Drug Development & Delivery

July/August 2014 Vol 14 No 6 www.drug-dev.com

Leveraging Identity Hubs

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

David Shoemaker, PhD
The US Biosimilar Approval Pathway: Policy Precedes Science

Vijay Takanti, MS, MBA
Leveraging Identity Hubs to Speed the Development & Delivery Process & Maximize Revenue Opportunities

Derek Hennecke
The Secret to Successful Global Expansion is to Bring Your RATs & CATs Together

IN THIS ISSUE

INTERVIEW WITH 3M DDSD'S VP & GENERAL MANAGER CINDY R. KENT, MBA

Innovation & Culture 19
Marshall Crew, PhD

Government-Based Research 26
Christi Bird

Regulatory Challenges 30
Erick Gaussens

Transdermal, Topical & Subcutaneous 38
Cindy H. Dubin

PDCs & ADCs 50
Archana Gangakhedkar, MS
Jyothi Thundimadathil, PhD

AFA & Nanoemulsions 55
Laura E. Forte
Srikanth Kakumanu, PhD

OUR CAPABILITIES JUST WENT FROM

BROAD TO BROADER

FROM SEMI-SOLIDS & LIQUIDS TO SOLIDS

FROM NON-STERILE TO STERILE

FROM CONCEPT TO COMMERCIALIZATION

FROM VIRTUAL TO LARGE PHARMA

The integration of DPT Labs and Confab expands our capabilities and expertise in dosage forms from semi-solids and liquids to include solid dose.

Learn more about what our integration can do for you.

www.dptlabs.com
www.confab.com

DPT®

Confab®

A DPT COMPANY

Insulet Corporation

Tried, tested, **trusted.**

The market-leading **tubeless**, wearable drug delivery system.

The Drug Delivery Manager

- Icon-based user interface
- Fully programmable
- Secure, HCP delivery rate configuration
- Self-monitoring and alarm notifications
- Complete event history logs

The Drug Delivery Pod

- Body worn, programmable drug delivery pump
- Variable fill volume from 0.85 ml to 2 ml
- Delivery rate from 0.5 to 300 µl/hr
- Automated catheter insertion
- Waterproof (IPX8 — 25 feet for up to 60 minutes)
- Over 20 million produced to-date




Contact us to see how the system can work for you.

email: **drugdelivery@insulet.com** tel: **866.941.4576**

This drug delivery system is approved for use in limited markets. The device shown is not approved for use in the United States. The OmniPod Insulin Management System can only be used with U-100 insulin. Using the OmniPod Insulin Management System for anything other than insulin is not safe.

Drug Development & Delivery

July/August 2014 Vol 14 No 6

Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
Tel: (973)299-1200
Fax: (973) 299-7937
www.drug-dev.com

Advertising Sales Offices

International
Ralph Vitaro
219 Changebridge Road
Montville, NJ 07045
Tel: (973) 299-1200
Fax: (973) 299-7937
E-mail: rvitaro@drug-dev.com

Global Sales & Marketing Director
John Kiesewetter
P.O. Box 8548
Eugene, OR 97408
Tel: (541) 338-0022
Fax: (541) 338-0044
jkiesewetter@drug-dev.com

Instruments & Machinery
Patricia Loyas
977 Wall St.
Diamond Point, NY 12824
Tel: (518) 668-4144
Fax: (518) 668-9794
E-mail: ployas@drug-dev.com

The **EXPERIENCE**

The **EXPERTISE**

The **COMMITMENT**

TO GO FROM
CONCEPT TO CLINIC TO MARKET

What separates one CDMO from another? At Metrics, we believe it comes down to experience, expertise and commitment. Like our formulators and analytical staff, who share decades of career experience and expertise. Or our commitment to continually surpass our clients' expectations by offering new capabilities and technologies. Moving your project through the pipeline efficiently and cost-effectively is our number one priority. And that's what separates us from the rest of the pack.

Metrics INC.

Potent Product Development.
Our state-of-the-art potent development suites feature total containment and no open processes.

Veteran Expertise.
Our PhDs, Master and Registered Pharmacists and Chemists average 17 years of professional experience.

4:1 Ratio.
We offer a healthy balance of four analytical chemists to every formulator to keep your project on track.

Pharmaceutical Development • Analytical Testing • CTM Manufacturing • Potent Products • Specialty Technologies

Metrics / Greenville, NC / 252-752-3800 / www.metricsinc.com

Compliance Is Key

"It is important to note the drivers of satisfaction and selection are not always the same across diseases and methods. For example, several novel oral therapies for MS offer advantages over standard injectable therapies. However, more than 55% of physicians treating MS are likely to switch from the currently prescribed branded drug if the drug were available in a transdermal patch form. This is in line with the 58% of MS patients willing to use a transdermal patch. Further, 57% of physicians treating Type 2 diabetes are most willing to switch from oral or injectable drugs to a topical treatment."

Table Of Contents

19 **Innovators & Corporate Cultures: Symbiotic Relationships**
Marshall Crew, PhD, explores some of the key features of people and organizations that lead to the innovations and products, and hopes that by example, insights can be acquired that will be useful in his colleagues respective organizations and that might ultimately lead to more innovation in the industry.

22 **The Secret to Successful Global Expansion is to Bring Your RATs & CATs Together**
Derek Hennecke shares his strategy for getting ahead in the global race by following the RAT/CAT virtuous cycle approach to creating and sustaining global advantage developed by Donald Lessard, Rafael Lucea, and Luis Vives in "Building Your Company's Capabilities Through Global Expansion," *MIT Sloan Management Review*.

26 **Sequestration Haunts Life Science Research Tool Market Into 2014**
Christi Bird, Senior Industry Analyst, Frost & Sullivan, believes the bleakest outlook provided for the life sciences industry is one without a clear light at the end of the tunnel, and successful companies will buckle down to determine long-term strategies for beating the lackluster numbers expected from a sustained austerity policy.

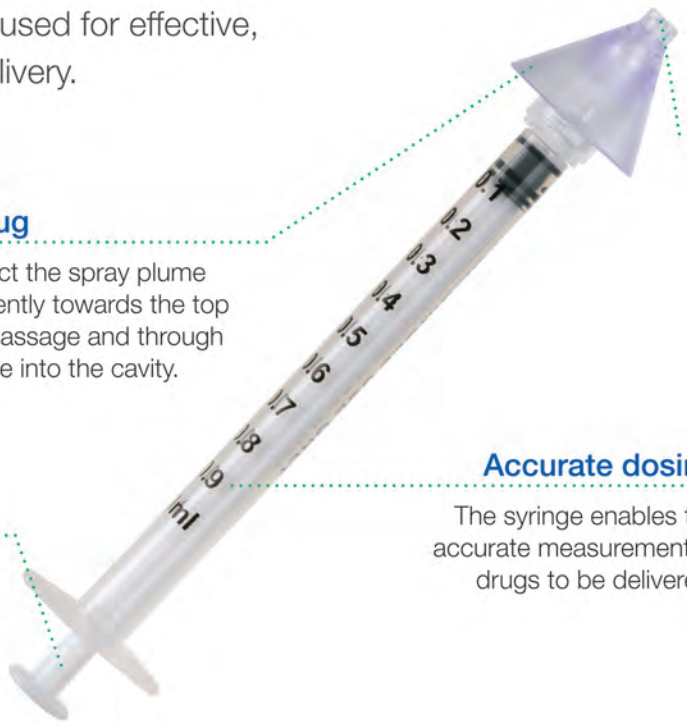
30 **Regulators Make Intentions Clear on Transparency & Harmonization**
Erick Gaussens says that continued emphasis on data transparency and on streamlining of the submission process - to the benefit of both regulatory agencies and pharma companies - create both opportunities and challenges for companies.

34 **The US Biosimilar Approval Pathway: Policy Precedes Science**
David Shoemaker, PhD, says the origin of the BPCIA had its roots in the Drug Price Competition and Patent Restoration Act of 1984 championed by Senators Waxman and Hatch, which has provided low-cost generic alternatives to prescription brand-name drugs for the three subsequent decades. What Congress failed to appreciate at the time was the current state of protein characterization science and consequently whether interchangeability could in fact be obtained or what level of biosimilarity was acceptable.

38 **Patients & Physicians Desire Transdermal, Topical & Subcutaneous Delivery**
Contributor Cindy H. Dubin recently interviewed several topical, transdermal, and subcutaneous product manufacturers to find out how they are working with patients and physicians to develop delivery systems that meet their needs for comfort, compliance, and more effective delivery.

A straight-forward solution for intranasal drug delivery

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



Atomization spray

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

Conical plug

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

Accurate dosing

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

Pressure

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

For use with drugs approved for nasal delivery.

Patent pending.

30-0374 Rev. 01/14

Phone +353 (0)1 896 4961 **Email** vaxinator@teleflex.com www.vaxinator.com

Teleflex

Leveraging Identity Hubs

"To survive in this increasingly competitive landscape, life sciences companies are turning to new sources of innovation. They are engaged with unprecedented intensity in collaborative efforts with external partners that lie beyond their virtual four walls. This decentralized collaborative environment encourages specialization and focus, which in turn accelerates innovation - speeding the drug development and delivery process so companies can take full advantage of revenue opportunities."

p.44

Table Of Contents

44 **Leveraging Identity Hubs to Speed the Drug Development & Delivery Process & Maximize Revenue Opportunities**
Vijay Takanti, MS, MBA, believes the Exostar Life Sciences Identity Hub is a proven implementation of the identity hub concept that provides the trust necessary for enterprises and individuals to collaborate with confidence.

50 **Peptides in Antibody & Peptide Drug Conjugates**
Archana Gangakhedkar, MS, and Jyothi Thundimadathil, PhD, indicate peptide-based linkers are promising counterparts in ADCs, providing tumor-specific cleavable and stable circulating linkers, and a new emerging class of PDCs is proving to be useful toward a broad spectrum of indications when compared to ADCs.

55 **Scalability of Adaptive Focused Acoustics™ (AFA) in Nanoemulsions: From Microliters to Continuous Flow**
Laura E. Forte and Srikanth Kakumanu, PhD, conduct a study demonstrating that Covaris' AFA can quickly and easily produce nanoemulsions on sample scales varying from 300 microliters to continuous flow.

60 **Addressing HPV-Related Cancers in HIV/HPV Co-Infected Population**
Eyal Talor, PhD, believes the goal of HIV care is empowering people to live well (long and productive lives) with the virus. When it comes to the risk of developing HPV-related cancers, HIV positive individuals need expanded arsenals that will be able to address their specific needs.

64 **3M Drug Delivery Systems Division: A Partner to Tackle Market Complexities**
Drug Development Executive: Cindy R. Kent, VP & General Manager of 3M DDSD, discusses her vision for the company and how developing trends are impacting the players in the pharmaceutical industry.

70 **PAREXEL: Simplifying the Journey to Market**
Drug Development Executive: Carol Collins, Corporate Vice President, Strategic Partnerships, PAREXEL, clarifies how Strategic Partnerships differ from other outsourcing approaches - and what makes them more effective.

Departments

Market News & Trends 12

Technology & Services Showcase 67

External Delivery 74
Increasing Your Reach & Frequency

Need drug delivery device or medical device information?

We have it, and much, much more.

PharmaCircle provides information that the whole team needs, from pharmaceutical sciences to clinical development to regulatory affairs to business development to manufacturing. PharmaCircle provides the kind of information that helps you and the team make better decisions. Call us for a demo and let us show you what you have been missing.

If you are with one of the top pharmaceutical companies your company most likely has a subscription. Contact your library services group or give us a call for login information.

PharmaCircle™

Providing best-in-class
online information
for Pharmaceutical Professionals

PHARMACIRCLE™

Online Information for Pharmaceutical Professionals

For more information or to request a demo contact us at:

T: +1-760-436-1199
E: contact @pharmacircle.com
W: www.pharmacircle.com

The EDITORIAL Advisory Board

Ingredients | BioPharma | Contract Services | Technology | Packaging

Join Bosch, DSM, Pfizer, Gerresheimer and many more now!

