues to grow in number, with 25 players in the market as of today, approaching twice as many as offering lipid-based solutions (Figure 3).

IT'S NOT JUST THE NUMBERS

In addition to new entrants, also characteristic of a market experiencing rapid growth is consolidation. While the number of players is represented in these growth charts, it's well understood that the number of new players doesn't convey market dominance, and that there's a natural evolution toward consolidation for a variety of reasons. These include the alignment of smaller companies with other players to benefit from economies of scale, or larger companies that "innovate through acquisition" as a strategy to provide more comprehensive services to their customers. This sorting out of the market is accelerating, with nearly 60% of all acquisitions of solubilization service providers since 1990 having occurred in the last 5 years[9] (Figure 4), and in some cases, companies have changed hands as many as 3 times over this same period.

As consolidation is a common route to growth for large companies, not surprisingly the largest CMOs in the solubilization space also have multiple platform offerings as a result of acquiring smaller, more specialized companies. Additionally, and with few exceptions, it is the large organizations that clearly dominate the market share for the delivery platforms examined. This work also shows that companies that are among the first to enter a particular market segment end up with the largest market share[10]. This trend is true for softgel, micronization, nanoparticles and solid dispersions. This finding is particularly interesting since even a short study of innovation diffusion shows that those with first-mover advantage often fail to capitalize on having been earliest to market, being displaced by more aggressive competitors even with lesser technology, or by providers offering a superior technical or economic solution. Yet our analysis doesn't surface instances of note or supporting evidence of these vulnerabilities.

Admittedly, the absolute number of companies and consolidations in the solubilization services space pale by comparison with the number of pharmaceutical companies and their mergers and acquisitions. However, given the preponderance of insoluble molecules in development today, our industry segment is becoming more broadly relevant. This is truly an exciting time, as this is the type of environment fosters innovation, as familiar and validated technologies are more broadly applied, and new technologies and technological combinations emerge.

"In addition to new entrants, also characteristic of a market in rapid growth mode is consolidation. While the number of players is represented in these growth charts, it's well understood that the number of new players doesn't convey market dominance, and that there's a natural evolution toward consolidation for a variety of reasons. These include the alignment of smaller companies with other players to benefit from economies of scale, or larger companies that "innovate through acquisition" as a strategy to provide more comprehensive services to their customers."

LOOKING FORWARD

Taking a snapshot of the solubilization sub-segment of the outsourcing market today reveals another interesting aspect relating to progress and growth potential. Today 35% of companies offer solid dispersion technology solutions, a greater percentage than those offering lipid/softgel solutions, once dominant at 60%. Of course, the largest players all offer this technology option, so this decrease in percentage reflects both consolidation and the emergence of additional popular solutions. The category of service providers not yet large enough to be categorized in the top four platforms, "Other" (Figure 3), has nearlyquadrupled since the 1980s. The growth in this subcategory could reflect new and diverse approaches to tackling solubilization, and may possibly hold the seeds of an emerging technology that could move the industry even further forward and become the next dominant solution. ◆

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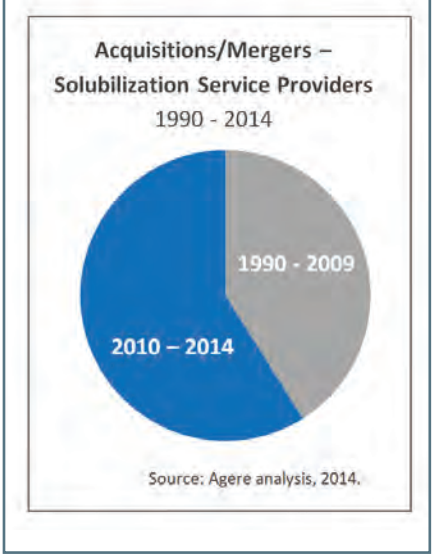
FIGURE 4



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6. Agere analysis; only new companies formed are counted; acquisitions and renaming of existing entities excluded.
7. http://www.drug-dev.com/Main/Back-Issues/BIOAVAILABILITY-ENHANCEMENT-Analysis-of-the-Histor-657.aspx.
8. The analysis did not make a distinction between size of company, and companies regardless of the service or services provided – research, development, clinical trial materials manufacturing or commercial manufacturing – are weighed equally, and only accounted for once.
9. Agere analysis December 2014.
10. This includes companies that were dominant, even if now an acquired part of a larger CDMO.

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Advanced Delivery Devices

Innovation Without Change: What is it & What Can it Mean for Pharmaceutical Manufacturers?

By: John A. Merhige, MEM, and Dan Thayer

INNOVATION IN SYRINGES & SAFETY DEVICES

The medical hypodermic syringe with a needle was first developed in 1853 by Charles Pravaz and Alexander Wood. The first glass syringe with an interchangeable barrel and plunger came from the Chance brothers in 1946, and the first plastic disposable hypodermic syringe came from Roehr Products in 1955. A year later, pharmacist Colin Murdoch was granted patents for a disposable plastic syringe similar to the one we know today, and Becton Dickinson followed with the Plastipack in 1961.[1] Since then, the pharmaceutical industry has burgeoned in the treatment of diseases and symptoms, leading to novel delivery devices and safety standards addressing products and production.[2]

The spread of infectious diseases through contaminated needles and needle reuse led to the Needlestick Safety and Prevention Act of 2000. First attempts at compliance mated existing syringes with "add-on" safety devices, such as shields, sheaths, and levers. A second generation employed manual retraction of the needle into the syringe body. These "active" devices require two hands and are often not engaged for fear of lost time or a needlestick; roughly 48% of sharps injuries occur despite the availability of sharps protection features.[3] As a result, needlestick injury rates have not declined as expected.[4]

A third generation of "passive" devices emerged, whereby the safety mechanism automatically engages after the injection. These products address previous issues but have drawbacks. Most add an exterior structure to the syringe, which can be obtrusive, cause anxiety, and impair visual inspection of the syringe contents. Due to the potential for premature activation of the safety mechanism, these designs often require user retraining or are incompatible with conventional techniques, such as purging air bubbles, performing aspiration, or reconstituting powders. Other passive products require significant changes to the drug's primary package.

WHAT IS *INNOVATION WITHOUT CHANGE*?

While these developments have moved the care of patients forward, innovation has not been fast enough. Due to inertia caused by the development and regulatory effort required to launch new drug delivery technologies, advances in delivery systems are too often kept out of the market. Drug companies have historically been forced to choose from a series of less-than-ideal options, either choosing to do nothing, choosing to implement advances and live with the long development path that usually comes with it, or choosing to seek a middle ground that includes a minimalistic approach to needlestick safety but misses the opportunity to differentiate. Because of the economic realities and supply chain risk that must logically be

considered, the crucial question is "What's in it for the pharmaceutical manufacturer to embark on such a change?" Too often, the answer has been "Not enough."

Innovation Without Change™ is a product design and business partnering philosophy that shifts the paradigm so that drug companies no longer have to make a bad compromise between the advances that innovation offers and the time, cost, and risk associated with those innovations. By offering the innovation of the final device without the traditional changes that require substantial development, regulatory effort, and supply chain risk, *Innovation Without Change* addresses both the end user performing the injection and the path to commercialization for the pharmaceutical manufacturer. The Credence Companion Safety Syringe System was born from this core philosophy.

Innovation Without Change incorporates a modular approach to the device design, leaving the primary package unchanged. This basic tenet has the dramatic impact of simplifying the commercialization path, reducing supply chain risk, and providing manufacturers enhanced flexibility to respond to market changes. Drug manufacturers have complete freedom to choose the critical primary package components from any vendor(s) they choose. They select the syringe, plunger/stopper, and tip cap components that are ideally suited for a specific drug, and the filling process is completely unaffected. The Companion plunger rod and Flex Finger Flange are added to the syringe in the common secondary assembly process; the needle is either included in the kit in the luer presentation or already affixed to the syringe in the staked presentation (See Figure 1).

FIGURE 1

While the Companion takes the novel modular approach of building integrated safety into an existing primary drug container, the concept of modularity is not new to the industry. Modularity has been available in the design of the primary package for years, with choices including the selection of syringe/drug container, lubrication, needle size/type, stopper, tip cap/needle shield, finger flange, and plunger rod.[5,6] *Innovation Without Change* builds on this modular concept by providing the delivery device with flexibility in the features selected. The result is an innovative device that provides marketable differentiation, life cycle management options, product line flexibility, and full compliance to safety legislation, all without changing the primary package. The Companion offers the best in anti-needlestick technology, fulfilling OSHA's recommendations for needled device compliance. It has fully integrated passive safety features, provides audible, tactile, and visual cues, allows single-handed operation with the user's hand remaining behind the needle, and is automatically disabled after use (See Figure 2). It is designed to be familiar to the end user, allowing

FIGURE 2

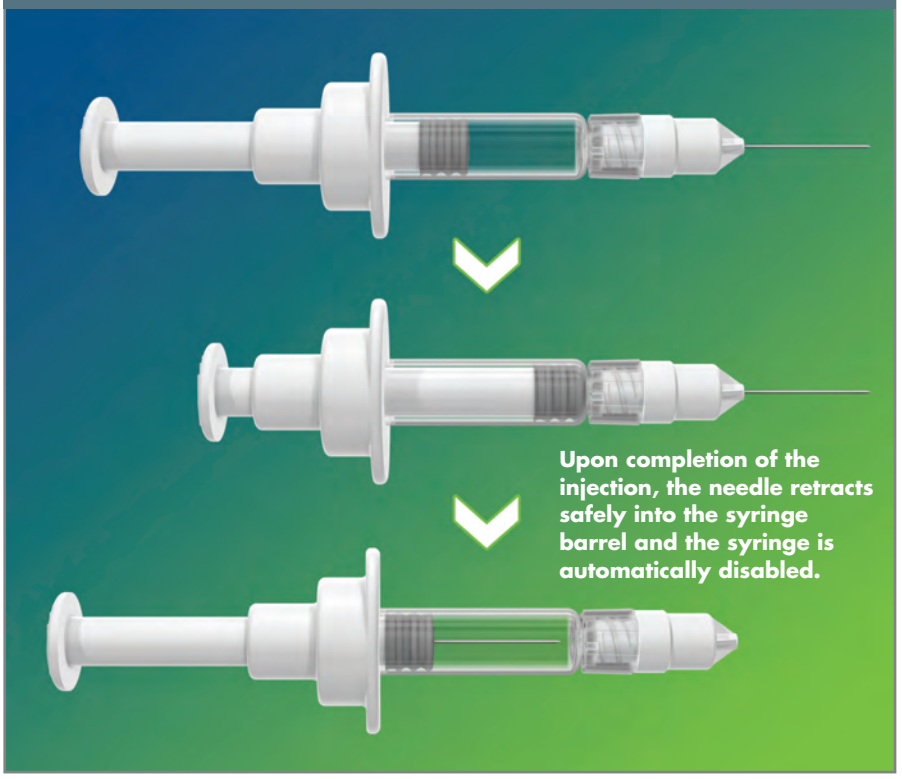
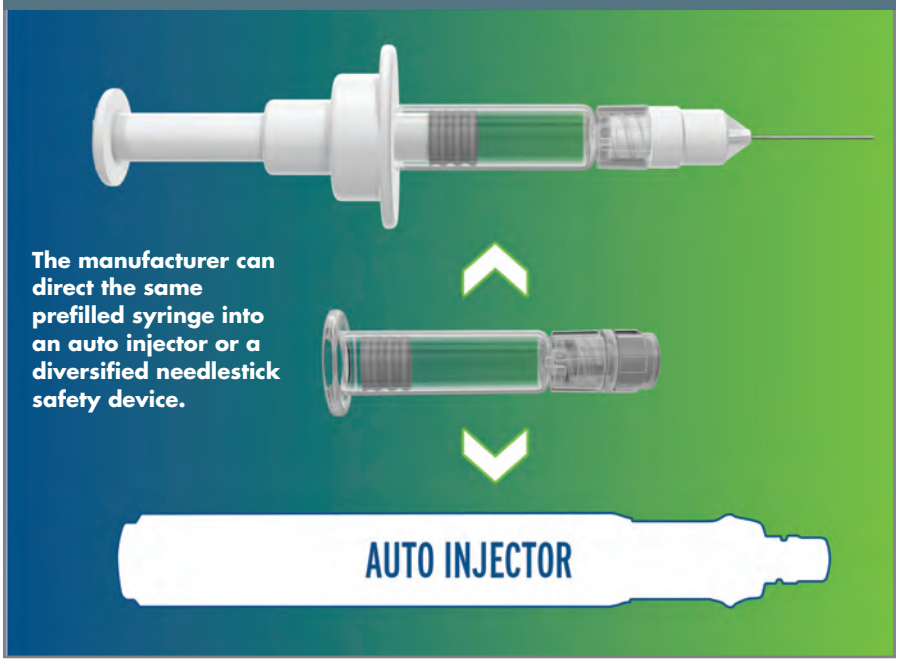


FIGURE 3



routine manipulations of the plunger rod for air bubble removal, aspiration, and reconstitution techniques, full visibility of the barrel and drug product, and comfort in employing all common hand positions. But what else can *Innovation Without Change* mean for our pharma partners, patients, and caregivers?

INNOVATION WITHOUT CHANGE SHORTENS THE PATH TO COMMERCIALIZATION

Changing a drug's primary package can cost several million dollars and extend from 6 to beyond 36 months.[7] The validation work includes container closure integrity, sterility, biocompatibility, stability, extractables/leachables analysis, reformulation, etc. The effects on the safety and efficacy of the drug must be assessed via an understanding of the impact on the molecule's strength, quality, identity, purity, and potency.[8,9] This change is designated by FDA as requiring Prior Approval before implementation and can necessitate changes to the filling line and manufacturing facility. Maintaining the existing primary package simplifies the path extensively, eliminating costly and timely variables that add risk along the way.

INNOVATION WITHOUT CHANGE DE-RISKS THE SUPPLY CHAIN

The industry and its consumers have benefitted from advances in the critical primary package components by leading suppliers that have the required expertise and capacity to provide reliable supply. Credence embraces this expertise by building the Companion with the versatility to work within the tolerances of these existing components. This provides pharma manufacturers the flexibility to choose their preferred components and multi-source from their preferred vendors. But *Innovation Without Change* extends from the product's design to Credence's partnering business model and the supply chain flexibility it provides. Just as the Companion allows a drug company to avoid changing from its preferred package, Credence's partnering approach allows a drug company to maintain important supplier relationships with its molding and assembly partners. This extends the multi-sourcing option to components of the Companion and capitalizes on the existing effective relationships with preferred vendors, thereby further reducing the risk of supply chain interruption.

INNOVATION WITHOUT CHANGE PROVIDES PRODUCT LINE FLEXIBILITY

The highly regulated environment has made it challenging for pharmaceutical manufacturers to respond quickly to changing external factors. The modularity and inherent flexibility of the Companion's design, in conjunction with forward thinking regulatory strategies, can provide newfound adaptability to changes in legislation, regulatory requirements, market trends, competitive actions, etc.

For example, different user populations have different device preferences. A small study shows user preference for a prefilled syringe compared to an auto injector ranging from 33% to 67%, depending on the disease state.[10] The ability to direct a sterile filled drug container into an auto injector or into a differentiated needlestick prevention safety syringe gives a drug company efficient flexibility (See Figure 3). Similarly, though developing nations have different

economic realities than developed markets, they have a great need for needlestick prevention and syringe disabling technology. Once again, the modularity of the Companion provides a viable solution. By changing the plunger rod, a drug company can provide more viable markets with passive needle retraction, while providing developing markets with active retraction. The drug company gains the flexibility to provide needlestick safety and single use technology to both markets while differentiating the cost of goods. Further, as needlestick prevention legislation expands to new geographies and new points of care (the home?), the ability to gain compliance and a market edge by building off of the existing drug container becomes critical. Prior to *Innovation Without Change*, this flexibility was much more difficult to attain.

INNOVATION WITHOUT CHANGE FACILITATES HUMAN FACTORS IMPROVEMENTS THAT INCREASE DRUG DELIVERY EFFECTIVENESS

Human factors improvements are often left behind when delivery system innovations don't make it to market, despite the fact that they can promote more accurate dosing and more efficient healthcare. By simplifying the commercialization path, the Companion facilitates getting important improvements into patient and caregiver hands. For example, the Companion's user has full visibility of the syringe barrel and drug product and can perform standard air bubble removal and aspiration techniques without fear of prematurely engaging the safety mechanism. Further, the flexibility of *Innovation Without Change* allows customization of the thumb pad and finger flange, whether the goal is to maximize user comfort or minimize footprint.

Needles represent another area of human factors focus. Long needles, such as those used for intramuscular injections, have been largely ignored by safety technology suppliers due to the challenge of passively protecting them, yet, these long needles may be the most dangerous. Perhaps due to the lack of adequate safety, long needles are not being used when they ought to be. Of the medications with an intramuscular route of administration, it is estimated that few women and about 15% of men actually receive the drug in the intramuscular space because the needle being used is not long enough.[11] This is an area where a luer needle can have a major impact; the Companion's luer solution allows the right needle to be selected for the specific patient, and it also provides passive needle retraction for any practical needle length. But traditionally, luer needles have been susceptible to improper connections between the needle and the syringe, resulting in complaints of spilled drug product, inaccurate dosing, and needles left behind in patients. To address this, the Companion Guide-On Needle Cover provides the user visual, audible, and tactile cues of a successfully connected needle. Further, the cover cannot be removed from the needle until the user has twisted the needle on properly to a designated torque level. Therefore, the user is prevented from attempting an injection with an improperly connected needle (See Figure 4).

This is extremely important in reconstitution applications where luer needles are required to provide a sharp needle for injection into the patient. The Guide-On Needle Cover helps ensure the needle is attached properly. Of further importance, the Companion can be used without fear of premature safety activation during the diluent delivery and subsequent drawing up of the reconstituted solution. These manipulations of the plunger rod often cause conventional safety devices to prematurely activate. The Companion

FIGURE 4

The Companion Guide-On Needle allows the correct needle to be used for the specific patient and helps ensure the needle is attached properly.

allows conventional reconstitution with passive needlestick safety (See Figure 5). Should the manufacturer wish to pursue a dual-chamber presentation, Credence's *Innovation Without Change* approach can also apply. It allows the pharmaceutical manufacturer the freedom to choose the desired reconstitution approach while still employing the best in needlestick safety.

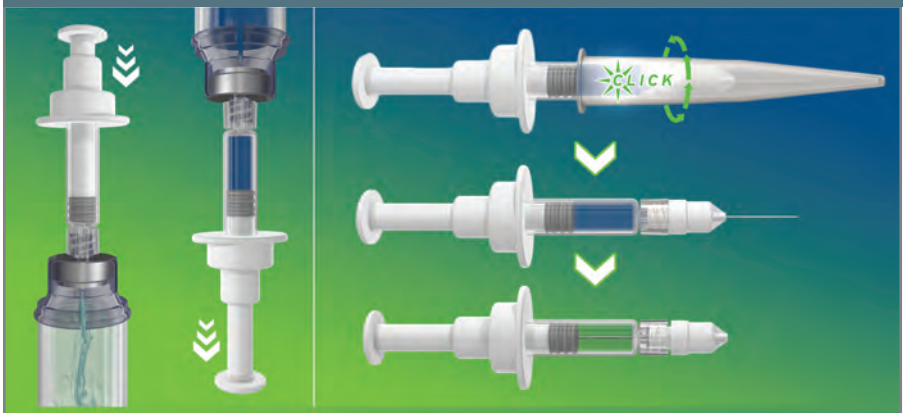
If the pharmaceutical manufacturer wishes to employ a staked needle because neither needle choice flexibility nor reconstitution is needed, the *Innovation Without Change* design philosophy can also allow this choice. The user experiences the same passive needle safety and human factors benefits but does not have to attach a needle. The manufacturer can still choose its desired syringe, stopper, and needle shield primary package components, just as is done with the luer solution, and the filling process remains unchanged. Further, because adhesive is not present in the Companion system, a risk of undesirable interaction with the drug substance is removed.

INNOVATION WITHOUT CHANGE EMPOWERS BRAND MANAGEMENT

Innovation Without Change provides innovator companies a means of extending the life cycle of their commercial drugs by enhancing safety and usability, thus placing meaningful barriers to competitive threats from generic follow-ons. This strategy can also be employed to differentiate follow-on molecules from the innovator and has particular value for biosimilars. The FDA's Proposed Guidance for Industry on Biosimilars allows for the potential use of delivery systems that are differentiated from those of the innovator product.[12] Biosimilar manufacturers can therefore capitalize on recent advances in delivery systems and also differentiate on something tangible other than price. So whether it is the innovator providing barriers to the follow-on, or the follow-on differentiating from the innovator, the delivery device becomes a meaningful and valuable tool; *Innovation Without Change* allows the differentiation to occur without the development path complexity and sourcing risk traditionally associated with the effort.

The modular approach also makes it easier for engineers and marketers to tailor the device specifically for the drug, user population, or brand. For example, specified colors or logos can be used, or the finger flange and thumb pad can be fashioned to provide a more robust interface. But *Innovation Without Change* can do something more revolutionary. As the trend toward home administration of injectable medications continues, home injectors will seek the kind of individual customization that is more typical in products from technology and consumer goods industries. Just as consumers select different covers and colors for their iPhones or will change backgrounds for their Apple Watches, what if consumer injectors could customize their safety injection device with à la carte component choices? *Innovation Without Change* provides the modularity needed for devices to be customized and built for individual tastes and preferences. When the modularity of the device converges with regulatory strategy vision and supply chain flexibility, the possibilities exist for the expression of "personalized medicine" in injection devices.

FIGURE 5



The Companion allows conventional reconstitution with the benefits of passive needlestick safety and automatic single-use technology, but eliminates the fear of premature safety activation or improperly connected needles.

SUMMARY

A rigorous, risky development and regulatory process forces pharmaceutical manufacturers into a bad compromise between advances in delivery systems and the time, cost, and risk associated with those advances. Often, the choice is to forsake the advances, even if the expected benefits can include life-saving safety improvements and human factors enhancements that lead to safer, more

efficient, and more effective healthcare. *Innovation Without Change* shifts the paradigm and affords drug manufacturers the flexibility they have not previously had. The Credence Companion Safety Syringe System, built around the foundation of an existing drug container and components, allows a modular "pick-and-choose" approach to the design of the delivery device. By minimizing the cost, time, and risk of commercializing their drugs with the Companion System, pharmaceutical manufacturers can incorporate the differentiating safety and usability features that their users need, that legislation requires, and that customers increasingly mandate. ◆

For more information, please visit www.CredenceMed.com or email info@CredenceMed.com. This product has not yet been evaluated by FDA.

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

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BIOGRAPHIES

John A. Merhige is Chief Commercial Officer at Credence MedSystems, leading the company's business development, sales, and marketing strategies. Previously, John was Vice President, Market Development at Sanofi BioSurgery. He joined Sanofi upon its acquisition of Pluromed, which he joined in its early stages and was a member of the executive management team. Previously, Mr. Merhige founded Prelude Devices to identify early stage medical device ventures and gained general management and commercial leadership experience at Ford and Avery Dennison. He graduated from Dartmouth College with a Mechanical Engineering degree and returned to Dartmouth for a Masters in Engineering Management from the Thayer School of Engineering and the Tuck School of Business. He is a member of MassMEDIC, MassBio, and has served on the Board of Directors of the MedDev Group (MDG).

Dan Thayer is Technology Director of Credence MedSystems, where he uses his deep industry knowledge to further the company's product development and intellectual property efforts. He is a successful entrepreneur and skilled problem solver. His experience includes ventures in the hospitality and auto industries; in the latter he performed as a racing and test driver for Toyota USA, GM, Mercedes, BMW, Anson, and Tiga race cars. More recently, Mr. Thayer has been focused on needlestick safety technology. His efforts have led to several technological breakthroughs designed to protect healthcare workers and patients.

FORMULATION DEVELOPMENT

Interactive Web Tool Helps Innovators Match Formulations to Drug Delivery Technologies

By: Kurt Nielsen, PhD

Catalent recently launched FormProRx™, an interactive web tool designed to help innovators match formulations to drug delivery challenges. The following will discuss how FormProRx allows users to assess multiple oral drug delivery technologies in order to establish which may be the most appropriate for their molecule.

Recent estimates indicate that up to 90% of drug candidates in pharma development pipelines are poorly soluble. Based on the FDA's biopharmaceutics classification system, which places pharmaceutical agents in groups based on their solubility and permeability, up to 70% of all NCEs are estimated to fall into Class II, with low aqueous solubility and high intestinal membrane permeability, and up to 20% may be Class IV compounds, with low aqueous solubility and low intestinal membrane permeability. The dilemma facing scientists is to find new compounds that combine activity and acceptable aqueous solubility and permeability for oral delivery. Given today's pressures to develop new drug products as quickly as possible, the result is often NCEs that show promising activity but have either poor solubility or poor permeability, or both.