CPhI Worldwide is the leading global event for the pharmaceutical industry.
Every year, 30,000+ buyers, manufacturers, suppliers and users attend to exchange ideas, form alliances and develop business relationships on an international scale.

Book your stand

CPhI worldwide

7-9 October 2014 • Paris Nord Villepinte • France

Co-located with

iCSE | P-mec | InnoPack

> "The visitors are of very high quality, with many decision makers attending. We always make a lot of good contacts at CPhI."
>
> **Marta Carbo**
> Marketing and Communication Director, Cafosa

www.cphi.com
"The world's leading pharmaceutical event"
Follow the pharma community @cphiww

Organised By:
UBM

SMARTag Toxicology Study Demonstrates Decreased Mortality & Better Tolerability

Redwood Bioscience and Catalent Pharma Solutions recently announced the results of an in vivo toxicology study, demonstrating that an Antibody Drug Conjugate (ADC) generated using the proprietary SMARTag platform has a better toxicity profile than a conventional ADC.

The study, conducted in a rat model by Redwood Bioscience, Inc., compared the effects of a single dose of 6, 20, or 60 mg/kg of a SMARTag ADC conjugated to a cytotoxic payload using the proprietary HIPS chemistry, to an ADC generated with traditional conjugation methods.

Results showed that the SMARTag ADC was well tolerated and provided statistically significant survival benefits versus the conventional ADC, particularly at high doses in which the conventional ADC resulted in mortality. Elevations in liver enzymes and decreases in platelet counts and reticulocytes were also observed with the conventional ADC at 20- and 60-mg/kg treatments, whereas these effects were only seen with the highest dose of the SMARTag ADC. In addition, the toxicokinetic analysis showed that the SMARTag ADC had greater exposure and longer circulating half-life than the conventional ADC comparator.

"In summary, the study showed that the SMARTag ADC was a less toxic treatment and, taken together with the efficacy studies, points to an improved therapeutic index for the SMARTag ADC compared to the conventionally conjugated ADC," said Dr. David Rabuka, Founder, President, and Chief Scientific Officer of Redwood Bioscience.

"This data provides further evidence of the potential benefits the SMARTag technology offers our customers developing next-generation ADC therapies, and their patients," added Barry Littlejohns, Catalent Pharma Solutions' President, Advanced Delivery Technologies.

In March 2014, based on compelling data generated using the SMARTag ADC platform, Catalent announced that it had increased its investment in Redwood Bioscience, which also provides Catalent an exclusive license to market Redwood Bioscience's proprietary SMARTag technology. Combined with Catalent's proprietary GPEx cell line expression system and its state-of-the-art biomanufacturing Center of Excellence in Madison, WI, as well as broad range of analytical and fill-finish services, this collaboration expands Catalent's capabilities to help its customers develop more and better biologic treatments.

Toxicology study results have been published and are available in the Journal of Bioconjugate Chemistry. Dr. Greg Bleck, Global Head of R&D for Catalent Biologics, also discussed the toxicology study results during a presentation at the BIO International Convention.

Redwood Bioscience is developing a precision protein-chemical engineering technology to produce next-generation antibody-drug conjugates and other semi-synthetic biotherapeutics. The proprietary SMARTag site-specific protein modification and cytotoxin-linker technologies developed by Redwood enable the generation of homogenous bioconjugates engineered to enhance potency, safety, and stability. The technology employs natural post translational modifications found in human cells to site specifically create one or more aldehyde tags on protein molecules. These chemical handles are then stably conjugated to cytotoxic payloads to prevent their systemic release. The SMARTag platform provides precise payload positioning and defined stoichiometry of payload-protein ratios. The control afforded by the technology enables identification of superior drugs from libraries of differentially designed conjugates.

Tech Group Receives 2014 Lilly Global Supplier Award

West Pharmaceutical Services, Inc. recently announced that its Tech Group Rockford facility has received a 2014 Lilly Global Supplier Award. Lilly presented the award at a special global recognition ceremony at Lilly corporate headquarters, Indianapolis, IN.

"We're extremely proud to receive an award from such a prestigious customer," said Mike Treadaway, Vice President and General Manager, The Tech Group. "The level of customer services we've provided Lilly along with the quality of the product is unmatched, and we're proud to be recognized for our commitment to our customer's needs."

To be nominated for a Lilly Supplier Award, the Tech Group Rockford manufacturing facility had to have a measurable impact on Lilly's corporate priorities through the delivery of exemplary quality, speed, service, and/or cost reduction. Donald E. Morel Jr., PhD, West's Chairman and Chief Executive Officer, joined Mr. Treadaway at the acceptance ceremony.

West is by the side of its healthcare partners from concept to the patient, designing and manufacturing packaging, diagnostic, and delivery systems that promote the efficiency, reliability, and safety of their products. Every day, West is leading the way with cutting-edge technologies and quality systems, a thorough understanding of global regulatory compliance, and an unmatched and growing knowledge base of pharmaceutical product testing, development, and packaging. Based in Exton, PA, West supports customers from sales, manufacturing, and research and development locations in North and South America, Europe, Asia, and Australia. West's 2013 sales reflect the daily use of approximately 100 million of its components and devices around the world.

Tech Group North America, Inc., a subsidiary of West Pharmaceutical Services, Inc., is a process driven, global contract manufacturer of pharmaceutical and medical devices. With nine locations in North America and Europe, Tech Group is focused on serving the needs of healthcare companies by providing a single-sourced solution from product conceptualization through manufacturing and final packaging. Capabilities include concept design, engineering development, prototyping, production scale-up, validation, and full-scale manufacturing. Tech Group's healthcare facilities are ISO 13485 certified and cGMP compliant.

Dimension Therapeutics & Bayer Sign $252-Million Deal

Dimension Therapeutics recently announced it has entered into a collaboration with Bayer HealthCare for the development and commercialization of a novel gene therapy for the treatment of hemophilia A.

Under the terms of the agreement, Dimension will receive an upfront payment of $20 million and will be eligible for potential development and commercialization milestone payments of up to $232 million. Dimension will be responsible for all preclinical development activities and the Phase I/IIa clinical trial, with funding from Bayer. Depending on the results of the Phase I/IIa clinical trial, Bayer will conduct the confirmatory Phase III trial, make all regulatory submissions, and will have worldwide rights to commercialize the potential future product for the treatment of hemophilia A. Dimension is eligible to receive tiered royalties based on product sales.

"Currently available replacement therapies for hemophilia A are often administered intravenously multiple times a week and may be required for life, depending on the severity of a patient's disease," said Thomas R. Beck, MD, CEO of Dimension Therapeutics. "Gene therapy offers the potential to transform the treatment of hemophilia by inserting a correct version of the faulty gene responsible for the disease. We are proud to partner with Bayer, a leader in the treatment of hemophilia A, to develop a therapy with the potential to significantly change the treatment landscape."

"Bayer is a worldwide leader in the treatment of hemophilia A, and we are highly committed to advancing innovative treatment options for patients with hemophilia A," added Prof. Dr. Andreas Busch, member of the Bayer HealthCare executive committee and Head of Global Drug Discovery. "We are excited to partner with Dimension Therapeutics to jointly harness the power of gene therapy to drive the development of new long-term options in treating this disease."

Dimension's AAV vector technology allows for systemic intravenous administration of the clotting factor gene in vivo, which has been shown in preclinical studies to target the liver, resulting in long-lasting expression of FVIII protein at therapeutic levels. Dimension's vectors are enabled by REGENX Biosciences' proprietary NAV technology.

Last Chance to Save on Registration is August 28. Don't Wait! Save up to $200.

The Parenteral Drug Association presents the...

2014 PDA Universe of Pre-filled Syringes and Injection Devices

October 6-8, 2014

HYATT REGENCY HUNTINGTON BEACH RESORT AND SPA
HUNTINGTON BEACH, CALIFORNIA

The device world is ever changing, especially now more than ever. Stay head of the curve and attend the *2014 PDA Universe of Prefilled Syringes and Injection Devices Conference* where you will attend sessions that cover all of the latest topics from industry experts, learn about case studies in many of the hot new areas and mingle with nearly a thousand delegates dedicated to helping patients improve their drug delivery experience.

This is a conference you don't miss! Gain the necessary knowledge needed for your company. Attendees can expect to:

- Identify critical attributes of end-user friendly devices
- Explain how innovation is helping patients to have a positive experience in managing their therapies and assuring compliance to dose regime
- Summarize manufacturing requirements of pre-filled syringes, injection devices, safety devices, and final drug/device combo products
- Discuss market, industry trends and new technologies
- And much more!

POST CONFERENCE WORKSHOP: 2014 PDA Drug Delivery Combination Products Workshop
October 8, 2014 | HYATT REGENCY HUNTINGTON BEACH RESORT AND SPA | HUNTINGTON, CALIFORNIA

Following the conference on October 8, will be the *2014 PDA Drug Delivery Combination Products Workshop*. Hear the real life experiences of pharmaceutical professionals detailing the challenges they faced during development, approval and manufacturing of their Drug Delivery Combination Products. Interact with the participants in panel discussions where you will hear the differences discussed as to what has worked, what no longer works and what strategies are likely to succeed in the future.

www.pda.org/drugdelivery2014

The PDA Training and Research Institute will be hosting four courses to complement your learning on October 9-10, 2014.

- Prefilled Syringe User Requirements – ***New Course***
- Syringes and Elastomers: Understanding the Effects on Quality and Demonstrating the Production Process, Influences and Needs
- Technical and Regulatory Challenges of Drug Delivery Combination Products – Prefilled Syringes, Autoinjectors and Injection Pens – ***New Course***
- Risk Management for Temperature Controlled Distribution

For more information and to register, visit **www.pda.org/prefilled2014**

EXHIBITION: OCTOBER 6-7 | COURSES: OCTOBER 9-10

J&J Innovation, Janssen Biotech & Dana-Farber Cancer Institute Launch $10-Million Collaboration

Johnson & Johnson Innovation, Boston and Janssen Biotech, Inc. recently announced a 3-year immuno-oncology lung cancer collaboration with the Dana-Farber Cancer Institute. Through the collaboration, Janssen scientists will work with the research team at Dana-Farber's Belfer Institute for Applied Cancer Science to determine the clinical setting for certain immuno-oncology agents in Janssen's lung cancer discovery pipeline.

"We are thrilled to be working with the scientists at the Belfer Institute," said Peter Lebowitz, Janssen Global Therapeutic Area Head, Oncology. "Their excellence in lung cancer translational research, which incorporates both tumor genetics and immunotherapy, will be critical to the development of personalized treatment options for patients in need."

Utilizing the Belfer Institute's proprietary immuno-oncology lung platform and lung cancer disease expertise, the research teams will also seek to identify rational immuno-oncology drug combination strategies and biomarkers, and to characterize mechanisms of resistance. The collaboration will also identify and validate novel targets for lung cancers.

"There is a growing recognition of the potential importance of immuno-oncology agents directed at a variety of cancers," said Robert G. Urban, PhD, Head of Johnson & Johnson Innovation, Boston. "Through our collaboration with the Dana-Farber Cancer Institute, we will be able to increase the probability of success and decrease development times for our important immuno-oncology pipeline in the critical area of lung cancer."

Lung cancer is one of three focus areas for Janssen Oncology based on its high unmet need. According to the American Cancer Society, lung cancer is the leading cause of cancer death among both men and women. Each year, more people die of lung cancer than of colon, breast, and prostate cancers combined. Overall, the chance that a man will develop lung cancer in his lifetime is about 1 in 13; for a woman, the risk is about 1 in 16.

Johnson & Johnson Innovation, LLC focuses on accelerating early stage innovation worldwide and forming collaborations between entrepreneurs and Johnson & Johnson's global healthcare businesses. Johnson & Johnson Innovation provides scientists, entrepreneurs, and emerging companies one-stop access to science and technology experts who can facilitate collaborations across the pharmaceutical, medical device, and diagnostics and consumer companies of Johnson & Johnson. Johnson & Johnson Innovation includes local deal-making capabilities with the flexibility to adapt deal structures to match early stage opportunities and establish novel collaborations that speed development of innovations to solve unmet needs in patients.

Janssen Biotech, Inc. redefines the standard of care in immunology, oncology, urology, and nephrology. Built upon a rich legacy of innovative firsts, Janssen Biotech has delivered on the promise of new treatments and ways to improve the health of individuals with serious disease. Beyond its innovative medicines, Janssen Biotech is at the forefront of developing education and public policy initiatives to ensure patients and their families, caregivers, advocates, and healthcare professionals have access to the latest treatment information, support services. and quality care.

EMD Millipore Launches RNA Reprogramming Technology

EMD Millipore, the Life Science division of Merck KGaA of Darmstadt, Germany, recently launched Simplicon RNA Reprogramming Technology, which uses synthetic self-replicating RNA to create large numbers of human-induced pluripotent stem cells (iPSCs) using a single transfection step. This efficient reprogramming of somatic cells is accomplished without viral intermediates or host genome integration, offering a more defined and safer system for iPSC generation.

"For stem cell researchers using iPSCs to study disease, differentiation, and regenerative medicine, there's a real need for a reprogramming method that's as efficient as virus-based techniques yet as safe as non-viral methods," said Christophe Couturier, Head of Bioscience, EMD Millipore. "Simplicon technology meets this need, with a single-transfection protocol that's significantly easier than other approaches."

The Simplicon RNA Reprogramming Technology uses a single synthetic, polycistronic self-replicating RNA strand engineered to mimic cellular RNA. The RNA strand contains the four reprogramming factors, OCT-4, KLF-4, SOX-2 and GLIS1, and enables the creation of integration- and virus-free iPSCs using only one transfection step. Once the cells are generated, the RNA and reprogramming factors can easily be eliminated from the cell culture medium in a controlled manner.

EMD Millipore launced the Simplicon RNA Reprogramming Technology at the International Society for Stem Cell Research (ISSCR) annual meeting being held June 18-21 in Vancouver, Canada.

Bionomics & Merck Enter New Research Collaboration

Bionomics Limited recently announced it has entered into an exclusive Research Collaboration and License Agreement with Merck, known as MSD outside the United States and Canada, for its BNC375 research program targeting cognitive dysfunction associated with Alzheimer's disease and other central nervous system conditions.

Under the agreement, Merck will fund all research and development, including clinical development, and will be responsible for worldwide commercialization of any products from the collaboration. Bionomics will receive upfront payments totaling $20 million and is eligible to receive up to $506 million for achievement of certain research and clinical development milestones and undisclosed royalties on any product sales.

"We are very excited to work with Merck to progress new therapies for cognitive impairment in conditions such as Alzheimer's disease," said Dr. Deborah Rathjen, CEO & Managing Director of Bionomics. "We believe that the combination of Bionomics' innovative approach and technologies, within its ionX platform, has the potential to rapidly advance new treatments."

"Bionomics continues to deliver on its business model that focuses on strategic partnering for the development and commercialization of selected programs within its pipeline," Dr. Rathjen added. "This significant agreement, our second with Merck, further validates our drug discovery platforms."

"Merck is pleased to add a new scientific collaboration with Bionomics," said Dr. Rupert Vessey, Head of Early Development and Discovery Sciences at Merck Research Laboratories. "Bionomics' capabilities and overall expertise in discovery and characterization of small molecules for this neuroscience target class is impressive."

In July 2013, Bionomics announced an option and license agreement with Merck to discover and develop novel small molecule candidates for the treatment of chronic pain, including neuropathic pain. Under the terms of that agreement, Merck has the option to exclusively license a compound from Bionomics for development and commercialization.

BNC375 is a key compound from the Bionomics research program licensed to Merck under this latest agreement. BNC375 and related compounds have displayed potent efficacy in animal cognitive impairment models.

Alzheimer's is the most common type of dementia and thought to be caused by damage to nerve cells in the brain. Symptoms are characterized by a decline in memory or other thinking skills; it affects a person's everyday activities and is fatal. One in 9 Americans older than 65 years has Alzheimer's disease (5 million people). It is the sixth leading cause of death in the United States. By 2025 the number of Americans aged 65 and older with Alzheimer's is forecast to rise 40% to 7.1 million (2014 Alzheimer's disease, Alzheimer's Association). More than 332,000 Australians suffer from Alzheimer's disease.

Exostar & SAFE-BioPharma Announce Strategic Partnership

Exostar and SAFE-BioPharma Association recently announced a new partnership that will enable Exostar to issue non-public key infrastructure (PKI) identity credentials at Levels of Assurance 2 and 3 (LOA 2, LOA 3) to its community of life sciences and healthcare customers via SAFE-BioPharma's government approved Trust Framework Provider (TFP) service.

In today's evolving marketplace, life sciences and healthcare companies are faced with the challenge of securely enabling business processes in the cloud while ensuring regulatory compliance and better alignment with evolving governmental online processes. The partnership will enable Exostar to issue LOA 2 and LOA 3 identity credentials, under the SAFE-BioPharma Trust Framework. Companies can leverage globally accepted identity credentials to provide secure and trusted access to proprietary toolsets, analytics, and other internal/external applications in the cloud to their business partners, outside researchers, government agencies, or even competitors.

"This is great news for the 500-plus organizations who currently utilize our Life Sciences Identity Hub to collaborate, as well as the rest of the industry looking to outsource development, testing, or supply chain initiatives. The ability to utilize a range of identity credentials compliant with the SAFE-BioPharma standard will create more business opportunities, and greatly increase the number of use cases possible across the extended life sciences and healthcare communities," said Daniel Pfeifle, Vice President, Sales and Marketing, Exostar.

"Using SAFE-BioPharma-compliant identities to conduct collaborative business processes via the Exostar Identity Hub offers life sciences and healthcare companies a platform to securely collaborate and a vehicle to transform business processes to the 21st Century digital world," said Mollie Shields-Uehling, President and CEO, SAFE-BioPharma Association.

Can Regenerative Medicine be the Cure for Cancer & Other Deadly Diseases?

Regenerative medicine has the potential to transform healthcare all over the world and usher human health into a new era of wellness. Currently, the majority of treatments for chronic and fatal diseases is palliative or to delay disease progression; in contrast, regenerative medicine is uniquely capable of altering the underlying disease mechanism and enabling cures.

New analysis from Frost & Sullivan's Global Regenerative Medicine Market finds the increasing approval rates and clinical activity buzz point to regenerative medicine being an extremely attractive sector for investors. It covers the segments of cell therapy (CT), tissue engineering (TE), gene therapy (GT) and small molecules and biologics.

"Cell-based models are anticipated to speed-up the discovery of new molecules and biologics, the safety and toxicity testing of newly discovered drugs, and provide a solid understanding of underlying disease mechanisms," said Frost & Sullivan Healthcare Senior Research Analyst Aiswariya Chidambaram. "As more pharma companies acquire profitable cell therapy companies or strategically invest in emerging cell and advanced therapy organizations, the consolidation wave is likely to rise higher in the industry."

A significant number of regenerative medicine products, particularly in CT and TE, are already commercially available. In 2012, the market witnessed the approval of as many as seven CT products by regulatory agencies worldwide, while only five such approvals were granted between 2009 and 2011, and none from 2002 to 2008.

However, despite the immense value of regenerative medicine, there is a lack of consensus and strategic interaction among members of the regenerative medicine community. There has to be greater assessment of activities at various federal agencies, including government, industry, academia, and patient advocates, particularly in the US, to identify areas of redundancy and eventually bridge the gap.

To set up a more efficient coverage and a solid reimbursement framework, the various stakeholders have to streamline regulatory policies. They could achieve this by establishing a clear point of contact at the national level that will act as an interface among the Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services (CMS), National Institutes of Health (NIH), National Center for Health Statistics (NCHS), other federal agencies and the private sector.

They will also do well to create fora/platforms to present recommendations for regulatory, reimbursement and research policies in order to foster product and clinical development.

Oxford Biomedical Research Centre Signs Contract With GENALICE

GENALICE recently announced that the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre's Molecular Diagnostics Centre has signed a contract for a larger model of the GENALICE VAULT, GENALICE's Next-Generation Sequencing (NGS) data processing appliance. This all-in-one bioinformatics appliance is preloaded with the ultra-fast and highly accurate NGS data processing software, GENALICE MAP.

GENALICE recently announced the upgrade of its groundbreaking DNA processing solution to include Variant Calling. This upgrade makes GENALICE MAP a complete processing workflow. The product is specifically designed to support high-volume DNA sequencing centers that require high throughput at high quality.

"GENALICE showed that MAP produces impressive throughput and storage space reductions," said Dr. Anna Schuh, Clinical Lead at the Oxford Molecular Diagnostics Centre. "It also detects complex mutations, which is crucial to be able to effectively use NGS data in a clinical setting and a key catalyst in allowing clinical use to contribute to large scale DNA data collection."

"The Oxford group is world renown and uses high quality standards. This is a major milestone in our continuous product validation and quality improvement process. The team in Oxford is gearing up for a more molecular profile driven diagnosis and treatment of complex diseases. We are excited to accelerate this process," added Hans Karten, CEO/CTO of GENALICE.

He continued, "In order to optimally support our customers in United Kingdom and Ireland, we have opened an office in the Innovation Center in Belfast, Northern Ireland. As well as customer support, the UK office will also carry out part of the product development and validation functions within GENALICE.

The Second Quadrant

Innovators & Corporate Cultures: Symbiotic Relationships

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

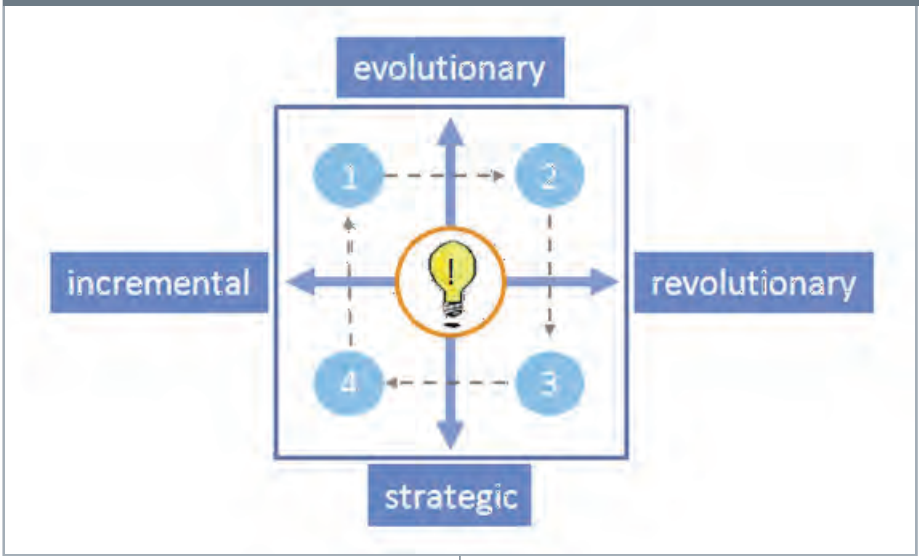
"Innovation champions: The lower they are in the organization hierarchy, the more innovative and tenacious they are."

The data and discussion in previous columns have shown that solubilization technologies are being adopted at an increasing rate. The need is clear, and while we can observe the effects of innovation diffusion - though the growth in related publications, patents, marketed drugs - there's a more personal story that deserves exploration. All of the results we are seeing are based on the creativity and tenacity of individuals and the corporate environments that nurture or, at the very least, tolerate change and innovation. In this column, I will explore some of the key features of people and organizations that foster creative ideas, paradigm shifts and new methodologies and products. I hope that by example, we can acquire insights that will be useful in our respective organizations and that might ultimately lead to more innovation in our industry.