A recent survey conducted by Catalent indicated that 74% of formulation scientists claim to have worked with compounds that are poorly soluble or permeable in the past year. These scientists need to rapidly assess a variety of drug delivery and bioavailability enhancement technologies if they are to meet the regulatory and performance demands of clinicians running trials, as well as global commercial markets if the drug ultimately gains approval. There is therefore a huge need for techniques that facilitate this fast assessment of the advantages and disadvantages of all available technologies if compounds are to be advanced into and through the clinic in a timely manner.

R&D teams at pharma companies – or the contract development and research organizations they have contracted to assist them – have a responsibility to use this rapid assessment of formulation technologies as an opportunity to create value for patients, payors and the industry alike. However, some may not consider all available technologies when making their evaluations. This may lead to a program being discontinued when there was a perfectly acceptable solution out there, if only they had the time and technical resource/capability to look more widely. Indeed, many drugs have failed in Phase II, and yet have been revitalized at a later stage, either by an in-house development team or at a another company with different clinical goals or commercial aspirations, where scientists have looked more widely for the optimal bioavailability enhancement or drug delivery technology. Furthermore, given the length of time a team works on a single NCE or a formulation, few formulators have the opportunity to gain a truly wide and deep knowledge of all of the drug delivery options that are available to each development program. They may be unaware – or inexperienced in – the perfect technique that would greatly enhance the therapeutic benefit of their molecule, or enable them to deliver it more efficiently.

One way in which a pharma company can expand its

horizons in this field is to partner with a specialist organization whose focus is the application of bioavailability enhancement and modern drug delivery technologies. These companies may have a wider view of what is possible, enabling the pharma company's own scientists to work in partnership with them to solve complex drug development problems. A technology-driven company that specialises in formulation will have that deep expertise in product development. Importantly, they will also be well aware of the additional challenges posed by scale-up through later clinical trial phases and on to commercial quantities, and final manufacturing processes – and have the experience required to suggest successful processes.

Simple tableting techniques are not always effective, and technologies such asparticle-size engineering, hot melt extrusion, lipid-based systems, spray drying, matrix tablets, and beads all offer potential benefits in specific formulation challenges. All of these technologies require experience and expertise if these benefits are to be fully realized. A technology-based formulation specialist will have already experienced the impact of lab setbacks, project failures, and process difficulties, and learnt the lessons these failures provided. Because they have seen projects fail, they are well placed to recommend actions that will prevent failures, will have designed-in program measures to fail weaker formulations at an earlier stage of development and avoid unnecessary cost. In today's budget-conscious environment, working in partnership with one of these experienced specialists allows the right

FIGURE 1

	HIGH SOLUBILITY	LOW SOLUBILITY
HIGH INTESTINAL PERMEABILITY	Class I Well absorbed, absorption rate is usually higher than excretion rate	Class II Bioavailability is limited by dissolution rate Correlation between the *in vivo* bioavailability and *in vitro* dissolution can be established
LOW INTESTINAL PERMEABILITY	Class III Absorption limited by the permeation rate, but the drug is solvated very fast	Class IV "Brick-Like" Poor bioavailability Usually not well absorbed over the intestinal mucosa, and high variability in absorption is expected

formulation solution to be identified at a fraction of the cost – and a fraction of the risk – than would be the case had they started from scratch in house. And, of course, being able to access this wider range of formulation "tricks" should not only save time and money, it will allow better treatments to be reliably supplied, to the benefit of patients.

In early 2013, Catalent launched the Catalent Applied Drug Delivery Institute, with the aim of developing and promoting better formulation as a means for improving treatment outcomes for patients. The Institute was created to harness the knowledge of the world's leading experts in drug development, delivery, and formulation, and partner with pharma companies and academia in order to achieve these better treatments. The Institute has already held a number of events in the US and Europe, with headlines that encompass the challenge being discussed such as "Overcoming Bioavailability Challenges", and where scientists from both industry and academia were brought together in an open forum to discuss challenges facing the products in their pipelines, and the new technologies that might be able to solve those challenges.

Another activity the Institute has overseen was a survey of more than 300 formulation scientists. This survey, run in 2013, was designed to gain a greater understanding of the challenges that are currently facing formulators who are looking to bring efficacious drugs to market (Catalent Drug Delivery Survey 2013). The results clearly showed that numerous technical concerns remain when looking to create ways to overcome solubility and bioavailability challenges. The number one issue that came up time and again in the responses received was that not only are formulation scientists increasingly seeing poorly water-soluble compounds in their pipelines, they are also more challenging in nature than was common in the past. The result is poor bioavailability, and if a solution cannot found, otherwise promising medicines will almost certainly be lost.

To achieve acceptable oral bioavailability, the most appropriate and stable form of the molecule must first be identified, and then delivered at a predetermined rate to a specific site in the body. A good example is the behaviour of APIs in the gastrointestinal tract. Some APIs that are not orally available in tablet form can be absorbed through the buccal membranes if formulations that disintegrate rapidly can

"A recent survey conducted by Catalent indicated that 74% of formulation scientists claim to have worked with compounds that are poorly soluble or permeable in the past year. These scientists need to rapidly assess a variety of drug delivery and bioavailability enhancement technologies if they are to meet the regulatory and performance demands of clinicians running trials, as well as global commercial markets if the drug ultimately gains approval."

be developed. The API's physicochemical properties will determine which excipients and manufacturing processes might be utilized to create an acceptable oral dosage form. The challenge facing the industry is to develop a formulation and associated manufacturing process that will meet all the necessary delivery criteria while also meeting demands for a long shelf-life, minimal restrictions on storage (for example, no requirement for refrigeration), and sufficient patent life to make the product commercially viable. In addition, the process and materials used must be optimized to ensure the cost of goods for the final dosage form is acceptable, and does not greatly outweigh the improved treatment value offered to patients.

Catalent has developed a patent-pending tool, FormProRx, which enables scientists to investigate how different drug delivery technologies could be applied to problematic APIs, based on the characteristics of the drug substance, and the desired properties of the drug product. Drug discovery scientists have used concepts, such as drug-likeness for many years, in an attempt to reduce the high attrition rates many drug development programs face. Yet, there has still been a rise in the number of molecules with higher molecular weights and higher lipophilicity coming through the pipeline. Such molecules all too often have those solubility and permeability problems baked into them because of their physical properties. If formulators and process development scientists had a tool that was easy to use and allowed them to make a quick assessment of all available technologies, then it would be much easier to pinpoint whether a suitable formulation might be available for any drug candidate, whether produced by *in silico* or experimental means.

The tool allows scientists to input the chemical characteristics of their molecule, and the product specifications they are looking to achieve. The proprietary algorithm produces dose form recommendations, based on 80 years of experience in bioavailability enhancement and applied drug delivery for challenging molecules. Whether the product is an NCE or a reformulation of an old treatment, the web-based tool will almost always be able to suggest new approaches that might improve pharmacokinetics, therapeutic profile, or even patient adherence.

The algorithm is broken down into five steps. It is important to note that a "don't know" answer is possible in most of the steps, which allows the user to work through the whole web tool, even if they are still in the very early stages of synthesis or product development. While clearly a fuller picture of the options will be available if as much information as possible is included, this will assist scientists in making informed decisions about the direction their work should go in next.

In the first step, the tool asks for the target product profile, which enables a number of different release profiles and coating systems to be considered that might enable the desired label claims to be achieved. Next, the tool gathers

information on the molecule's solubility and permeability. The third step goes through the various physicochemical properties of the molecule, allowing the tool to assess the formulation challenges that might be expected in achieving the desired dosage form. The most important aspect of this set of questions is the molecule's sensitivity to a variety of different forms of degradation. It asks the user to choose all of the most common physical and chemical conditions that apply in which the formation of impurities or degradation products would likely be most prevalent. These include hydrolysis, heat, liquid phase, oxidation, light, and moisture, and form the basis for the choice of processing techniques that will be included in the final recommendation.

Fourth, the tool goes through questions about expected dosage amounts, and handling classifications in terms of its potency. Finally, information is gathered about how the API will likely be processed, for example milling or salt formation. Optimal API processing can be one of the most straightforward and least costly approaches for enhancing solubility and bioavailability. However, exploiting all available options requires an understanding of the molecule's acid/base properties, as well as its likely solubility and precipitation properties in the different parts of the gastrointestinal tract.

As a result of all this information provided by the scientist, the algorithm creates a set of drug delivery options for further investigation. Its recommendations are split into three groups – best fit, potential, and not an option. This gives the formulation team a starting point to direct their investigations, saving them a good deal of time by discounting some of the options entirely, and pointing them in the direction of the best potential options first. It also provides a brief description of the drug delivery technique in order to facilitate the design of future experiments and validate the results. Suggestions it might present include softgel technology, tablets, capsules (in either immediate-release or modified-release form), hot melt extrusion, or fast-dissolve dose forms. In addition, a molecule profile is generated. This includes a summary of the inputs as a reference that can be shared across a team of scientists.

The challenge for pharmaceutical companies is thus how to maximize the bioavailability of molecules that demonstrate activity, but are often poorly soluble and/or permeable *in vivo*, by selection and careful utilization of the optimal formulation and drug delivery technologies. With the development of new drug delivery technologies and strategies for enhancing bioavailability, companies can begin to think about the oral delivery of drugs that currently have to be given via injection, like insulin or calcitonin. Tools like FormProRx can assist in this process, by sorting through all the many potential options and suggesting the best few, a process that should help accelerate a molecule's path to market. ◆

FormProRx can be accessed at http://www.catalent.com/index.php/FormProRx

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

BIOGRAPHY

Dr. Kurt Nielsen has served as Catalent's Chief Technology Officer and Senior Vice President - Innovation and Growth since February 2010. Prior to joining Catalent, Dr. Nielsen was with URL/Mutual Pharmaceutical Company in Pennsylvania as Executive Vice President, Pharmaceuticals. In his role at URL/Mutual, Mr. Nielsen devised the strategy and led the execution for activities in the company's new product portfolio, employing a variety of business arrangements. Prior to that role, he was Vice President of R&D. Before joining URLMutual, Dr. Nielsen held executive positions with TEVA Pharmaceuticals USA; McNeil Consumer Products; Energy Biosystems, Inc.; Bachem Bioscience; and Hercules, Inc., Arco Chemical Company, and Chubb National Foam. He earned his PhD in Chemistry from Villanova University and his BS in Chemistry from the University of Delaware.

Special Feature

Analytical Testing: A Critical Element in Drug Development

By: Cindy H. Dubin, Contributor

Catalent's technical experts have developed a screening tool (FormProRx™) that considers the physical properties of the molecule along with its solubility and permeability attributes and handling requirements when proposing solid oral drug delivery.

The PharmaCircle Drug Delivery and Formulation Newsletter and Blog

Opinion and Analysis from PharmaCircle on Recent Trends and Developments and the Implications for the Pharmaceutical Sciences Community

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In addition to providing industry leading content, PharmaCircle now delivers a weekly newsletter and blog that focus on issues of interest to the formulation and drug delivery community.

The PharmaCircle Blog: Launched in September, the blog offers analysis from Dr. Josef Bossart, PharmaCircle's Executive Editor, of recent product and technology innovations, pipeline developments, and industry trends. Check for updates weekly at http://blog.pharmacircle.com.

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There is intense competition within the pharmaceutical market – both with regards to developing cutting-edge therapies and in getting them through development quickly to take advantage of patent exclusivity. One of the critical elements in the drug development process is analytical testing. "Analytical testing is required at all phases of development, and it is critical that this support is accurate and efficient," says Eric J. Hill, MS, MBA, President, Impact Analytical. "It is used to verify drug chemistry, and therefore can be a barrier to moving to the next phase in the development process."

The importance of analytical testing is evident by the growth of the CRO sector. ISR's report, "2014 CRO Market Size: 2012-2018," points out that the CRO market was projected to reach $23.6 billion in 2014. With a 7.9% CAGR from 2014 to 2018, CROs are benefiting from the increased rate of outsourcing and increasing R&D budgets from biotech and specialty/generics companies.

This annual report from *Drug Development & Delivery* magazine highlights some of the leading players in the analytical testing space and how they are working with pharma clients to develop quality formulations, get drugs to market faster, and reduce risk.

ABC Labs recommends approaching analytical development as an iterative process of continuous refinement so that the improved/validated techniques are completed as the drug progresses through commercialization.