Diana Day observed that a combination of champions from opposite ends of the spectrum, from the bottom-up (individuals who innovate) along with top-down support (the right management and corporate cultures), can create the petri dish in which ideas can foment and flourish.[1] There are numerous examples of champions who succeed in bringing new ideas to fruition in spite of all odds and against the expressed wishes or direction of management. For example, the vision and tenacity of Toshiba's Tetsuya Mizoguchi brought about the introduction of the world's first mass-marketed laptop in 1985. The interesting part of the story is that the executive team, with their vast experience, believed laptops were a passing fad and refused to fund the project. But Mizoguchi persevered, scraped together the resources, and built a prototype. It took 2 years but ultimately he found success, and no one would question the brilliance of his vision today.

I'm sure many readers can identify with Mizoguchi and two key take-aways from this example. First, individual innovators with determination can effect large changes in their segment of an industry. Second, imagine what could happen given a corporate

FIGURE 1



culture that actively empowers individuals to overcome challenges and to find new opportunities leveraging imagination, intellect, tenacity, and technology.

Throughout the first two quarters of 2014, I've had the opportunity to meet and dialogue with pharmaceutical and biotech research experts across the industry and university communities at a number of conferences. I've also had the benefit of gaining insight from experts in the study of innovation and the diffusion of technology. As you might imagine, in addition to discussions about the general state of the industry and industry trends, the issue of drug delivery challenges and, more specifically, overcoming poor bioavailability has been a common thread. World experts have presented innovative strategies for overcoming hurdles in the delivery of poorly soluble drugs and the benefits of utilizing drug delivery technology platforms, including co-crystals, lipids, hot- melt extrusion, solid dispersion technologies, and emerging technologies, including silica-based solutions and microneedles.

The most recent conference I attended was sponsored by the Catalent Applied Drug Delivery Institute (ADDI) and was held at the 3M Innovation Center in St. Paul, MN. The mission of Catalent's ADDI is stated as follows: "Our passion is improving treatment outcomes for patients, providers, and innovators with an intense focus on transforming the application of drug delivery technologies."[2] As most of you know, 3M is recognized as a world leader (if not *the* world leader) in innovation, and I can't imagine a more appropriate venue to underscore Catalent's goals, and a better company than 3M to serve as a role model for creativity and innovative solutions. It was my first time on the 3M campus, and I'm certain that most of you who've visited 3M have had the same reaction I did: creative energy is in the atmosphere, and it is contagious. But the success of 3M did not come overnight. In fact, it has taken over a century of dedicated focus to create, preserve, and nurture an environment that continues to sustain this great company.[3] It is worth taking a look at 3M to see if there are lessons we can adapt to our needs as we face the challenge of overcoming poor bioavailability.

HISTORY & BACKGROUND

3M started in 1902 with the goal of mining corundum in northern Minnesota (hence the Minnesota Mining and Manufacturing Company – 3M) to focus on businesses requiring abrasives. The mine they acquired, however, was devoid of the valued hard mineral but contained the worthless mineral anorthosite. Despite that major setback, and through perseverance, hard work, and creative problem-solving, the business evolved to become a manufacturer of sandpaper. And from that basis, 3M built what would eventually become the leading innovation company it is today. The business results are more than impressive: $31 billion in annual sales in 2013, nearly 90,000 employees producing more than 55,000 products. 3M has a technological and business footprint in adhesives, abrasives, laminates, electronic materials, car-care products, electronic circuits, optical films, and medical products. In fact, as Dr Steve Wick (3M's Vice President, Research & Development) said at the recent ADDI conference, "…you are never more than a few inches away from a 3M product."

While it is true that 3M is developing innovative drug delivery technology to overcome significant bioavailability challenges (ie, hollow microneedles), for the purposes of this column my interest is more in what can be understood about the environment and culture they've created that could be more broadly applied to our idustry. As you may already know or can certainly imagine, a vast amount of research has referenced 3M, discussing the company's successes and analyzing the methodologies by which they have created, reinvented, and preserved the corporate culture that has

served them so well.[4] The exchange of ideas - from people within an industry sector and from without - is a key attribute of the 3M culture.

In Gundling's book on 3M, he presents a multidimensional model used by the company that accommodates four types of innovation and their hybrids and how 3M has experienced revolutionary breakthroughs as incremental and evolutionary ideas - such as Post-Its - evolve from the 1st quadrant (shown in Figure 1) into a revolutionary product and create a new market.[3,5]

PEOPLE, CROSS-FERTILIZATION & INNOVATION

3M has a well-known policy of allowing employees 15% of their time - after their key responsibilities are met - to pursue ideas that may not be endorsed by the company, but that employees believe have promise in serving business goals. Employee empowerment allows 3M to continually extend its reach into areas that may not at first appear promising (to management), but that might just move the company toward an opportunity based on the passion, commitment, and tenacity of an individual. This policy is coupled with another key aspect of the 3M culture and the ongoing effort to attract and hire employees who are a good fit and have compatible attributes and attitudes.[3] The people they recruit appear to have qualities that enable the company to run with new ideas, break down barriers through creative and innovative problem-solving, and exploit resources from a broad array of disciplines. One personal attribute the company looks for in future "3Mers" is broad areas of interest; the benefits of this strategy seems to be reflected in the product areas they have expanded into and the creative application of technologies across industry sectors.

In 1951, 3M established the Tech Forum, to "encourage the free and active interchange of information and the cross-fertilization of ideas."[6] These once-a-year gatherings were designed to facilitate interactions among employees from all technological areas to allow them to share ideas, network, and allow intellectual cross-pollination. The belief that "one idea leads to the next" is an axiom on which much of the culture of 3M is based.[7] This philosophy - along with that of the 15% rule - creates an environment that inherently allows ideas to continue, evolve, and become refined even when naysayers would cancelled a project.

IMPLICATIONS FOR SOLUBILIZATION

3M has enviable breadth and depth in expertise, industries, and technologies; they have made significant contributions in introducing new technologies and delivery systems that can address poorly bioavailable drugs, and we can expect more. In previous columns, we've discussed how platforms have been borrowed from other industries throughout the past several decades to help us tackle solubilization, including spray-drying and micronization. If those of us in the industry strive to accomplish even more cross-fertilization, thinking about a "virtual 3M approach," I'm convinced that together we can tackle more of the barriers we face faster and with new innovations.◆

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

REFERENCES

1. Day DL. Raising radicals: different processes for championing innovative corporate ventures. Organizational Science. 1994;5(2):148-172.
2. Catalent Applied Drug Delivery Institute, www. http://www.drugdeliveryinstitute.com/about-us/.
3. Gundling E. The 3M Way to Innovation, Balancing People and Profit. Published by Kodansha International, Ltd.;2000.
4. Since 1975, nearly 8,000 articles have mentioned 3M as an example when discussing best practices. Agere analysis, GoogleScholar.
5. Ernest Gundling, Adapted by Agere for this article.
6. 3M website.
7. 3M website.

Marshall Crew
President & CEO
Agere Pharmaceuticals, Inc.
crew@agerepharma.com
LinkedIn: https://www.linkedin.com/profile/view?id=17815140

Management Insight

The Secret to Successful Global Expansion is to Bring your RATs & CATs Together

By: Derek Hennecke, CEO & President, Xcelience LLC

Indulge me a moment for bragging, but this month, my little CDMO made a very big jump. We became the first American CDMO with revenue under $1 billion dollars to set up operations overseas, opening a clinical packaging and distribution facility near Birmingham, UK.

We're the first, but I very much doubt we'll be the last. This is just too obviously necessary a move. As we stood on the Florida coast, squinting across the pond and thinking about a possible UK expansion, our clients didn't so much ask us to make our move, as throw us into the water. One client, whose support and business we very much appreciate, financed our set up costs. A week after our June 4th MHRA audit (that's the UK version of the FDA), we have two more clients already lined up and ready to begin work.

The UK is a first step on our learning curve. We will be moving into other markets as well, beginning most likely with Latin America. As CEO, it's my job to champion a strategy that will set a course for our future expansion. I'll let the CAT out of the bag, and share my strategy for getting ahead in the global RAT race (apologies). We are following the RAT/CAT virtuous cycle approach to creating and sustaining global advantage developed by Donald Lessard, Rafael Lucea, and Luis Vives in "Building Your Company's Capabilities Through Global Expansion", *MIT Sloan*

Management Review, Winter 2013.

The RAT/CAT model proposes that any global expansion strategy must first meet the RAT test. RAT stands for relevant, appropriable, and transferable. I'll explain that in a moment. What excites me most about this strategy is that the RAT keeps company with a CAT; the cat being criteria for learning and transferring knowledge gained abroad back to home office. Most expansion strategies are so focused on exploiting the target country(ies) that they fail to take the time and energy to learn from their new markets. The RAT is only half the picture; you need a CAT to really make the most of your expansion.

THE RAT TEST

The RAT test is used to determine if what you have to offer is a fit for the market you are targeting. It is a one-directional view; from home country to target market. Is the new market relevant? Is it appropriable? Can your capabilities be transferred there?

Relevant

The first step in launching a global strategy according to Lessard, Lucea, and Vives is to ask yourself, is what we do relevant to the customers in our target market? Do we offer something they want? Do we create value for these customers?

Appropriable

If so, is what we do hard enough to copy that the local market won't just replicate our offerings and run with them? Are all the necessary suppliers we need already there? Could those suppliers have undue power over us once we started operating?

Transferable

Can we effectively transfer what we do in our home market to this new market without losing too much value in the translation?

Walmart is a classic case study for global expansion. Does Walmart meet the RAT test? In most countries, unequivocally yes. The company's discount model is both new and desirable in most target markets abroad. In Germany, however, Walmart's initial expansion failed because too many local discounters were already offering a similar model. They were unable to offer value to their customers that their customers didn't already have access to.

Xcelience clearly meets the relevancy test for the UK/EU market, though our case is a little unique because we aren't entering the UK/EU market for the Europeans or the British. We are over there because our US clients want us to. This move is extremely relevant for our target (US) market. The combined UK/EU market is home to a population of roughly 570 million potential clinical trial patients. Increasingly, US companies need to look beyond North America to achieve the patient numbers they need for Phase II/III trials, and the UK/Europe is a convenient, developed market. All of our management team has worked in the UK/Europe, and two of our team, including myself, have lived and worked there.

Only two other companies, besides Xcelience, offer a full suite of services with locations on both continents. Both are massive CMOs, and as such, their target American markets are different. It takes a big fish to sate the commercial appetite of such companies. They won't turn away a small fry; but the smaller companies will never be their priority. Who does that leave to accommodate the legions of smaller companies that are the engines of biotech growth in the US? That's the market Xcelience is

targeting.

Don't misunderstand me, as our shiny new UK facility fills up with American clients, we will eventually examine our relevancy, appropriability, and transferability to UK/European clients. There's a good chance that our 313 million potential US patients may be useful to the Europeans also. Again, another surprising fact: there are no small UK-based companies with operations in the US to serve UK clients. None. I'm also very excited to explore this anomaly.

THE CAT TEST

Many companies are so focused on transferring knowledge and capabilities from home to their new foreign market that they forget to take the time to learn from the new market and bring those lessons home.

You can learn from the new country by buying an up-and-running foreign company that is already master of a particular area, or you can build ground up and learn to survive and thrive as you go, according to Lessard Lucea, and Vives. Whichever your approach, the key to successfully transferring ideas back to home is to determine whether the new capabilities complement the mother company, and if so, whether they are appropriable and transferable back. Science fiction fans will immediately recognize this as the BORG strategy, of Star Trek fame.

Some companies actually put the CAT process ahead of the RAT process, choosing to set up in what Lessard, Lucea, and Vives call "lead markets," which are those markets that are considered global leaders in a particular area. Shimano, a sporting gear manufacturer from Sakia, Japan, is the poster child for this strategy. Shimano set up a shop in the US right after WWII, at a time when the then-new technology called cold forging was developing. Acquiring this new capability significantly leapfrogged Shimano's manufacturing capabilities. Later, in the 1970s, Shimano established marketing and technical operations in Europe, which at the time was home to the industry's most discerning bicycle consumers and competitors. In the mid-80s, it used the same strategy in the West Coast of the US to better understand the emerging mountain bike market. In each case, the Japanese manufacturer learned something that made it better able to compete not only in the target market, but in all of its markets.

Some new capabilities and processes, however, simply can't make the jump to other markets. Lessard, Lucea, and Vives propose the CAT test to evaluate new capabilities. The CAT test, like the RAT test, is one-directional, but its direction is from target market to home market. The CAT test asks if the new capability, asset, or process is:

Complementary - Does it complement the existing capabilities of the mother company that create competitive advantage at home?

Appropriable - Can the mother company glean sufficient value from these new capabilities, or will other companies harvest the value that the capabilities/resources supply?

Transferable - Can head office get the new capabilities from the target market back to the mother company and integrate them without losing their value in the process?

Again, Walmart provides an example of a successful CAT transfer. In 2010, the discount retailer rolled out a new small-store format called Walmart Express, which targeted rural and urban areas without grocery stores in close proximity. The idea was learned from the company's experiences in Brazil,

Mexico, and Argentina, and is enjoying strong success at home.

CEMEX, the Mexican cement company, achieved many successes through the 1990s by acquiring new operations and transferring head office's capabilities and processes into each new facility. But they also created an examination process through which they exhaustively inventoried operations in the existing facility and evaluated and transferred new ways of doing things back to the mother company. Through this process, CEMEX was one of the first to introduce cheaper alternative fuels, reduce its cost of capital, and improve the use of its capacity by pooling demand regionally, according to Lessard, Lucea, and Vives.

I'm optimistic about CAT transfers from the UK to Xcelience. The UK is a technology hotspot for CMC work, and in some cases, the British standards are even higher than ours. In fact, a few years back, the MHRA came to the US and shut down the operations of two CDMOs for exporting to the UK. UK practices led to the introduction of quality agreements and airlocks in manufacturing. The UK requirements raised the cleaning verification levels to where they are today. I tip my hat to the MHRA; the regulatory agency has done a great deal to add to the world's understanding of cGMP. At Xcelience, we are looking forward to improving our operations in the US as a result of the lessons we learn from being there.

The RAT/CAT virtuous cycle is not a one-time thing. A cycle is only a cycle if it repeats. All organizations must constantly renew, and continual revisiting of local practices for RAT/CAT transferability should be ongoing.

The first step abroad is the hardest. In making our jump across the pond, we had to acquire a basic understanding of international accounting, international law, and significantly improve our ability to make tea. Now, we are institutionalizing the RAT/CAT cycle for exploiting new markets and enhancing core operations as we move into the next country. We hope to impress you with our mojitos soon, among other newly acquired best practices. ◆

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

BIOGRAPHY

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

MARKET BRIEF

Sequestration Haunts Life Science Research Tool Market Into 2014

By: Christi Bird, Senior Industry Analyst, Frost & Sullivan

INTRODUCTION

While sequestration measures officially hit the books on March 1, 2013, life science research tool suppliers started feeling the effects far in advance. For much of 2012, US academic and government end users reliant on National Institutes of Health (NIH), National Science Foundation (NSF), and other government-based research funding spent their budgets cautiously with the threat of austere fiscal policies looming. With researchers preparing for the possibility of reduced budgets in 2013, the majority of suppliers witnessed a slowdown in sales over 2012. The threat and buzz of possible budget cuts alone caused researchers to slow purchases, even as it appeared sequestration could be avoided. While spending was mostly down, some vendors reported minor upticks from July to December 2012 to help close the otherwise lackluster year. This is likely the result of laboratories making high-priority purchases in preparation for sequestration measures for the unforeseeable future, or simply due to buying cycles where customers must exhaust their spending budgets by the end of the fiscal year. Overall, however, most life science research tools companies did not meet expectations in 2012. Sales of laboratory products to the academic sector declined nearly 1% in 2012 and decreased over 2% for government laboratories. Unfortunately, the disappointing performance in 2012 has been met with even deeper struggles through 2013 in these sectors, with declines around 3.5% to 6% from government funding-dependent laboratories, with academic labs the low end of cuts and government-based labs showing more drastic sales reductions. Suppliers should not have expected major relief toward the end of 2013 from either end-user segment, as labs are holding tight to budgets in fear of further sequestration measures beyond. While there is hope that the academic sector will improve sometime in 2014, as funding levels return close to the 2012 amount, it is likely government labs will continue to endure deep austerity measures.

After the 2009 American Recovery and Reinvestment Act injected new life into the NIH budget, the government has since abandoned stimulus efforts in favor of the opposite. Without a clear path to fiscal responsibility in sight, is it likely government and academic labs will struggle with stark budgets and ever-decreasing buying power over the next several years.

In March 2013, President Obama signed an order of continuing resolution initiating sequestration measures following the 2011 Balanced Budget and Emergency Deficit Control Act. The policy required the NIH to cut 5% or $1.55 billion of its fiscal year (FY) 2013 budget, reducing the operating budget to approximately $29.2 billion.

The NIH applied the cuts evenly across all NIH institutes and centers (ICs), meaning no application area will be spared cuts. The 2013 reductions compared to 2012, include:

- Approximately 700 fewer competitive research project grants issued
- Approximately 750 fewer new patients admitted to the NIH Clinical Center
- ICs to issue all non-competing awards at levels below the FY 2013 commitment indicated on the notice of grant award, with an average cut of 4.7% expected

- Intramural research budget reduced by roughly $140 million, or 4.1%
- No increase in stipends for National Research Service Award recipients in FY 2013
- No inflationary increases allowed for all grants
- Salary caps remain flat or lowered
- Delayed hiring at NIH intramural research division
- Reduced administrative services contracts at NIH intramural division

Individual NIH institutions have made separate decisions on how to administer budget cuts, either through funding fewer grants in 2013, dispensing across-the-board grant reductions, or a combination of both. ICs rolled out these strategies in early 2013, with most opting for set non-competing grant reductions and the ability to fund competing grants at discretionary levels. The announced funding strategies of select key NIH ICs are summarized below.

While National Institutes of Health cuts are most relevant to life science research tool providers, cuts to other government research agencies, such as the National Science Foundation (NSF), Department of Defense (DOD), National Institute of Standards and Technology (NIST), Department of Agriculture (USDA), Department of Energy (DOE), and National Aeronautics and Space Administration (NASA), will further contribute to the bleak market challenges in 2013.

TABLE 1

FY2013 Funding Strategies for Select NIH ICs

Institute	Non-Competing Grants Reduction	Competing Grants Strategy
National Center for Advancing Translational Sciences	6% to 8%	Appropriate levels based on programmatic recommendations
National Cancer Institute	6%	Discretionary based on peer review evaluation
National Human Genome Research Institute	4.5%	Discretionary based on institute priorities
National Heart, Lung & Blood Institute	4.8%	Reducing grants or direct costs by 4.8%, eliminating inflationary increases, adjusting grant durations to 4 years
National Institute of Allergy & Infectious Diseases	6%	Reducing competing grants by 6% (excludes certain mechanisms), reducing competing initiatives 20%
National Institute of General Medical Sciences	3.5%	Overall average costs will remain at FY2012, no inflationary increases
National Center for Advancing Translational Sciences	6% to 8%	Appropriate levels based on programmatic recommendations

Source: FY2013 Funding Strategies; Frost & Sullivan

The NSF research and development (R&D) budget funds only academic research, as the agency does not house any intramural research labs. Thus, the agency's cuts almost entirely impact the academic research community. The major impact of sequestration is seen in reductions to the number of new NSF research grants and cooperative agreements awarded in FY 2013. NSF anticipated that the total number of new research grants would be reduced by approximately 1,000. However, all continuing grant increments in FY 2013 were awarded as scheduled and there was no impact on existing NSF standard grants. Thus, life science suppliers will continue to see growth in current NSF-funded customers, but new business will be limited greatly.

Meanwhile, the DOD funds approximately $1.6 billion to academic laboratories. The DOD R&D budget was cut by roughly 8.6% in 2013, according to the American Association for the Advancement of Science. The science and technology portion of the budget took a smaller cut at 4.6%. Overall, the result is a decline of more than $100 million available for academic labs. Nevertheless, the Defense University Research Instrumentation Program awarded $38.7 million in June 2013 to 140 university researchers to support the purchase of research instrumentation and equipment. In comparison, the DOD impact is a far cry from the $1.55-billion budget cut to the NIH.

Elsewhere, the USDA's Research, Education and Economics (REE) National Institute of Food and Agriculture (NIFA) partners with universities in carrying out extramural research, higher education, and extension activities. About 49% of the $2.7 billion 2012 REE budget was allocated for NIFA grants, for approximately $1,323 million going to this program. NIFA relayed the following measures would take place in

response to sequestration: a reduction of $13 million for the Agriculture and Food Research Initiative (AFRI), competitive grants program, resulting in fewer new proposals that were funded during FY 2013, reductions totaling almost $37 million for capacity/formula funding, and reductions for other research, education, and extension programs totaling over $10 million. The bright spot was no impact on AFRI Continuation awards from previous fiscal years, with funding moving forward, evaluated on performance and success on meeting stated goals. Looking forward, in 2014, the USDA is expected to provide 47% of the $2.8 billion REE budget to NIFA, resulting in a $1,316 million budget, still a decline over 2012 levels.

NIST cuts fell largely on grants, contracts, equipment procurements, deferment of open positions, and cuts in the repair and maintenance of NIST facilities, which will negatively impact NIST's ability to keep them in acceptable working condition. The DOE's Office of Science announced it would reduce research grants both in number and size, affecting researchers at national labs and universities. Meanwhile, at NASA, sequestration measures necessitated a reduction in funding for competed research projects by about 2%, resulting in about a 5% reduction in new awards to support labor and jobs at universities, businesses, and other research entities.

Overall, the buying power in academic and government laboratories has reached an all time low, as budget growth has fallen significantly off the pace of inflation. While laboratories will deal with these limited budgets and weak buying power in various ways, certainly all grantees will attempt to maintain personnel levels and will be expected to meet grant research aims within the reduced grant amounts. Therefore, researchers are expected to become more cost-conscientious when purchasing research reagents whenever possible and adjust capital equipment budgets considerably. Typical in lean funding years, instrumentation is likely to take the biggest hit as researchers can delay product upgrades and new technology purchases, or opt for used equipment should purchasing guidelines allow. Given the aforementioned grant reductions, instrumentation providers saw sales to the academic and government sectors decline 5% to 7% in 2013. Meanwhile reagents and consumables must be purchased to keep laboratories running, and, therefore, the market remained flat or slightly declined through 2013. Overall, sales of life science research tools to the academic and government sector declined in the 4% to 5% range over 2013. Beyond 2013, funding to the sectors remains unclear, yet overall remains bleak. The adopted continuing resolution extends FY 2013 budget levels partway into FY 2014, until the House and Senate can resolve a $6.5-billion disconnect in 2014 budget levels. With the threat of continued sequestration measures in 2014 reducing discretionary spending by another 2% over FY 2013 levels, labs are likely to remain highly frugal until the budget is resolved in early 2014. This means another two quarters of near-guaranteed anemic spending conditions for life science research tool suppliers from these sectors. With inflation rates continuing to reduce buying power for these sectors, even if research funding returns to FY 2012 levels, budgets will not stretch to produce sales equivalent to 2012. Thus, the research tools market should suspend any major growth expectations from these end-user segments and focus attention on emerging regions and healthier business sectors.