ABC LABORATORIES—ADDRESSING CRITICAL ROLE OF CMC IN BIOPHARMACEUTICAL IND

Early-stage drug developers generally have their sights firmly set on the initiation of clinical trials, and rightly so: the outcomes of toxicological and pharmacological studies generally determine whether a drug candidate is viable for development. But as many pharmaceutical innovators have learned, the importance of Chemistry, Manufacturing and Control (CMC) data should not be underestimated. Insufficient data or a poorly thought-out approach to CMC can be pivotal to IND approval.

Meeting FDA expectations for CMC requires careful planning. This is particularly true of biopharmaceuticals due to their inherently complicated structures, multiple degradation sites, and cell culture impurities. While the FDA does not require complete characterization of the biopharmaceutical at the IND stage, it does expect a wide variety of issues to be addressed in a submission, such as identification of protein sequence, an activity assay based on binding, assays to demonstrate safety, purity and stability of drug substance and drug product, and determination of immunogenicity and the presence of anti-drug antibodies (ADA) in plasma, a safety concern unique to biopharmaceuticals that presents an additional analytical challenge.

"The diversity of CMC requirements for a biopharmaceutical IND present a variety of analytical challenges, and they require a myriad of analytical methods," says Glenn Petrie, Ph.D., Senior Scientific Advisor, ABC Laboratories. "Many drug developers are overwhelmed by the multitude of options and decisions that must be made. Consequently, they often tend towards 'analysis by

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paralysis.' Rather than prioritize, they perform each and every study reasoning that they have covered all the bases relative to FDA requirements. This results in a tremendous waste of time and resources. Perhaps more importantly, the inclusion of superfluous data in a submission can lead to confusion and delays in the approval process."

How can a drug developer ensure a safe, pure, and stable drug in the most efficient manner possible? Dr. Petrie suggests that studies need to be phase-appropriate, performed in parallel and proceed as a continuum. Up to and including Phase 1, analytical methods need only be qualified, not validated. Linearity, precision, accuracy, and specificity will suffice at this stage. When planning an approach to analytical methods, it is important to evaluate several possible techniques simultaneously and determine which are optimal for your application. Finally, it is important to approach analytical development as an iterative process of continuous refinement so that the improved/validated techniques are completed as the drug progresses through Phase 2, Phase 3, and commercialization.

AVOMEEN ANALYTICAL SERVICES—STAFF AND EQUIPMENT DEVELOP RELIABLE TESTING METHODS

Modern CROs have to evolve to meet the growing needs within the pharmaceutical industry. As products become more complex the required analytical testing associated with them also builds in complexity, thus newer more sophisticated methods and instrumentation are required to meet ever increasing demands. The skills of a company that can properly meet these needs are strongly desired by many companies within the industry and are needed more and more every day.

"It's interesting to see that problems that were once considered impossible not too long ago are now becoming realities in the pharma world, although the burden is on analytical chemists to provide safety easements and to develop reliable release testing methods for these products," says Shri Thanedar, Ph.D., CEO & Chief Chemist of Avomeen Analytical Services. "One example of this is targeted drug delivery to a specific part of the body. This modern technique requires the development of a formulation that can not only successfully navigate and travel to a specific part of the body, but can do so without destroying or harming the API it contains."

Dr. Thanedar explains that Avomeen assisted a client by developing an analytical method that tests for an otherwise insoluble

component that the FDA required to be analyzed due to a particular ingredient. "We have developed an extraction and functionalization that is capable of quantifying that specific component," he says. "This ability to solve for unknowns, overcome complex problems, and the utilizing of a unique blend of experienced staff from multiple industries and disciplines was critical to the success of this project."

"What was once innovative just a few years ago is now considered routine and the level of sophistication needed to solve these modern problems grows daily," continues Dr. Thanedar. "Much of the low-lying fruit is gone and companies have to reach farther to get a product on the market."

To address its clients' complex needs, Avomeen relies on its experienced staff and has a completely redesigned, customized 2,500-sq. ft. facility equipped with many segregated laboratories that contain state-of-the-art equipment, including GLP/GMP labs, R&D labs, formulation suites, ISO-7 compliant clean rooms, and more.

CATALENT PHARMA SOLUTIONS—OPTIMIZING SOLID-STATE FORMS

Programs in the early stages of development are often challenged by complexities associated with the chemical and physical properties of the drug. These properties can, in turn, lead to challenges developing analytical methodologies and delivering the drug in a manner that enables its safety and efficacy to be clearly established. Thus, it is recommended to partner with workforces comprised of highly trained scientists and analytical testing and development partners who have accumulated extensive libraries of experiences that span a range of molecule diversity and attributes. Many of these organizations have partnered with hundreds of companies to advance molecules over both technical and regulatory hurdles. Cultivated from these experiences are sophisticated and efficient workflows that drive fundamentally sound technical outcomes.

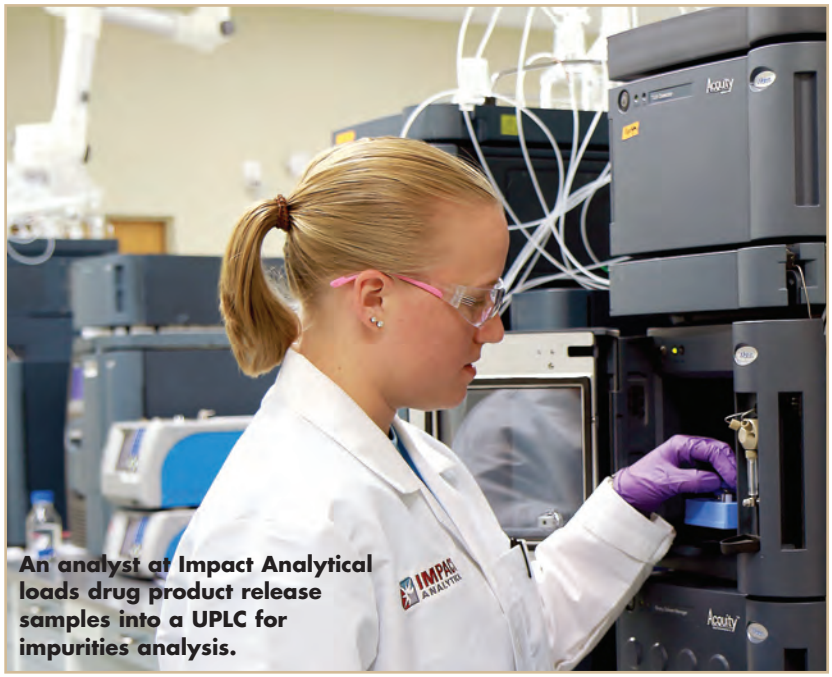
One example of this is Catalent Pharma Solutions' Optiform® technologies platform. This platform combines sophisticated informatics and automation tools to design and assemble salt and crystal-form screening studies. "When combined with high-end solid-state analytical capabilities (e.g., high-throughput FT-Raman, X-ray powder diffraction, and thermal analysis) and a highly experienced technical workforce, an optimized solid-state form can be selected in a short period of time utilizing a relatively small quantity of drug substance," says David Igo, Director Product Development with Catalent. These materials can then be employed in early PK studies to support a fast-to-fail development model.

Development organizations draw their strength from an integration of services that begin with preformulation activities and extend through clinical and commercial manufacturing support. Through this integration, they are able to develop both broad and deep partnerships with clients that are supported by comprehensive analytical services. The services critical to the success of development programs include an agnostic preformulation service that allows the physico-chemical properties of the active pharmaceutical ingredient to be evaluated against attributes important to the intended product profile (e.g., solid-oral dosage form, subcutaneous injection) without being biased by a target drug-delivery technology.

"At Catalent, our technical experts have developed a screening tool (FormProRx™) that considers the physical properties of the molecule along with its solubility and permeability attributes and handling requirements when proposing solid oral drug delivery," says Dr. Igo.

IMPACT ANALYTICAL—A THREE-PRONGED APPROACH TO QUALITY RESULTS

Intense competition among drug developers has placed pressure on analytical testing providers to generate quality results quickly. Impact Analytical has responded to this pressure by assembling an experienced staff, equipped them with top-notch equipment, and



An analyst at Impact Analytical loads drug product release samples into a UPLC for impurities analysis.

designed a laboratory around its work process.

The team of scientists is experts in their respective areas, such as the latest cGMP regulations and USP methods. "Having this experienced team ensures efficient transfer of knowledge between the development scientists and the analytical team," explains Eric J. Hill, MS, MBA, President, Impact Analytical. "It also ensures the right experiments are undertaken to meet the demands of development, while meeting all regulatory requirements. If problems or unexpected results arise, an experienced team can react quickly without compromising the overall timeline."

Just as important as staff is access to up-to-date equipment that is properly qualified and maintained. The Impact Analytical lab contains multiple UPLC, HPLC, GC, GC-MS, and LC-MS systems. "This gives us the bandwidth to handle large project loads, while ensuring the equipment can handle the demands of regulatory work," says Mr. Hill. "We attempt to dedicate systems to common set ups (eluent sets, carrier gases, etc.), which decreases set-up time."

Finally, lab set-up can be a contributing factor to throughput. Mr. Hill explains that Impact Analytical has deviated from the traditional set-up of segregating analytical disciplines in separate laboratories (LC, GC, molecular characterization, etc.). "When we built our new facility, we created two main laboratories–a prep laboratory and an instrument laboratory. This reduces contamination by segregating chemicals and standards away from instruments. It also creates a better team atmosphere that promotes instrument sharing and cross-training. This set up matches our work processes, which improves throughput, safety, and accuracy."

METRICS CONTRACT SERVICES—STAYING AHEAD OF NEW USP TESTING GUIDELINES

The pharmaceutical industry is facing substantive changes being made by the U.S. Pharmacopeial Convention (USP) concerning the testing of elemental impurities. The new guidelines take effect in December 2015.

Until recently, testing for metal impurities in pharmaceutical products has been limited to a few compendial procedures in excipients, residual catalysts, and a metal detector at the end of the production line to check for shards. That will change with the implementation of the USP's new guidelines. The intent is to replace the existing benchtop, heavy-metals procedure with more modern and effective techniques, such as ICP and ICP-MS. The guidelines also introduce the requirement to monitor finished product for possible metal shed from processing equipment and container closures. Once the rollout is complete, manufacturers will be expected to have results for their products, as well as some assessment of process to assure minimal contamination.

Theoretically, testing for elemental impurities is like any other analytical procedure – the sample is prepared, tested on an instrument versus calibration standards, and the levels of impurities are calculated and reported. But practically, it requires specialized equipment for both preparation and analysis that many

pharmaceutical labs do not currently operate.

Microwave digestion is the sample preparation tool of choice for ICP and ICP-MS. It is fast, effective, uses minimal sample, and is applicable to nearly all kinds of samples. Metrics offers different models that can be selected based on the required throughput. Sequential or batched digestion is available.

Once digested, the analyst will select ICP-OES or ICP-MS based on the sensitivity required. Because the required limits are scaled by the daily dose, ICP-MS will be used for the majority of analyses, especially for injectable or high-dosage products. The latest ICP-MS systems also use interference correction systems to reduce the risk of false positives. Conveniently for the analyst, both ICP-OES and ICP-MS can determine more than 50 elements simultaneously.

Metrics operates a dedicated trace elements laboratory. "We currently operate two microwave digestion systems as well as late-generation ICP and ICP-MS instruments, and can leverage existing methodology to diverse products and dosage forms," says Krzysztof "Chris" Golebiowski, Vice President of Analytical Services at Metrics Contract Services. "While these new requirements make a step into unfamiliar territory for a number of manufacturers, Metrics is positioned well ahead of the implementation of the new chapters with the experience and equipment that is needed."

TABLE 1

Dosage Form	Sample Preparation	Analytical Technique
Oral, 1g/day	Microwave	ICP-OES, ICP-MS
Oral, 10 g/day	Microwave	ICP-MS
Mucosal	Microwave	ICP-MS
Topical	Microwave	ICP-MS
Parenteral	Neat	ICP-MS
Inhalant	Dilution	ICP-MS

Metrics Contract Services: Sample preparation and analytical techniques by dosage form

PARTICLE SCIENCES—SHORTENING TIMELINES AND MINIMIZING RISKS

The Analytical Services Department at Particle Sciences consists of 21 dedicated scientists trained to characterize drug products at stages of drug development from proof-of-concept through support of clinical trial material release and stability testing. The group works in GMP-compliant laboratories in cross-functional teams led by internal project management. Combined, the group has more than a century of pharmaceutical analysis experience with small-molecule APIs and complex delivery systems for biologics. Using state-of-the-art instrumentation including HPLC, particle size analysis, mass spectrometry, rheology, gel electrophoresis, and other modern analytical techniques, the group provides timely and critical information on the drug product to guide formulation development, explains Laurie Goldman, Director, Analytical Services for Particle Sciences.