GROWTH STRATEGIES

When the economic climate causes reduced sales volumes, there are several strategies companies employ to offset the decline and maintain positive growth. Unfortunately, the simple method of shifting resources into end-user markets that are growing quickly is nearly irrelevant given few bright spots exist in the industry today. The pharmaceutical industry seems to have put double-digit growth of R&D budgets in the rear view mirror. While some companies are slashing R&D budgets, others are adjusting to low single-digit spending growth year over year. With many drugs coming off patent in the next few years and few blockbusters in sight to take their places, other pharmaceutical companies are restructuring their R&D divisions to account for erosion by generics. This has resulted in a slow-growing market for research tools, effectively doing little to overcome the challenges in the academic and government sectors. However, applied markets are increasingly more desirable with food and beverage, water, and environmental testing growing in awareness worldwide. Many research tools suppliers have observed shifts in their customer makeup

over the past 5 years, trending toward the more robust applied markets to compensate for lackluster sales elsewhere. This trend is expected to continue, especially as increasing standardization in these fields globally will expand testing and require facility improvements.

In addition, several successful strategies exist outside of shifting end-user focus and internal austerity measures. With little opportunity for organic growth outside of true innovations, companies will look for alternative strategies for growth. An increase in merger and acquisition (M&A) activity is highly, likely as companies look for growth opportunities outside of current stagnant markets. In 2013, the life sciences research tools industry had seen several acquisitions occur, including the largest in recent history involving Thermo Fisher Scientific and Life Technologies. Other recent acquisitions include Bio-Rad's acquisition of AbD Serotec, Illumina's acquisition of Verinata Health, Moleculo and NextBio, Life Technologies' acquisition of KDR Biotech Co. and Life Science Korea, Qiagen's acquisition of Ingenuity Systems and CLC Bio, and many others. We expect to a continued stream of M&A deals close through 2013, as big companies look to benefit from high-growth markets, such as bioinformatics, molecular diagnostics, the Asia-Pac region, or smaller niche markets. Other partnerships and research agreements are expected as alternatives to full M&A deals. For example, Agilent made a huge $21 million strategic investment in gene synthesis startup Gen9 to secure an equity stake and place on the board. In addition, Illumina formed a technology assessment deal with TroavaGene, perhaps a segue to a future acquisition. Overall, industry consolidation and alliance activity is expected to increase as companies look outside of current product lines for growth. Ultimately, however, none of this activity can replace pure innovation leading to products that improve research workflows and create future cost-savings in ancillary product expenses or laboratory efficiency. Companies that fulfill on unmet needs and provide significant value-adds for cost-conscientious researchers can certainly overcome the unpromising economic climate.

CONCLUSION

Perhaps the bleakest outlook provided for the life sciences industry is one without a clear light at the end of the tunnel. There is no clear indication that government-based research funding will return to growth equivalent or above inflation in the near-term. Successful companies will buckle down to determine long-term strategies for beating the lackluster numbers expected from a sustained austerity policy. Innovations that provide cost-savings, consolidation, and unique alliances are some of the key strategies we expect to see more of as companies settle into the realities of a bleak market outlook. ◆

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

BIOGRAPHY

Christi Bird is is a Senior Industry Analyst with Frost & Sullivan's global Life Sciences practice. Her knowledge base covers a broad range of sectors within scientific disciplines including genomics, proteomics, molecular biology, microbiology, translational research, assay platforms, and instrumentation.
For more information on Frost & Sullivan's global Life Sciences practice and offerings, please email jennifer.carson@frost.com or visit www.frost.com.

Regulators Make Intentions Clear on Transparency & Harmonization

By: Erick Gaussens

INTRODUCTION

As we get deeper into 2014, pharmaceutical companies have been and are preparing to tackle some significant regulatory challenges - as well as to welcome some advances - all in the name of improving transparency, harmonization, and collaboration.

For regulatory authorities, the top priority remains patient safety, which has led those agencies to require from pharma companies both more data and greater collaboration between regulatory authorities, aimed at sharing and comparing product safety data. But the European Medicines Agency and the US Food and Drug Administration (FDA) are also eager to improve the processes by which submissions are made, reports are created, and companies liaise with regulators.

Internal shake-ups, too, are aimed at improving efficiency and helping regulators become better prepared to tackle a variety of challenges. For example, the European Medicines Agency recently announced a reorganization with views to: (1) provide better support for the scientific work done by agency committees, (2) enhance knowledge and information sharing, and (3) improve how the agency works with partners and stakeholders, such as marketing authorization holders, industry organizations, and patient groups.

THE XEVMPD REVISITED

Most significant for pharma companies in 2014 is the European Medicines Agency's decision to revisit the Extended EudraVigilance Medicinal Product Dictionary (XEVMPD). The initial announcement of the XEVMPD occurred in 2011, when the agency informed companies that as of July 2012, they would be required to submit product information. That information was to include basic facts, such as name, date of approval, therapeutic area, and dosage as well as more-detailed information, such as known adverse events. The process, however, was drawn-out, and it was complicated by poor communication between the agency and industry, by delays in the issuance of guidances, and by industry concerns and uncertainties.

The purpose of creating the XEVMPD database was to ensure increased transparency of data and better product identification. However, once the agency began reviewing the data, it discovered that the quality of data entered was poor, and so the XEVMPD was put on hold for several months.

In November 2013, the agency began issuing quality control notices and said it would provide new guidance in January 2014, though it would issue draft guidance by December. Delays in releasing that draft guidance have led to industry concern about whether there will be opportunities to test the draft guidance before the final guidance gets issued.

Companies are now facing challenges in meeting the upcoming December 2014 deadline for updating their records, and uncertainly remains about the impact on companies as they seek to put in place all of the changes required, and to update their software and processes accordingly.

PUSH ON TRANSPARENCY

Data transparency has become a regulatory priority on all fronts, and regulatory agencies have taken further, vigorous steps in that direction. Certain medicines that have become identified as ones needing close monitoring will have to carry black inverted triangles on their package leaflets. In some cases, when the same active ingredient is marketed by several companies, all of those involved as marketing authorization holders are affected. And the impact is the affected companies will have to not only revise package inserts to include the black triangle - which means having to make changes to the summary of product characteristics in all of the languages of all of the countries where the drug is marketed - but also resubmit the documents for regulatory approval.

The European Medicines Agency also wants pharmacovigilance to become more than simple surveillance of a drug but, rather, continuous analysis and evaluation of safety information regarding the impact of each drug or active ingredient on exposed populations. Such analysis and evaluation will become greater priorities this year as new modules of the good-pharmacovigilance-practice guidelines aimed at driving that goal get released for public consultation. The new modules cover (1) public participation in pharmacovigilance; (2) continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action, and planning of public communication; and (3) international cooperation.

Regulators are also paying close heed to the pediatric investigation plan (PIP), which seeks to ensure the necessary data on drugs are obtained through studies on children, when safe, in order to expand the number of medicines dedicated specifically to children. The regulation came into force in 2007, and the European Commission published a report in June 2013 that covered the first 5 years of the regulation. According to the report, legislation has improved the situation for child patients, though certain concerns raised by stakeholders are expected to lead to greater improvements in 2014. Those improvements would deal with the facts that no single strategy fits all PIP applications, that most PIPs get agreed to only after major modifications, and that there is significant variance in the time from submission to plan agreement, depending on the complexity of the PIP. Stakeholders have also said the study's feasibility remains a concern for industry.

One area stakeholders would like to see greater improvement in involves alignment between the European Union (EU) pediatric plan and the US pediatric plan. In the United States, two pieces of legislation have been enacted with the goal of increasing the number of studies of medicines in children. The first is the Best Pharmaceuticals for Children Act, which serves as an incentive for companies to conduct pediatric studies at the request of the FDA; the second is the Pediatric Research Equity Act of 2007 (PREA), which requires that under certain circumstances, companies study products for children. In 2012, Congress reauthorized the PREA and gave the FDA: (1) the authority to grant extensions to companies on certain grounds if those companies have made the right request and (2) the authority to send noncompliance letters to companies that fail to obtain a deferral or that do not submit pediatric studies by the final agreed date. The FDA began publishing such noncompliance letters on an FDA Web page in August 2013.

An area that has resulted in much consternation on the part of industry is the European Medicines Agency's announcement that it was planning to start publishing data submitted for regulatory review through the European Clinical Trials Database beginning this past January. Several companies have taken legal action in a bid to prevent their data from being made public. Even though the FDA announced in June 2013 that it was seeking input with regard to making de-identified clinical data available in an effort to improve the drug development process, to date, US regulators have not taken as provocative a stand as their EU counterparts.

SUBMISSION CHANGES

This year is expected to streamline the delivery of electronic submissions, though some of the changes will require that companies adapt their own processes to some extent. When making submissions through the centralised procedure, marketing application holders have for some time been able to use the agency portal, but until recently, they had

to physically ship CDs or DVDs when submitting through the national procedure, the mutual recognition procedure (MRP), or the decentralised procedure (DCP) for most agencies. The Netherlands and the United Kingdom have portals and permit electronic submission. In mid-2013, the agency made available the Common European Submission Platform (CESP) for submitting regulated documents by means of all procedures other than the centralised procedure, which has its own, European Medicines Agency portal.

For companies, the CESP is expected to simplify the submission process by cutting the time from submission to acknowledgement of receipt by the regulators, while at the same time saving companies from having to burn and ship CDs. The CESP is widely accepted in Europe, though not by all authorities. For example, French agency l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) has said it won't permit CESP submission across the board because it still requires paper submission for a subset of variation types for non-electronic Common Technical Document (eCTD) dossiers. The ANSM is piloting a move toward electronic submission through the CESP, though currently for generics only.

In a further move to improve the submission process, the MRP and DCP have been moved to a comprehensive model and away from what was known as the parallel model, whereby companies had to submit independent eCTD life-cycle sequences for each country. The move is in keeping with the planned requirement for eCTD submissions through the DCP from 2015, and it places the onus on companies to get their organizations ready to comply with comprehensive model management and eCTD-format production during 2014. For companies, the challenge will lie in aligning the processes between a company's corporate headquarters and its affiliates.

In early 2014, the European Medicines Agency plans to launch a new, common repository whereby regulatory authorities can store submissions centrally, thereby eliminating the need to copy the same submission for each local authority. This will likely have little impact on companies - apart from a positive knock-on effect from regulators that are improving their own processes.

Regulators are also working toward greater harmonization around pharmacovigilance on several fronts. With regard to pharmacovigilance case databases, companies will in the future be able to send these in electronic format, meaning that there will no longer be a need for each country in Europe to have its own pharmacovigilance case databases. The electronic format will save companies from having to re-create pharmacovigilance case reports in paper format before sending them to the agencies. The next step is to gather the data in a centralized database, from which the national authorities will be able to access their own data.

There are also efforts under way to facilitate greater harmonization between: (1) Periodic Safety Update Reports (PSURs), which are for products on the market; (2) Development Safety Update Reports (DSURs), which are required during clinical trials; and (3) the risk management plan (RMP). The goal is to permit the use of individual sections that are common to more than one aspect of a report. The hope is to encourage consistency and avoid unnecessary duplication while also improving efficiency for companies. However, it will require companies to adjust their own processes in order to manage commonalities between the reports, organize bibliographic sections, and coordinate their signal management, risk-benefit assessment, PSURs, DSURs, and RMPs.

GOING GLOBAL

The already strong relationship between the FDA and the European Medicines Agency grew closer still over the past year. The two agencies have been allowing cross-access to pharmacovigilance databases, and their officials meet regularly to compare their findings for the same products. In 2013, that collaboration was reinforced to ensure greater cooperation over the PSUR. Such liaisons will become increasingly more commonplace in 2014, with the two agencies announcing an initiative to share information findings from inspections of bioequivalence studies submitted to either agency and to regulatory authorities in some of the EU member states with regard to marketing authorization applications for generic medicines.