Assessment includes physical testing as well as chemical characterization on a range of dosage forms, including solid oral dosage, topical/mucosal/transdermal delivery, nanoparticulate and microparticulate injectables, ocular administration, and combination drug-eluting devices. Methods are developed with the intent of providing immediate feedback on stability and delivery of drug. As such, methods are developed to be stability-indicating and indicative of *in-vivo* release.

PSI uses stability-indicating methods in early stages of development to correlate how the manufacturing process influences the stability of the API. These results inform the formulators in their choices and direction. In later stages of development, stability-indicating methods are used in ICH-compliant long-term product stability studies. *In-vitro* release studies are used in early stages of development to compare delivery from various dosage forms and formulations. In later stages of development, they may be used as quality control tests to indicate if changes in the product over time have resulted in any change to the release of drug substance from the

drug product. Once *in-vivo* data is available, an *in-vitro* method that has been established to show *in-vivo/in-vitro* correlation can be used to assess potential changes to the drug product or manufacturing process.

Methods are developed to be fit-for-purpose, providing a level of confidence in the results produced from them. When appropriate, methods are validated according to ICH Q2B guidelines to a level appropriate to the development phase being supported. Physical characterization methods are performance-verified for support of GMP studies. In early stages of product development, when validation is not necessary, a more limited evaluation of analytical methods is performed to assure results generated from them are scientifically sound.

Compliance to GMP regulations is mandatory in all laboratories. Compliance is ensured by a combination of ongoing training of analysts on the techniques in use, formal qualification of instrumentation, and method validation. "These fundamentals provide the foundation on which solid, reliable methods are used to generate and interpret the critical information necessary for efficient and effective drug product development," she says.

SGS LIFE SERVICES—A FOCUS ON BIOLOGICS

About 10 years ago, SGS Life Science Services took a step towards large molecules by opening its first biologics testing laboratory in Wavre, Belgium, and continues to invest in biologics testing. This was achieved through both the acquisition of the M-Scan Group and through the development of specific, large-molecule testing services in a number of the existing, traditionally small molecule, SGS laboratories in its global network.

"For companies new to the biopharmaceutical market, they see SGS very much as a consultative partner rather than a service provider, and look to us for advice as to how to design experiments and how to deal with regulatory issues, whereas previously clients would approach us with a pre-determined list of tests to conduct," says Dr. Mark Rogers, Senior Vice President, Life Science Services, SGS North America Inc. To reduce development times, especially amongst smaller and mid-size biotech companies, it is becoming more common for clients to engage with service providers earlier and on a more collaborative basis.

"The industry has the same types of challenges it always had, but technology has moved on and continues to influence the rate of change," explains Dr. Rogers. "Clients, although all working in the same "industry," will always have unique requests based on their experience and particular field of research. There is always the potential for a client to have an unexpected and immediate need for a unique test or expertise. It is up to service providers to anticipate the industry's needs."

Such an example is in the specific area of biologics testing. Dr. Rogers says that clients look for service providers to define higher order structures as the rule, rather than the exception. Such techniques are now applied in characterization of primary products, as well as for comparability studies such as in the testing of biosimilars. "This service has been offered by SGS for several years but has recently seen increased numbers of requests," says Dr. Rogers. "Consequently, SGS has made investments in its capacity within its global laboratory network. The challenge will continue to be meeting the demand for increased rate of testing, with greater orders of precision and accuracy."

SGS recently opened a facility in Carson, CA, to provide bioanalytical testing, its first facility in North America. Sites in France and Belgium have validated more than 700 methods and this experience can be transferred to Carson for clients who would be looking to have this testing performed in North America.

XCELIENCE—DEVELOPING ANALYTICAL DATA FOR BETTER FORMULATIONS

Quality Control is an important part of release testing for both commercial and clinical drug products. The accurate quantitation of drug in the dosage form is critical to ensure that the patient is neither under or over dosed. In addition, during formulation development, it is necessary to provide accurate testing results to help guide the formulators in the development and optimization of the dosage form. Better formulations and processes are proposed and defined based on the analytical data.

"Xcelience formulators work closely with the analysts to generate data that can be used to optimize the formulation," says Yide Chang, Ph.D., Manager, Analytical Services, Xcelience. "The goal is to provide a simple, accurate and robust testing method that provides the necessary information. The analyst must always balance maintaining quality with the need for speed and cost."

The principle types of analytical methods for new drug development are potency of the drug, impurities, and dissolution in various media. For potency and impurities, scientists develop simple and robust methods for their intended uses, which include monitoring stability of new drugs or new formulations. Method parameters and appropriate sample preparation procedures are critical in the development of new methods. For dissolution testing, the analytical team will develop suitable methods for water soluble or for highly soluble active pharmaceutical ingredients. Initially, the early methods will be used to compare different formulations. These methods should be developed well enough to provide formulators direction for decision making. Suitable analytical methods need to be well developed and evaluated.

Once the formulation is finalized, it will be a simple process to validate the analytical methods. Later, the methods will be used for quality control, performance of drug products in stability studies, IVIVC, or other purposes. "Xcelience's expertise and focus during development has been extremely advantageous in our later activities for manufacturing for clinical and for commercial production," says Paul Skultety, PhD, Vice President, Pharmaceutical Development Services, Xcelience. "Robust development results in test methods that can deliver accurate results with less chance for repeated testing, out of specification or out of tolerance results or other testing failures, as well as analytical results that can be reported with a high level of confidence."

One of the biggest challenges for the Xcelience analysts is that there are more potent compounds in early development that require dosage strengths as low as microgram levels. These formulations present a challenge to the analyst to accurately quantitate the active compound and the quantitation of related substances or degradant compounds. Solutions for these challenges include increasing the sample concentration and/or injection volume of the sample.

In addition, online procedures for concentrated sample preparations, UPLC, and/or detection, other than traditional UV/VIS, could be employed to meet the challenges. For dissolution testing, small-volume dissolution apparatus may be used and more efficient testing methods may be developed. "Use of techniques such as these has allowed Xcelience to provide analytical support of low-dosage form development," says Dr. Chang.

For the fastest approach to get an active in First in Human clinical studies, Xcelience uses Xcelodose technology, which can fill active pharmaceutical ingredients directly into capsule shells to provide doses in the microgram levels. In addition, low-dose capsules or low-dose tablets can be developed. ◆

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When we talk about an aging facility, we are, in most cases, talking about not only the facility but also the manufacturing processes and analytics used in producing the drug substance or drug product. How does one approach the task of modernizing an aging facility, taking into account the complex financial, technical, regulatory, and supply chain impacts?

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Shri Thanedar, PhD
CEO & Chief Chemist
Avomeen Analytical Services

"Our model as a customized full-service CRO has proven to work, and as we continue to grow, so does our capacity to better serve the pharmaceutical marketplace. No one will ever question why you decided to use Avomeen, but they may question why you didn't."

Avomeen: A Unique Approach to the Traditional Analytical CRO

Avomeen Analytical Services breaks the mold of a traditional CRO by bringing multidisciplinary experts from a range of industries together into a large state-of-the-art facility. This unique blend of talent allows the fast-growing laboratory to break away from just routine projects and allows them to effectively solve even the most complex problems that often times arise within the research and development stages of a pharmaceutical product. Headquartered in Ann Arbor, MI, the analytical testing laboratory has seen tremendous year-over-year growth due to its clients' appreciation to the customization they receive, reliability of results, and exemplary customer service. Drug Development & Delivery recently caught up with Shri Thanedar, PhD, CEO & Chief Chemist at Avomeen Analytical Services to discuss what sets his company's analytical laboratory apart from other CROs that serve the pharmaceutical industry, some of the laboratories non-routine service offerings, and how their unique approach has helped them to maintain the incredible year-over-year growth of the company.

Q: What makes Avomeen's pharmaceutical development program unique?

A: Many CROs only work on projects within a limited scope in order to complete a high volume of routine tests with little to no customization to the individual client being served or the specific sample being analyzed. The caliber of our staff and our ability to solve both unusual and highly complex problems sets Avomeen apart from these types of laboratories. At Avomeen, more than 70% of our scientists are PhDs or Masters Level, which is a much higher percentage than you will find in companies geared toward high- volume routine work. Our model is geared toward customizing every project to meet the specific needs of the client. Our clients like that we are able to create definitive methods on complex products, such as an API that is difficult to solubilize or if they have an active ingredient to be analyzed that is not a small molecule

but instead is something larger, such as what is found when testing an oatmeal based product what sets Avomeen's analytical laboratory apart from other CRO's that serve the pharmaceutical industry, some of the laboratories non-routine service offerings, and how their unique approach has helped them to maintain the incredible year-over-year growth of the company.

Q: Avomeen has about 35 current employees, what is the appeal of a laboratory your size?

A: We are a smaller CRO, this helps us to be nimble and react to our clients' needs in a faster manner. When a new project comes onboard' we put together a dedicated specialized team of scientists whose skillsets are tailored specifically to that type of work. We appeal to smaller and mid-sized companies as a better choice than going with a large CRO because they are primarily focused on multi-billion dollar pharma companies and often do not treat smaller companies with the same level of respect or attention as their more profitable clients; whereas for us, small to mid-sized pharmaceutical companies are our sweet spot. That is who we service most often, and as we are not a volume-based company, we are able to provide them a higher quality and more reliable service.

When you have a molecule you are relying on for the future of your company, you want someone to take care of it and treat it as important as you would yourself, that is where is we come in. Conversely, there are also many very small CROs composed of just a few people. These laboratories don't have the necessary sophistication, quality systems, or advanced state-of-the-art analytical instrumentation that we offer. So we are not among the monstrous organizations that only look for large billion-dollar clients, and we are also not one of the really small 3 to 5 person mom-and-pop-type laboratories.

Q: What does Avomeen offer when it comes to pharmaceutical development?

A: We provide preformulation and formulation development, a complete range of CMC analytical testing services, method development, validation, and transfer services, clinical trial manufacturing, stability, degradation, extractables/leachables analysis, and more. The focus of our testing is taking the API and getting it into the clinic as fast as possible. We are also unique in that we can assist pharmaceutical developers and researchers at any stage of their development process. Whether preclinical, clinical, or after market, we are able to support the clients' individual needs and quickly jump into action.

Q: Do you offer any services or expertise that other CROs do not?

A: Many CROs have skilled pharmaceutical scientists, but most lack multidisciplinary scientists. They lack the polymer, material, and metallurgy experience that our staff possesses. Because Avomeen also services other commercial and industrial industries, we have a broad base of expertise that includes inorganic chemists, organic chemists, chemical engineers, pharmaceutical scientists, material scientists, polymer chemists, and more. Due to this, we are able to handle situations that land outside of the traditional drug molecule testing. For example, many extractables/leachables studies are performed on rubber stoppers and other items that are polymer based. So while many CROs do not have multidisciplinary expertise, we have the polymer specialists you will require in-house that work together with our pharmaceutical scientist to create a better E&L study for a rubber stopper and other unique items than a typical CRO could.

Q: In addition to your broad expertise, does Avomeen differ from typical CROs in any other ways?

A: Absolutely, one of the key differences is our size. As a mid-sized laboratory, we are neither too small nor too big. We are not so large as to only appeal to companies like Pfizer or Merck who often look for laboratories with high volume and narrow focus. Instead, we can cater to companies that require a customized approach from a laboratory that offers a range of services, this helps insure their drug product gets to market as quick as possible and at a lower cost.

Our customer contact is another thing that sets us apart; from the initial project discussion through the completion of your project, our clients are in communication directly with one of our technical directors and their dedicated team of chemists. One thing that our clients really appreciate is that even our internal business development team is composed of

TABLE 1

Tableting/Capsuling Instrumentation

Granulation

- High Energy Granulators
  -Littleford, Fielder, Diosna, Vector, Glatt
- Medium Energy Granulators
  -Planetary, Ribbon, Sigma
- Low Energy granulators:
  -V-Blenders, Double Cone, Fluidized Bed Granulators (FBG)

Milling

- Dry Particle Milling
- Low-Medium Shear Mills
- Quadro Comil
- Oscillating Granulator
- Medium- High Shear Mills
- Fitzpatrick Fitzmill
- Tornado Mill
- Hammer vs. Blade Hit Type

Blending

- Drum Blenders
- Patterson Kelly V-Blender
- Twin or Single Shell
- Optional Intensifier Bar
- Low Energy

Compression

- Rotary Press
  -B3B Manesty 16 Station Tablet Press
  -Manual or Automatic Compression
- Single Station Press
  -521-2 Stokes
  -F Stokes

experienced PhD scientists; what this means for them is they get an experienced scientist helping them right from the start by offering advice and suggestions during a complementary initial consultation that helps to insure the project quoted and taken on will solve exactly what they are looking to complete. We have had a number of clients request a large package of services but unknowingly not include an item in their request list that would have left them with regulatory troubles and delays further on down the line had our staff not picked up on it. That's the difference you get when you work with our sales staff who are experienced chemists versus most laboratories sales staff who are composed of individuals who aren't as familiar with the industry and its regulatory requirements.