Efforts are also under way to enhance collaborations on certain quality sections and chemistry, manufacturing, and control

sections that are relevant to quality by design (QbD), which, if well managed, could considerably ease batch delivery and minimize inspections for companies that follow the QbD process. The FDA and the European Medicines Agency are working extensively through information sharing and ongoing meetings to ensure that QbD gets used effectively.

In addition, Japan's regulatory authorities: the Japanese Ministry of Health, Labour and Welfare; and the Pharmaceuticals and Medical Devices Agency began during the second half of 2013 to enter information on good-manufacturing-practice (GMP) compliance – as such compliance involves Japanese manufacturers - in the European Union drug-regulating authorities' good-manufacturing-and-distribution database, which the European Medicines operates to support the exchange of information on GMP compliance.

In Europe, the European Medicines Agency has been unifying regulatory processes with medicine assessments made by health technology assessment bodies, with the goal of speeding up and improving access to authorized medicines for patients.

Other parts of the world are working toward greater harmonization of electronic submissions. For example, Saudi Arabia has said the electronic Common Technical Document (eCTD) will become the preferred submission format from January 2014. The Saudi Food and Drug Authority (SFDA) began with draft guidelines in 2012 for electronic submissions that differed from eCTD and non-eCTD electronic submissions (NeeSs). The criteria turned out to be difficult to manage for companies, and the country moved toward the eCTD. The final guidance, reworked in 2013, made the format for Modules 2 through 5 identical to International Conference on Harmonisation requirements, with only Module 1 having differences, as is standard in most regions. It is now much easier for companies to prepare a Saudi dossier from an existing NeeS or eCTD submission. As of January 3, 2015, only the eCTD will be accepted, according to the SFDA's road map. An eCTD pilot phase is also being conducted in South Africa, with the Medicines Control Council expected to open eCTD submission to the entire industry during 2014.

SUMMARY

Continued emphases on data transparency and on streamlining of the submission process - to the benefit of both regulatory agencies and pharma companies - create both opportunities and challenges for companies. During 2014, companies need to get their own processes in order and manage their regulatory information to become able to respond to requirements involving product information, including the XEVMPD, while also taking advantage of improvements in methods of delivery of electronic submissions to regulators. ◆

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

BIOGRAPHY

Erick Gaussens, PhD, is Co-founder, Principal Consultant, and Chief Scientific Officer of ProductLife Group, providing deep insights into risk management and regulatory sciences in the life sciences industry, as well as expertise in cognitive science. He can be reached at egaussens@productlife-group.com.

BIOSIMILARS

The US Biosimilar Approval Pathway: Policy Precedes Science

By: David Shoemaker, PhD

INTRODUCTION

With the passage of the Biosimilar Price Competition and Innovation Act (BPCIA) in 2009, the US created new pathways for development and approval of biosimilar and interchangeable products [Section 351(k) of the Public Health Service (PHS) Act (42 U.S.C. 262)], in the hopes of creating a low-cost alternative to expensive, innovator-marketed biologics whose patent terms were expiring.[1] The BPCIA was intended to be a major cost-containment mechanism of the Patient Protection and Affordable Care Act of 2010. The origin of the BPCIA had its roots in the Drug Price Competition and Patent Restoration Act of 1984 championed by Senators Waxman and Hatch, which has provided low-cost generic alternatives to prescription brand-name drugs for the three subsequent decades. What Congress failed to appreciate at the time was the current state of protein characterization science and consequently whether interchangeability could in fact be obtained or what level of biosimilarity was acceptable.

FDA DRAFT GUIDANCES

As has been well documented in the years prior and subsequent to the passing of the BPCIA, the analogy of "generic" does not transfer well from the realm of small molecule drugs to that of biologics, due primarily to biologics' considerably larger molecular size and complexity of manufacturing that may affect the final product in terms of tertiary structure or post-translational modifications (Prugnaud and Trouvin, 2013). The FDA has issued four draft guidances to help clarify expectations regarding the concept of "biosimilarity" and thereby to assist manufacturers in the development and approval of biosimilars.

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (PDF - 576KB)
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (PDF - 432KB)
- Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCIA of 2009
- Guidance for Industry: Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (PDF - 272KB)

However, despite the availability of these guidances, no biosimilars have been approved by the FDA to date. The primary reason is that the additional work required to demonstrate similarity of the efficacy and safety of the biosimilar molecule to the original approved biologic is sufficiently burdensome to make approval via the original approval pathway for biologics [351(a)] equally attractive to biosimilar manufacturers. Also, by choosing the 351(a) BLA innovator biologic pathway, the company is entitled to a 12-year marketing exclusivity period associated with this development pathway versus as little as 12 months of marketing exclusivity if it was approved as a biosimilar [351(a)(6)].

The FDA espouses that clinical and

nonclinical work will be abbreviated for biosimilar approval, and that approval will be granted on the basis of the "body of evidence" provided by the manufacturer, but that each application will have to be handled on a case-by-case basis. However, this is potentially much more labor intensive than the traditional biologic development process familiar to pharmaceutical and biotechnology companies. Development of a biosimilar currently requires significant comparability work be agreed upon a priori with the FDA, and this work must be "front-loaded" in the development program. Depending upon the results of this comparability nonclinical and manufacturing work, additional work most likely will be required.

SUCCESS IN EUROPE

There are several companies that have successfully gained marketing approval for biosimilars in Europe that are effectively currently assisting the FDA in determining the data package that will eventually be required for approval of a biosimilar in the US. The difficulties stem to some degree from the division of the US FDA into the Center for Biologics Evaluation and Research (CBER) and the Center for Drugs Evaluation and Research (CDER) due to evolutionary organizational reasons. The European Medicines Agency (EMA) is able to bring to bear the same scientists to evaluate both small molecules and biologics, and consequently, there is not the same degree of separation of opinions about how each type of molecule is regulated within one agency. Consequently, the EMA was able to foresee this biosimilar pathway's emergence much earlier and issue a number of class specific guidances that contain specific recommendations for development.

EFFICACY VS. SAFETY

In addition, achieving an FDA determination of true interchangeability of a biosimilar versus an original biologic product as exists for generic and innovator small molecule drugs will not be accomplished until a great deal more is understood about the biochemical processes generating these molecules and the contributions of the various regions of the molecules to efficacy and safety concerns. Of primary concern is the contribution of the various structural elements of the biosimilar molecule to the safety concerns in clinical studies. Efficacy can more easily be demonstrated in a reasonably sized clinical development program, but it is safety that regulators struggle to define the minimum number of subjects that represent a sufficient safety database to warrant marketing approval.

The scientific methods that are used to determine molecular similarity are currently insufficient to specifically identify the relationship between differences between a biosimilar and an original biologic. For example, assigning an adverse event observed in a clinical study to a specific peak in a mass spectrometry profile is imprecise at best, but we are nowhere near this level of precision at the current time. Consequently, the regulatory authorities emphasize that the "body of evidence" will determine their judgment as to the biosimilarity of a molecule. The FDA has championed the need to begin to consider the safety of pharmaceuticals and biotechnology products as a science, but as yet the integrated effort required to produce these types of results has not been embraced by industry, academia, or governmental agencies. Until much more work is done defining the relationship between structural elements of a biological molecule and the adverse events observed in the clinic, the determination of biosimilarity with regard to safety remains largely subjective.

BIOSUPERIORS

Consequently, while many large pharma companies have announced their intention to develop biosimilars, many manufacturers have chosen to develop alternative products designed to be more than just biosimilar - biosuperiors or biobetters .2 These are products similar to the original approved biologics, but with some measurable superiority, such as extended therapeutic effect time or a reduced adverse event profile. These products are being developed and approved via the traditional 301(a) BLA pathway for biologics and are required to demonstrate efficacy and safety without the necessity of comparability studies designed to demonstrate their similarity to the originator molecule.

This approach has several advantages.

First, it relieves the product sponsor from conducting a large Phase III active-control clinical study versus the innovator biologic demonstrating equivalence.[3] These types of studies are larger and less scientifically rigorous than clinical studies versus placebo and carry all the vagaries of generating meaningful data from a clinical study (ICH E3, Section 9.2). Of course, the efficacy of the biosuperior product has to generate efficacy and safety data demonstrating a risk/benefit ratio of the same approximate magnitude as the innovator product, but not in a head-to-head comparison. The biosuperior developer will be measured against the results obtained by the innovator in their current package insert. Consequently, the work required for approval of a biosuperior would more closely resemble the 505(b)(2) New Drug Approval (NDA) regulatory pathway for "improved" approved drugs leveraging the FDA's knowledge of previously approved innovator products as opposed to the 505(j) NDA pathway for generic drugs with its expectations of interchangeability.

In fact, the 505(b)(2) pathway has already been utilized in the approval of biosimilar molecules that fall under the purview of the Center for Drug Evaluation and Research (CDER) as opposed to those that fall under the Center for Biologics Evaluation and Research (CBER). For historical reasons, hormones are regulated by the Food Drug and Cosmetics Act of 1938 and not the Public Health Service Act. Consequently, well-characterized hormone molecules, such as insulin and somatropin, have several products competing for the market and undoubtedly put pressure on the original innovator price of these products. In Europe, where there is no distinction between the approval pathways for drugs and biologics, several molecule-specific guidances have been issued to assist product sponsors with the development of these well-characterized molecules (ie, insulin, somatropin, erythropoietin, granulocyte-stimulating hormone, follicle-stimulating hormone, and interferon).

One might say that focusing on biosuperiors defeats the original purpose of legislation for development of biosimilar products, ie, the reduced sales cost to the consumer that has been well documented in the generic drug market. However, due to the complexity of development of biologics, the expected sales price of biosimilars was anticipated to originally be in the range of 70% to 80% of the originator molecule as opposed to the approximately 30% of the originator drug that has been documented for generic drugs.[4] Consequently, the price competition that might result from the presence of viable biosimilars on the market was never expected to be game-changing for consumers the way that small-molecule generics have been. For biosuperiors, the degree of superiority represented by the biosuperior competitor may alter this dynamic significantly, perhaps leading to a premium price for the biosuperior relative to the innovator product. In general, it is safe to assume biosimilars and biosuperiors will not realize anywhere near the degree of price discount seen with small molecule generics.

DEBATE AROUND INN

Aside from questions around how to prove "biosimilarity" or the likely effects on product pricing, the current debate raging between the companies manufacturing biosimilars and innovators revolves around the International Nonproprietary Names (INN) convention for biosimilars.[5,6] The companies manufacturing biosimilars, reasoning along the same lines as the intent of Hatch-Waxman for generic drugs, argue that all derivatives of an innovator molecule must possess the same INN name. However, the manufacturers of the innovator molecules argue that while similar, the subsequently approved biosimilar molecules will likely possess significant differences in glycosylation and tertiary structure and consequently should be examined separately for adverse events that may not be affiliated with the safety profile of their innovator molecules. However, until a bona fide biosimilar is approved in the US, this discussion is perhaps premature and assumes that regulatory protein science will eventually evolve to the point where detailed molecular structural information can definitively be matched with the safety and efficacy events a biological product demonstrates. In fact, the FDA has recently stated it wants its biosimilar naming guidance released before approving an application.