Q: What type of facilities and instrumentation do you have?

A: Avomeen has state-of-the-art facilities for our pharmaceutical development services, and we are constantly expanding on our growing capabilities. We have multiple ISO 7-Compliant clean rooms of various sizes spanning 1200 square feet of laboratory space. We have the equipment to perform both wet and dry granulation as well as tablet presses and capsule manufacturing capabilities in order to create and prepare clinical trial supplies. A few highlights of our tablet and capsule instrumentation are shown in the table.

Our laboratory is a 25,000-sq-ft facility consisting of segregated labs, including Clinical Trial Manufacturing (CTM) Suites, GLP/GMP Labs, Instrumental Analysis Labs, R&D Specialized Labs, Chromatography & Spectroscopy Labs, Formulation Suites, and more.

Q: Has your unique approach to CRO services proven beneficial?

A: We believe so; we have been a fast growing company, averaging 40% to 70% year- over-year growth for the first 3 years of the company. In the next 3 years, we expect to double our size once again. This impressive growth is due to how much mid-sized pharmaceutical companies appreciate our service offerings and technical expertise, with many of our clients coming back to us with additional larger projects after a successful timely completion of their project the first time around. Our model as a customized full-service CRO has proven to work, and as we continue to grow, so does our capacity to better serve the pharmaceutical marketplace. No one will ever question why you decided to use Avomeen, but they may question why you didn't.

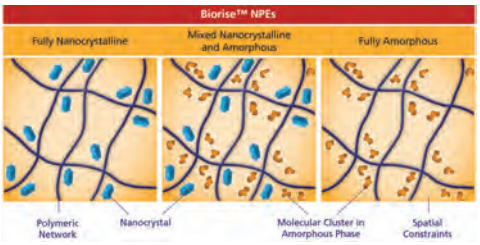
Technology & Services Showcase

Analytical Support Services

better insight
better outcomes

ABC provides IND-enabling, registration, and post-commercialization support for the development, quality control, and lifecycle management of innovative therapies and generic medicines. Our personalized, results-based approach to development strategy is backed by decades of experience delivering GLP- and CGMP-compliant analytical testing services across all types of APIs and formulations. Through development know-how, cross-disciplinary technical expertise, and applied experience with evolving global regulatory frameworks, we help efficiently advance and manage programs for large and small molecule drugs, medical devices, and combination products. Our mission is to become a trusted extension of our client's product development teams, helping them meet the global demand for safer, more effective products. Our approach to doing business promotes relationships beyond a simple transaction. This, in turn, improves decision-making, expedites development, and reduces risk. In other words, "better insight, better outcomes." For more information, visit ABC Laboratories at **www.abclabs.com**.

Bioavailability Enhancement Technology



Aptalis Pharmaceutical Technologies is focused on developing high-value products with robust, defensible proprietary positions that grow the commercial value of our partners' portfolios. We develop new formulations or out-license existing product formulations that leverage our broad range of proprietary technologies, which include taste masking and orally disintegrating tablets (ODTs), customized drug release, and bioavailability enhancement. Biorise™ Bioavailability Enhancement Technology enhances bioavailability of drugs that are poorly soluble at physiological pHs. This technology creates new physical entities (NPEs) with better solubility profiles. NPEs are produced by transforming the original crystalline form of the drug into a nanocrystalline and/or amorphous, thermodynamically activated solid form–characterized by higher solubility–thereby enhancing the rate and extent of absorption in the gastrointestinal tract. Transform the value of your portfolio by visiting us at **www.AptalisPharmaceuticalTechnologies.com**.

Specialty Ingredients

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

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Technology & Services Showcase

US-Manufactured Tromethamine

BioSpectra's cGMP, US-manufactured ICH Q7-based Tromethamine, for use as an API, will be produced in its new FDA-registered facility in Bangor, PA, in Q4 2014. Regulatory Packets, Validation Reports, and Type II Drug Master File Authorization are scheduled for contract customers of Bio Active Tromethamine during Q2 2015. Bio Active Grade Tromethamine, Product Code TR22, will be manufactured in a qualified, validated ICH Q7-compliant API manufacturing suite as a highly purified crystal with optimum solubility, purity, and traceability. Future versions of will include liquid and spray-dried forms, both of which are currently scheduled for release in Q3 2015. This product will be added to the current portfolio, which already includes BioSpectra's Bio Excipient Grade Tromethamine, Product Code TR32, which is an ICH Q7-compliant Excipient supported by a Type IV Drug Master File. For more information, contact BioSpectra at (877) 982-8333 or visit **www.biospectra.us.**

HPMC Capsules

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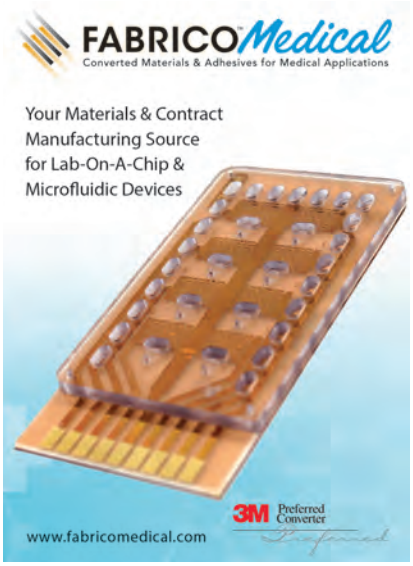

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TOPICAL DELIVERY

The Importance of the Right Formulation in Topical Drug Development

By: Vijendra Nalamothu, PhD

BACKGROUND

Topical formulations for pharmaceutical delivery are becoming increasingly popular. Topical delivery has a number of advantages: the ability to deliver drug substance more selectively to a specific site, avoiding fluctuations in drug levels, inter- and intra-patient variations, improved compliance, and an enhanced suitability for self-medication. Skin provides an ideal site for the delivery of drug substances for both local and systemic effects. However, it also acts as a mechanical barrier to the penetration of many drug substances.

In a survey by Frost & Sullivan, reported in the July/August 2014 issue of *Drug Development & Delivery*, physicians indicated that they prefer topical delivery and are willing to switch to topical delivery from their current mode of therapy. All of the advantages of topical therapies rely on having the right formulation. A small change in the formulation can make a large difference in the efficacy of topical treatments.

With topical therapies, the formulation is as important as the molecule itself because the interaction of the vehicle with the skin can alter the efficacy of the penetrant. The formulation ensures that the drug substance is delivered to the right target site and that it maintains dosage integrity, drug transport, and active duration.

For example, the drug substance in a psoriasis treatment may have some efficacy simply from the hydrating or soothing effects of the formulation. Whether the molecule maintains purity, potency, and delivery to the right target site may be masked by the ingredients that surround it. Both the mechanical barrier properties of the top layer of skin, stratum corneum, and the physicochemical properties of the drug affect the transportation of the drug substance from formulation vehicle to the site of action.

In addition to the formulation components, a simple change in properties, such as pH, viscosity, the relative amounts of oil, water, surfactants, stabilizers, droplet size, ionic nature, or the method of preparation, can often influence skin absorption and efficacy.

Good formulation development should have preformulation studies and careful selection of excipients, including stabilizers and permeation enhancers, early stability studies, cell line/tissue toxicological studies, IVRT and skin penetration studies, and finally formulation development and optimization.

THE RIGHT COMBINATION OF DRUG/EXCIPIENTS

The selection of the right excipients for topical formulations is extremely important. The drug substance may be efficacious, but its interaction with excipients may alter the following:

- Its ability to permeate through skin

- Its stability through shelf life
- Its ability to not metabolize in skin
- Its ability to stay dissolved at right concentrations
- Its capability to achieve desired release rates

For a recently developed topical formulation, Tergus optimized an emulsion cream to dissolve the drug up to a certain concentration. The excipients were chosen to optimize the solubility of the drug substance and to prevent oil and water phase separation. However, a change in formulation to increase the drug concentration, so it could accommodate the toxicology study requirement, resulted in phase separation due to inadequate emulsifiers. The formulation was redone to optimize the concentration of emulsifiers, as well as the addition of a viscosity-building excipient. A non-homogenous cream could have resulted in erroneous toxicology outcomes.

For another project, Tergus worked with a novel molecule that had undergone preformulation, solubility, and selection of excipients. Analysis showed drug substance degradation and increasing impurity levels. Forced degradation studies were performed to prove which kind of degradation was affecting the molecule.

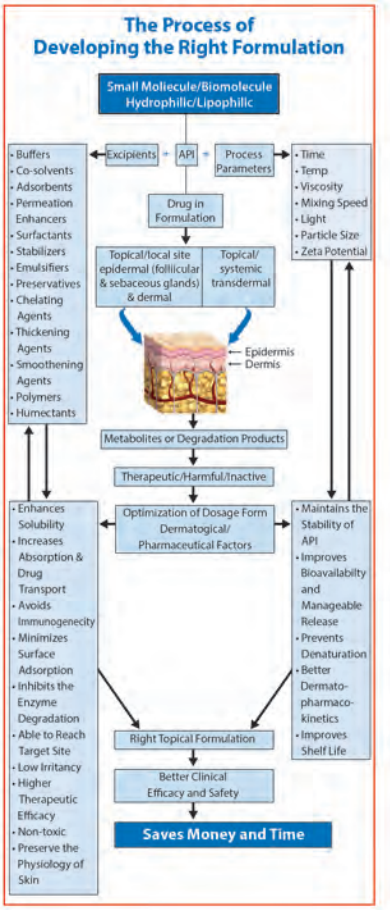
It was discovered the drug was undergoing oxidative degradation in the formulation. Steps were taken to prevent oxidation through the careful selection of excipients, limit exposure to atmosphere, and minimize drug degradation. Investigation into the root causes were conducted and found that trace levels of peroxides were in one of the excipients. Early stage development used the same excipient in a pure grade, so oxidation was not prevalent. During scale-up, another supplier of the same excipient was chosen, and this particular supplier's material had low levels of peroxides which degraded the drug substance. Once the cause of oxidation was determined, the formulation was manufactured with the right grade of the excipient.

During the early stages of development of topical formulation, attention must be given to the permeation enhancers. The bioavailability of the drug in the desired location, ie, epidermis or dermis, must be considered when choosing the right excipient. A solvent that forms a depot of drug concentration may not be ideal for a drug that has site of action in stratum corneum or epidermis.

Similarly, during a product development project at Tergus, it was discovered during skin permeation studies that the efficacy was best when two permeation enhancers were combined. Early detection of such issues is crucial and helps in selection of right formulation before expensive clinical trials are conducted.

While researching excipient compatibility and selection for drug substances/peptides targeted to the dermis, it was discovered that impurities rose in line with increasing pH of 4-7. In skin permeation studies, the release of the peptide was very poor. Homogenates of epidermal and dermal layers of skin at different periods of time showed more stability of the peptide in the dermal layer when compared to the epidermal layer. By explaining the peptide

FIGURE 1



concentration in skin tissues, Tergus found that the peptide was going through degradation with proteolytic enzymes.

Formulation optimization proved that a more acidic environment delivered the peptide to the right target layer while avoiding degradation and maintaining efficacy. The pH in formulations, particularly how it reacts to pH factors in different layers of skin, is very important. The epidermal layer is more acidic, acting as a defense and barrier, so creating a more acidic environment for the formulation allowed this particular peptide to be delivered to the target site.

IMPACT OF MANUFACTURING PROCESS PARAMETERS

It is a well-known fact that scale up and certain other process parameters impact the drug release rate from the formulation. The FDA has developed guidance for the industry to study the impact of Scale Up and Post Approval Changes (SUPAC) for the marketed product. The same principles can be applied to the study of the impact of manufacturing process parameters in choosing the right formulation.

The amount of shear produced by the equipment during the emulsification can impact the formulation. In a recent project, the formulation for Phase II supplies was being scaled up from Phase I. The viscosity differences led to the need for process optimization to prevent product efficacy differences between two phases of clinical study.

In another project, the order of addition of the drug phase made a huge difference in drug stability/compatibility with the formulation excipients. The drug-solvent solution was added to the cream when it was cooled to 40°C, as opposed to adding it to water phase at 70°C. By making this change in the order of addition, the drug stayed in solution without precipitation. If not addressed early and if the right formulation manufacturing process was not chosen, expensive late-stage development efforts would have been needed to address drug crystallization issues.

BARRIERS & CELLULAR DRUG INTERACTIONS

The epidermal and dermal barriers inhibit drug transport. The right excipient selection can minimize surface adsorption, have less immunogenicity, and avoid degradation.

While performing formulation optimization studies, to also study the viability of different epidermal and dermal cells allows us to know the dermatological factor compatibility and to find the proper selection of excipients. The analysis of drug/peptide levels in different skin tissue barrier homogenates will allow the researchers to measure the drug/peptide stability and to also find where the drug is targeting.

Topical formulation products that are involved in different cellular interactions depend on the drug action, skin metabolism, pharmaceutical, and dermatological factors.

FORMULATION FOR UNSTABLE MOLECULES

Tergus conducted formulation, scale up, and tech transfer work on a molecule that was unstable, temperature sensitive, and converted to an isomer. Initial drug loading was 97%, which fell to 50% after 1 month. The challenge was to find a formulation that increased stability and maintained potency.

Because the drug substance was very potent, very low concentrations were needed for therapeutic efficacy. A specific mixture of solvents/viscosity builders were needed to optimize the formulation and improve scale up.

SUMMARY

The type of optimal formulation is determined by the properties of the drug substance, excipients, and the intended target area. Great improvements can be found by considering both the properties of the skin and the properties of the drug substance/excipients. Topical formulation selection is also based on the type of cellular transport and can be analyzed during skin-permeation studies.

The importance of the right formulation and delivery method in topical pharmaceuticals is critical. It can mean the success or failure of drug substance. Getting the preparation right from the outset saves money and time. ◆

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BIOGRAPHY

Dr. Vijendra Nalamothu is CEO and Co-founder of Tergus, which specializes in complete topical development services, analysis, testing, manufacturing for clinical trials, and regulatory support. Dr. Nalamothu earned his PhD in Pharmaceutics from University of the Science's Philadelphia College of Pharmacy. His efforts over the past 18 years in various dermatological companies have led to many commercial products in the market today. Dr. Nalamothu draws from his exceptional background that combines scientific study with pragmatic, hands-on experience to solve R&D challenges. He has co/authored numerous publications and has patents for a few of his inventions. He serves as a member of the Society for Investigative Dermatology and the AAPS and CRS. Dr. Nalamothu also serves on the board of Pharmaceutical and Technology companies and is a member of several pharmaceutical research focus and discussion groups.

LAB DEVELOPED TESTS

FDA Working on LDT Guideline: Implications & Questions

By: Aish Vivekanandan, Industry Analyst with Frost & Sullivan's Global Life Sciences Practice

BACKGROUND

In the past several years, it seemed that a cry for regulation of Lab Developed Tests (LDTs) was falling on deaf years at the FDA. However, after a thorough and intricate letter from the Senate and public outcry for regulations, it seems that the FDA is finally taking action. After serving the 60-day legal notice to congress, the FDA has finally begun the process of setting rules for the regulation of LDTs.

The past several weeks after the FDA's announcement, there has been a range of reaction from the public. There are many who are relieved about this decision for stricter regulation in a previously uncontrolled segment of the healthcare. However many of the corporate companies are uncomfortable, to say the least, regarding this situation. They are unsure about the consequences this could potentially pose on their revenues and position in the market. The FDA has already forewarned these companies that this is going to be a long and arduous process, especially when there are about 11,000 LDTs currently offered by over 2,000 labs. Many are unsure and unaware of what the regulation process could look like, so here is a quick overview of what it might entail:

OVERVIEW OF THE REGULATION PROTOCOL

The FDA is going to use a similar protocol to the regulation imposed on the IVD industry. Here is a quick overview of the regulations for the LDTs. The FDA is using a risk-based classification approach similar to the IVD market. Class I devices, which are subject only to general controls, generally represent the lowest-risk category of devices, while Class III devices, which are subject to general controls and premarket approval, generally represent the highest-risk devices.

There is very little regulation or the FDA intends to exercise enforcement discretion for the class I LDT products, which are low-risk LDTs; LDTs for rare diseases and traditional LDTs that existed when the enforcement discretion policy was initially implemented; and finally there are the LDTs for unmet needs that will receive enforced discretion when there are no other FDA-approved or cleared equivalent devices available.

This is a different ball-game when looking at moderate (Class II) and high-risk (Class III) LDTs. Adverse reporting begins at the 6 months mark after the guidance is finalized. And the pre-market review will only begin after the high-risk (Class III) LDTs are completed. The high risk LDTs (Class III), where registration begins at the reporting begin 6 months after the finalizing the guidance and pre-market review will occur after a year. One of the other requisites to this regulatory framework is the emphasis on the use of clinical studies for validation of their products. These regulations will have serious implications for these labs. Some are as follows:

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"There is very little regulation or the FDA intends to exercise enforcement discretion for the class I LDT products, which are low-risk LDTs; LDTs for rare diseases and traditional LDTs that existed when the enforcement discretion policy was initially implemented; and finally there are the LDTs for unmet needs that will receive enforced discretion when there are no other FDA-approved or cleared equivalent devices available."

Increased Competition - One of the implications of this regulation is that it is going to create tough competition between these labs due to the interference of the FDA in approving each of these products. This industry is going to change and replicate to a similar system seen in the IVD industry. Once the rules are in place, the FDA is going to receive a huge influx of application for the LDT products and the backlog for approvals is going to significantly affect these labs in terms of delayed revenues

Accessibility of the Products & Lack of Innovation - The FDA is already under a lot of pressure from the different industries with regard to regulation. The time it takes to review each of these products even though necessary, takes a phenomenal amount of time. The decreased efficiency in product launches to patient care is of concern to many. Many pathological procedures developed by the labs have had enormous impact in patient care in diverse fields from oncology to infectious diseases. These slow approval processes could really impede accessibility to the patients in terms of availability and cost of the products

In a similar vein, due to these additional layers of regulatory protocols those are required for labs to follow. There is concern that this would impede innovation and development of products and the practice of medicine. The FDA regulation is needed for LDTs despite their impact in the medical field. The lack of it had its own set of consequences that cost lives. Hopefully, with efficient regulation of the LDTs, there will be a chance for a more ideal form of patient care for the future.◆

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BIOGRAPHY

Aish Vivekanandan is an Industry Analyst with Frost & Sullivan's Global Life Sciences practice. She has extensive industry knowledge identifying emerging technologies and tracking technological and market developments across the life sciences domain. She has particular expertise in drug discovery technologies and tools, and clinical and in vitro diagnostics. For more information about Frost & Sullivan's global Life Sciences practice, email Jennifer Carson, Corporate Communications at Jennifer.Carson@frost.com.

THERAPEUTIC FOCUS

Targeted Payload Therapies Radiate Potential to Attack Various Cancers

By: Kaushik J. Dave, PhD, MBA, and Dragan Cicic, MD, MBA

INTRODUCTION

A majority of cancer treatments fall broadly into three categories: surgery, chemotherapy, and radiation. There are other forms of treatment like hormonal therapy, phototherapy, cryotherapy, etc., but these tend to be less frequently administered. The utility, safety, and appropriateness of each approach varies depending on the type of cancer and how advanced the cancer is.

In early stage cancers, where the disease is localized, surgery to remove the tumor can prove effective. Often, this is followed up with focused radiation therapy. Any cancer that has metastasized (later stage cancers) or is not localized (for instance, as in blood-borne cancers) tends to require chemotherapy to address the disease systemically. Broadly speaking, chemotherapies are either cytotoxic or targeted.

Cytotoxic therapies are simply the poisoning of the cancer cells. Cytotoxic treatments would be ideal if they only poisoned the harmful cells, but healthy tissue is always at risk. In a sense, the physician is trying to kill the cancer with a poison before the cancer or the poison can kill the patient.

TARGETED THERAPIES

Targeted therapies offer an alternative because, as their name suggests, they are targeting the cancerous cells in a region of the body rather than the entire region itself.

The National Cancer Institute explains "Targeted cancer therapies are drugs or other substances that interfere with specific molecules involved in cancer cell growth and survival. Traditional chemotherapy drugs, by contrast, act against all actively dividing cells. Targeted therapies act on specific molecular targets that are associated with cancer, whereas most standard chemotherapies act on all rapidly dividing normal and cancerous cells. Targeted therapies are deliberately chosen or designed to interact with their target, whereas many standard chemotherapies were identified because they kill cells. Targeted therapies are often cytostatic (that is, they block tumor cell proliferation), whereas standard chemotherapy agents are cytotoxic (that is, they kill tumor cells). Targeted treatments are cytostatic rather than cytotoxic."

The NCI also notes "Targeted cancer therapies that have been approved for use against specific cancers include agents that prevent cell growth signaling, interfere with tumor blood vessel development, promote the death of cancer cells, stimulate the immune system to destroy cancer cells, and deliver toxic drugs to cancer cells."

Targeted cancer therapies rely either on small molecules or on monoclonal antibodies [mAb]. The difference is one of size, and therefore, that part of the cells they target. Small-molecule compounds are best suited to attacking targets located inside the cell because such agents are able to enter cells relatively easily. Monoclonal antibodies are relatively big compared to small molecules, and therefore, they are used to attack targets outside the cells or on the surface of the cells.

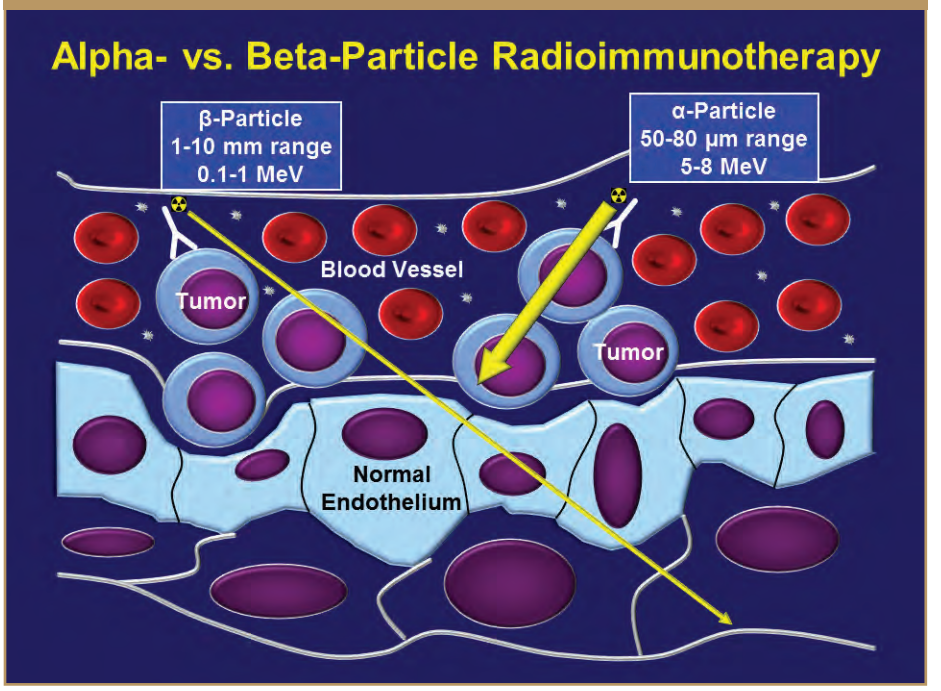
mAbs are engineered to attach to the specific markers on the cancer cells, essentially mimicking the antibodies that the immune system should produce to fight the disease. A number of studies of a vast array of mAb treatments has shown such treatments to possess many positive aspects.

For instance, mAbs are useful because they can make the cancer cells more visible to the patient's immune system. As the Mayo Clinic experts state "The monoclonal antibody drug rituximab (Rituxan) attaches to a specific protein (CD20) found only on B cells, one type of white blood cell. Certain types of lymphomas arise from these same B cells. When rituximab attaches to this protein on the B cells, it makes the cells more visible to the immune system, which can then attack."

Furthermore, mAbs can also block growth signals and thus impede the growth of new cancerous cells. For instance, Cetuximab (Erbitux), an mAb approved to treat colon cancer and head and neck cancers, attaches to receptors for epidermal growth factor on cancer cells, thereby slowing or even stopping the cancer from growing.

In addition, mAbs can stop new blood vessels from forming, choking off the blood supply to any tumor. Bevacizumab (Avastin) is an mAb that targets vascular endothelial growth factor (VEGF) used by cancer cells to stimulate growth of new blood vessels. This mAb prevents the cancer from growing by slowing down growth of new blood vessels.

FIGURE 1



But cancer cells often find ways to protect themselves against the activities of monoclonal antibodies. For example, soon after the mAb is attached to a cancer cell, the cancer cell "swallows" the mAb so that it cannot trigger the immune response. Or if the mAb blocks effects of a certain ligand, cancer cells activate an alternative pathway that allows them to keep growing. To overcome these and other similar mechanisms, one can arm the mAbs with cell-killing agents, like radioisotopes or toxins turning them effectively into delivery devices. The cancer-fighting agent is delivered right to the spot where it is needed - the mAb is sort of a guided missile and the agent is the warhead.

NUCLEAR MEDICINE

Nuclear medicine has been around almost as long as science has understood nuclear power. On December 7, 1946, 15 months after the US used atomic bombs to end World War II, the Journal of the American Medical Association published a Sam Seidlin article that described a successful treatment of a patient with thyroid cancer metastases using radioiodine (I-131). This is usually considered to be the first piece published on the use of nuclear medicine. Nuclear medicine has since added imaging to its capabilities, and it remains a pillar of oncological science.

Texas Oncology states "Radiation therapy may be delivered externally or internally. External radiation delivers high-energy rays directly to the cancer

"Researchers believe that alpha-particle emitters, such as bismuth-213 or actinium-225 currently being investigated by Actinium Pharmaceuticals, may be more effective and efficient at killing cancerous cells not currently treated with radiation while simultaneously decreasing nonspecific cytotoxic effects."

from a machine outside the body. Internal radiation, or brachytherapy, is the implantation of a small amount of radioactive material (seeds) in or near the cancer. Radiation can also be delivered as an isotope into a vein, as in the use of radioactive iodine for the treatment of thyroid cancer."

In its early years, external radiation therapy was more art than science. However, the treatment has evolved significantly. While hitting the right spot with the right dosage in the 1950s contained a significant element of chance, today's oncologists can be much more precise and effective. However, the basic problem of hitting the target with the right dosage while sparing healthy tissue remains.

Internal radiation treatments have overcome some of the precision difficulties, but they still have shortcomings. In the case of brachytherapy, the radioactive material remains in the patient for a long time and cannot target cancer cells far away from the site of radioactive seeds implantation, ie, distant metastases.

There is, however, a promising type of targeted treatment known as radioimmunotherapy (RIT). It uses an mAb to deliver radiation to the cancer cell. This is far safer and more efficient than using an external radiation beam that causes significant damage to the healthy tissues it passes through in order to reach cancer cells. Unlike brachytherapy, mAbs are not limited to the region immediately surrounding the radioactive seed and can therefore target distant metastases or even widely spread blood cancers.

Currently available radioimmunotherapies rely on beta-particle-emitting isotopes like iodine-131 or yttrium-90. These are good at eliminating large tumor burdens, but they are efficient mostly in lymphomas that are very sensitive to radiation. Researchers believe that alpha-particle emitters, such as bismuth-213 or actinium-225 currently being investigated by Actinium Pharmaceuticals, may be more effective and efficient at killing cancerous cells not currently treated with radiation while simultaneously decreasing nonspecific cytotoxic effects.

The physics of alpha particles versus beta particles is the secret to their differing radiobiological effects. Beta particles are highly charged electrons with a range of 800 to 10,000 micrometers, and their linear energy transfer (LET) level is around 0.2 to 0.6 mega electron volts per millimeter. Alpha particles are composed of two neutrons and two protons (essentially a helium nucleus). Their range is just 50 to 80 micrometers, but their LET is around 100 mega electron volts per millimeter. In short, while their range is limited to only the targeted cells and those right next to them, they pack a much bigger punch. It can take just one or two alpha particles to kill a target cell. As a result, non-specific cytoxicity should be lessened when using alpha-emitters compared to beta-emitters.

THE AML EXAMPLE

Leukemia comes in four general groups: chronic lymphicytic, chronic myeloid, acute lymphocytic, and acute myeloid leukemia. The latter type is the version under consideration here. The American Cancer Society says "Adult acute myeloid leukemia (AML) is a cancer of the blood and bone marrow. This type of cancer usually gets worse quickly if it is not treated. It is the most common type of acute leukemia in

adults. AML is also called acute myelogenous leukemia, acute myeloblastic leukemia, acute granulocytic leukemia, and acute nonlymphocytic leukemia." It accounts for a relatively small percentage of cancer deaths in the US, just 1.2%. However, as the population ages, this figure is expected to rise.

AML is a good-news, bad-news disease. The good news is that standard induction therapy, using cytarabine and an anthracycline, produces complete responses in half to almost three-quarters of cases. The bad news is that long-term survival is at 20% to 40%; when a patient relapses, salvage chemotherapy results in remission only one in five, possibly one in four times. Unfortunately, the benefits of the standard treatment accrue very little to older patients. For those over 65, the survival rate is only 5% survival rate over 5 years.

To improve these odds, researchers have been using RIT to get at the diseased cells while sparing the healthy tissue. Lintuzumab is an mAb that targets CD33, a 67-kDa cell surface glycoprotein that finds expression in myeloid leukemia cells. This makes it an ideal delivery mechanism for radioactive material.

When used with beta-emitters like iodine-131 or yttrium-90, Lintuzumab gets the substance to the receptor. However, there is nonspecific cytotoxicity because of the physical properties of the aforementioned beta emitters. Consequently, recent research has turned to alpha-emitters conjugated with Lintuzumab.

One promising alpha-emitter so used is bismuth-213 (213Bi). In a single agent Phase I trial, 18 patients were treated with a 5-minute infusion of 213Bi-Lintuzumab two to four times a day. Of the 18 patients, 17 had AML and one had chronic myeloid leukemia. All 17 of the AML patients experienced myelosuppression. The 213Bi-Lintuzumab rapidly localized to the bone marrow, liver, and spleen and was retained. Meanwhile, the kidneys were not visualized. The absorbed dose ratios between those sites and the whole body were 1,000 times greater than with beta-emitters.

Fourteen of 15 patients who were evaluable (93%) had reduced circulating blasts and 78% (14 of 18) had reductions in their bone marrow blasts. Relatively low specific activities of the 213Bi-Lintuzumab and large tumor burdens likely accounted for no patient achieving CR. Be that as it may, this was proof of concept in humans for alpha-particle emitters in immunotherapy.

Hypothesizing that a reduction in the tumor burden could increase the number of 213Bi atoms delivered to diseased cells and thereby induce remissions, the researchers conducted a Phase I/II study in which 213Bi-Lintuzumab treatment was preceded by a dose of non-remittive cytarabine in 31 patients. Significant marrow blasts reductions were seen across all dosage levels.

ENTER ACTINIUM 225

However, 213Bi isn't the only alpha emitter, and in fact, there are more useful alpha emitters available. Because of its short half life (just 45.6 minutes), 213Bi is of limited utility. Animal studies suggested that actinium-225, with a half life of slightly over 10 days, is effective and won't decay too rapidly for easy handling.

Memorial Sloan Kettering Cancer Center (MSKCC) and Actinium Pharmaceuticals are conducting a first-in-man Phase I dose-escalation trial to determine the safety, pharmacology, and biological activity of Actimab-A (Actinium's name for a mAb conjugated with actinium-225) in AML. Eighteen patients (median age, 64 yrs; range, 45 to 80 years) with relapsed/refractory AML were treated to date. Patients received a single infusion of Actimab-A at doses of 0.5, 1, 2, 3, or 4 microCurie/kg (total dose, 23 to 390 μCi). No acute toxicities were seen. Dose limiting toxicity (DLT) was suppression of the entire bone marrow lasting over 35 days and consequent death due to sepsis. It occurred in one patient treated with 3 microCurie/kg and in both patients receiving 4 microCurie/kg. Toxicities outside of the target organ (bone marrow) were limited to transient grade 2/3 liver function abnormalities. With follow-up from 1 to 24 months (median, 2 months), no evidence of damage to kidneys due to radiation was seen. Peripheral blood blasts (leukemia cells) were eliminated in 10 of 16 evaluable patients who received a full treatment dose. Bone marrow blast reductions of over 33% were seen in 10 of 15 evaluable patients at 4 weeks, including 3 patients with 5% or fewer blasts.

After receiving clearance from the FDA, the company started a Phase I/II multi-center AML trial with fractionated doses of Actimab-A. ATNM has engaged six participating trial centers so far (MSKCC, Johns Hopkins Medicine,

University of Pennsylvania Health System, Fred Hutchinson Cancer Center, University of Texas MD Andersen Cancer Center and Baylor Sammons Cancer Center). The Phase I (dose escalating) portion of the trial is ongoing. In the current, Phase I/II study, patients are eligible if they have previously untreated newly diagnosed AML according to World Health Organization criteria, are age 60 years or older, and are unfit for or decline intensive chemotherapy, or are 70 years or older with newly diagnosed AML. This target population has had better outcomes than relapsed and refractory patients who have been most of the patients in ATNM's previous trials.

Maximum enrollment in the Phase I portion of the trial is 21 patients in dose escalating cohorts of 3 patients each with the goal of determining the maximum tolerated dose (MTD) for Actimab-A. There is a 6-week interval between dose levels. Once MTD has been determined, it will be used as the dose level for the Phase II portion of the trial which will enroll up to 53 patients. There are 4 planned dose levels in the Phase I portion of the trial.

Recently reported, positive interim data from the ongoing Phase I/II trial of Actimab-A in older patients with newly diagnosed AML demonstrated median overall survival ("OS") of the seven secondary AML patients (with prior myelodysplastic syndrome, or MDS) in the study was 9.1 months, which is a prolongation of life compared to historical norms of typically 2 to 5 months. Older AML patients are already higher risk, with secondary AML patients considered to have the more severe and less treatable form of AML, and the shortest expected survival.

In this interim analysis, a total of 9 patients were evaluated thus far with a median age of 76 (range 73-81). All had intermediate or poor risk cytogenetics, and 7 of 9 patients had secondary AML as a result of prior MDS. These 7 secondary AML patients had a median OS of 9.1 months from study entry (range 2.3-24 months). Of these, 2 patients lived longer than 12 months and the longest surviving patient lived greater than 24 months. Overall, for all 9 patients median OS was 5.4 months (range 2.2-24 months).

Two dosing levels have been evaluated to date (0.5 or 1.0 µCi/kg/fraction), and the study is ongoing at higher doses until the maximum tolerated dose ("MTD") is reached. Despite not having yet reached MTD, the Company has observed significant bone marrow blast reductions, another important marker of efficacy. Of the 7 evaluable patients in the overall study, 5 patients (71%) had bone marrow blast reductions with a mean of 61% reduction. Whether there is an even better isotope than Actinium 225 has yet to be seen. However, the evidence clearly suggests that alpha emitters have more targeted effectiveness than beta emitters, as the physics would lead one to believe. Combined with mAbs to deliver them, alpha emitters may well be opening up a new way to attack cancers. ◆

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BIOGRAPHIES

Dr. Kaushik J. Dave is the President & CEO of Actinium Pharmaceuticals. He joined the company from Antares Pharmaceuticals Inc., where he was the Executive Vice President of Product Development. Prior to Antares, he was Vice President Product Development at Palatin Technologies Inc., where he obtained approval of NeutroSpec (a radiopharmaceutical monoclonal antibody product). Prior to Palatin, he was employed at Schering-Plough Inc. and Merck & Co. Inc., responsible for steering the development of several pharmaceutical product development programs. He earned his Pharmacy degree from the University of Bath, UK, and his PhD in Pharmaceutical Chemistry from the University of Kansas. Dr. Dave also earned his MBA from the Wharton School of the University of Pennsylvania.

Dr. Dragan Cicic is the COO and CMO of Actinium Pharmaceuticals, Inc. (ATNM). He joined the company in 2005 and previously held the position of the Medical Director with Actinium Pharmaceuticals, Inc. Dr. Cicic joined ATNM from the position of Project Director of QED Technologies Inc., a life sciences strategic consulting and transactional group focused on emerging biotech, pharmaceuticals, and medical devices companies. Prior to joining QED Technologies, Dr. Cicic was an investment banker with SG Cowen Securities. He graduated as a Medical Doctor from the School of Medicine at The Belgrade University, and earned his MBA from Wharton School at The University of Pennsylvania. He was also a Nieman Fellow at Harvard University.

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