BIOSUPERIORS ADVANTAGE

Was it possible to see the evolution of biosimilars and biosuperiors prior to the passage of the BPCIA? Much of the prior debate focused on whether it was even possible to manufacture a biosimilar to the exacting standards required to mimic the efficacy and safety of an approved biologic. Large pharma emphasized the inability of biosimilar manufacturers to replicate the complex structure of biologics and hence predicted the introduction of unknown safety concerns attributed to the changes in structure. Nonetheless, many large pharma companies stated their intent to refocus some of their efforts on biosimilars while others steadfastly avoided this commitment or expressed their intent to pursue biosuperiors. The development of biosuperiors will no doubt also encounter some regulatory hurdles not experienced during the innovator molecules' development. For one, it will be of critical importance for the developers of biosuperiors to convincingly demonstrate to the FDA their advantage over the innovator molecule if they intend to advertise that distinction. Hence, the current state of protein science seems to augur approval decisions and court battles focused on the clinical relevance of the superiority rather than the similarity of biosimilar compounds to innovator molecules. ◆

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

REFERENCES

1. Prugnaud J-L, Truvin J-H, eds. Biosimilars: A New Generation of Biologics. Springer-Verlag France, Paris, 2011.
2. Armstrong W. MedImmune Bets Its Fate on "Biobetters" 2011. PharmExecBlog. www.PharmExecBlog.com.
3. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceutical For Human Use. Structure and Content of Clinical Study Reports. E3. 1995. Section 9.2 p 6.
4. Use of Generic Prescription Drugs and Brand-Name Discounts. National Conference of State Legislatures Briefs for State Legislatures. In Health Cost Containment and Efficiencies. 2010; No. 8.
5. Karlin, Sarah. Naming Rights: Biosimilar Influence Efforts Continue Before Products Take the Field. "The Pink Sheet" 2013;75(43):5-7.
6. Pollock B. What's in a Name? GPhA Says, Everything – for Biosimilars. 2013; Lachman Consultants Blog. www.lachmanconsultants.com.

BIOGRAPHY

Dr. David Shoemaker is Senior Vice President R&D at Rho, with more than 25 years of experience in research and pharmaceutical development. He has served as an advisor for multidisciplinary, matrix-managed project teams and has been involved with products at all stages of the development process. He has extensive experience in the preparation and filing of all types of regulatory submissions, including primary responsibility for four BLAs and three NDAs. He has managed or contributed to dozens of INDs/CTAs and over a dozen successful NDAs, BLAs, and MAAs. Dr. Shoemaker has moderated dozens of regulatory authority meetings for all stages of development and supported several companies at FDA Advisory Committee meetings. He has authored or overseen dozens of Orphan Drug Designation applications, has developed several successful Accelerated Approval programs, and has secured several Priority Review applications.

Special Feature

Patients & Physicians Desire Transdermal, Topical & Subcutaneous Delivery

By: Cindy H. Dubin, Contributor

The $82 billion U.S. drug delivery market is showing no signs of saturation, with major patent expiries, generic competition, tightening Food and Drug Administration (FDA) regulations, and emerging drug delivery systems continuing to provide momentum. Among the 15 drug delivery systems surveyed by Frost & Sullivan, physicians prefer topical delivery, either as a transdermal patch or topical gel/cream, and expressed willingness to switch their current mode of therapy to one available in these forms.

In fact, an end-user survey of more than 220 physicians and 650 patients by Frost & Sullivan, *Drug Delivery Technology: End-User Preferences, Utilization and Perceptions* analysis, found that regardless of disease area, physicians select drug delivery methods that drive consistent patient compliance and effective outcomes. The survey traced usage patterns, analyzed preferences and opportunities among physicians and patients, and assessed their willingness to switch therapies based on the drug delivery method.

"All things considered, physicians usually toward t the treatment they feel will be most acceptable to their patients in order to ensure good compliance," said Frost & Sullivan Vice President of Global Research

Caption: Adhesives Research and ARx, LLC adhesive formulations take wear duration, activity levels, and drug compatibility into consideration.

Monali Patel Shastry.

"When selecting the optimal drug delivery method, reimbursement incentives for improving adherence and impact on formulary decisions are proven to be important factors," added Frost & Sullivan Life Sciences Senior Industry Analyst Deborah Toscano. "Drug development pipelines are full of innovative drugs and biologics, and differentiation is increasingly important in this crowded market to gain and maintain market share."

It is important to note the drivers of satisfaction and selection are not always the same across diseases and methods. For example, several novel oral therapies for multiple sclerosis offer advantages over standard injectable therapies. However, more than 55% of physicians treating multiple sclerosis are likely to switch from the currently prescribed branded drug if the drug were available in a transdermal patch form. This is in line with the 58% of multiple sclerosis patients willing to use a transdermal patch. Further, 57% of physicians treating Type 2 diabetes are most willing to switch from oral or injectable drugs to a topical treatment.

Drug Development & Delivery magazine recently interviewed several topical, transdermal, and subcutaneous product manufacturers to find out how they are working with patients and physicians to develop delivery systems that meet their need for comfort, compliance, and more effective delivery.

ADHESIVES RESEARCH & ARX, LLC—FORMULATING ADHESIVES FOR PATIENT COMFORT AND ENHANCED DRUG DELIVERY & EFFICACY

As adhesives are a key component of transdermal systems, patch manufacturers are taking a more judicious approach in adhesive selection to assure compliance with FDA guidelines for safety (skin irritation and sensitization) and minimizing residual drug content. Adhesives Research offers customized services to formulate and manufacture both bulk adhesives and adhesive laminates for transdermal applications and sister company, ARx, LLC, takes this a step further in the creation of drug-loaded adhesives and films for specific APIs.

"Our formulations take into consideration prescribed patient wear duration, activity levels, drug compatibility/solubility, and system stability," says Susan Newsom, Pharmaceutical Business Manager, Adhesives Research, Inc.

Megan Greth, Business Manager for ARx, LLC adds, "By leveraging Adhesives Research's foundational expertise, ARx, LLC custom formulates and manufactures adhesives and dissolvable films for transdermal and mucosal patches with the selected API and provides developmental and filing support for products with added benefits, such as less API, rapid onset, or increased patient comfort when compared to those currently available."

Adhesives Research's bulk adhesives – available in acrylic, PIB and silicone chemistries – are formulated for drug-in-adhesive transdermal patch matrices, and may be sold separately or provided to ARx for the development of a complete drug delivery system in support of ANDA or NDA filings. Adhesives Research also develops and manufactures adhesive laminates for skin-attached devices, such as patch pumps and infusion sets intended for subcutaneous delivery.

Adhesives Research specializes in the development of skin adhesives systems that demonstrate secure and comfortable wear over prescribed wear times with easy and clean removal from the skin. "Our platforms address wear durations from minutes to 7-plus days, and applications where a weighted device must be bonded to skin such as bolus injectors, patch pumps, and active transdermal delivery devices like microneedles and iontophoresis," says Ms. Newsom.

Ms. Greth adds, "One of the biggest issues in transdermal patch development is in the selection of the appropriate adhesive polymers and final formulation to enable the desired drug release without skin irritation. ARx's fundamental knowledge of polymers and skin variation contributes to program success in skin irritation, sensitization, and clinical studies."

Working together, Adhesives Research has expertise in adhesive formulation, polymerization, mixing, and coating processes as well as specialty release liners, while ARx has expertise in the custom formulation, process development and commercial manufacture of both ANDA and 505b2 drug-loaded adhesive and film patch applications. ARx also offers development support in CMC documentation, analytical method development, validation, and final product release.

EI SOLUTIONS—A ONE-STOP DEVELOPMENT & MANUFACTURING SERVICE

With not a lot of new molecular entities in the topical space, the repurposing of older drugs for new indications fill important medical needs. “Many APIs were never studied topically, and certainly not for orphan disease states, so there will be some promising products hitting the market in a few years,” says Roger Martin, President of Ei Solutions.

Ei provides turnkey development, formulation, analytical, procurement, manufacturing, and filling services in topical liquid and semi-solid dosage forms. Ei is structured and resourced to be a one-stop-shop for customers looking for myriad development and manufacturing services in the topical market. Ei works with its suppliers to source and procure specialized, possibly single-sourced delivery systems that allow competitive immunity for its clients, explains Mr. Martin.

For one client, Ei used its Valois/Aptar filling line to package a product without head space to enable the stable perseveration of the product. He says: “It was a simple, yet incredibly effective solution to their product that historically showed oxidation.”

Looking ahead, Mr. Martin sees growth of 505b2 applications using unique delivery systems, such as vacuum-filled pumps, dual-chamber pumps, or new and improved unit-dose applicators.

“In the future, we also see unit-dose continuous spray (non-aerosol) delivery systems being very attractive for our topical clients, both in terms of a unique value proposition for our customer, and convenience for the patient,” he says.

TAPEMARK—PASSIVE & ACTIVE TRANSDERMAL, ORAL TRANSMUCOSAL & TOPICAL DRUG DELIVERY

Tapemark, a full service contract developer and manufacturer, provides transdermal, oral transmucosal, and topical drug delivery systems that meet consumer needs for increased convenience/compliance for active lifestyles as well as reduced side effects/increased safety and improved efficacy.

Tapemark has expanded its passive transdermal (drug in matrix) and oral thin film transmucosal drug delivery capabilities and physical facilities. Blending, mixing and coating have been added to existing converting and packaging capabilities to provide full service capability. Tapemark’s oral thin film SoluStrip™ capabilities include oral transmucosal delivery, buccally or sublingually allowing for greater drug bioavailability and rapid onset of action.

Tapemark also provides active transdermal drug delivery systems including iontophoresis. The iontophoretic drug delivery technology delivers drugs via low level electrical current through the skin’s pores. This can provide faster and more controlled delivery than passive transdermal delivery. It can also deliver larger molecule drugs.

One example is the IontoPatch® product technology from Travanti Medical, a business unit of Tapemark, currently used in the Physical Therapy market. IontoPatch is a localized time-released electronic transdermal drug delivery system. A proprietary self - contained flex battery embedded in the patch produces current to carry the drug molecules non-invasively through the skin’s pores to underlying tissue.

In topical drug delivery, Tapemark has had success with its patented Snap® and Snapplicator™ single dose, convenient packaging formats. Snap conveniently dispenses a precise, portion-controlled dose of a variety of creams, gels, lotions and ointments. “Snapplicator incorporates an applicator pad for “no-touch” application, avoiding patient contact with the drug or the treated condition, if desired”, explains Robert Arnold, Vice President, Sales & Marketing, Tapemark.

3M DRUG DELIVERY SYSTEMS—INTRADERMAL DELIVERY OF BIOLOGICS

With expansion of the global biologics market, development of delivery systems uniquely positioned to meet needs of this segment remains paramount for drug development and delivery providers. To meet unique formulation and bioavailabity

Tapemark's single-dose Snapplicator® has an applicator pad for no-touch application of the drug or the treated condition.

3M Drug Delivery Systems' hollow microstructured transdermal system (hMTS) is intended for intradermal delivery of biologic formulations from 0.5 ml to 2 ml via microneedle technology.

profiles, the market is looking for advances in intradermal delivery, especially critical for viscous or otherwise difficult-to-deliver formulations, explains Lisa Dick, MTS Lab Manager, 3M Drug Delivery Systems. "Specifically, we are seeing an emphasis on devices that provide more consistent reproducible delivery of liquid formulation into intradermal space, which can be difficult to achieve using regular syringes via Mantoux method."

In response, 3M Drug Delivery Systems Division has leveraged proprietary 3M microreplication technology for developing solid and hollow microneedle delivery systems. 3M's hollow microstructured transdermal system (hMTS) is intended for intradermal delivery of biologic formulations from 0.5 ml to 2 ml via a patient-friendly microneedle technology. "We have recently announced availability of 3M hMTS for pharmaceutical and biotech companies interested in conducting preclinical studies," says Ms. Dick.

With patients' needs in mind, human factor refinements to the 3M hMTS include a textured grip, capability for non-specific actuation and a visible dose indicator. In the case of Radius Health Inc., for example, the company was looking for an innovative approach to treatment of Osteoporosis and was looking for an alternative to subcutaneous delivery method for the Abaloparatide (BA058), explains Ms. Dick. 3M was selected to develop and commercialize BA058-TD in a short-wear time patch based on 3M's patented microstructured transdermal system technology. Earlier this year, Radius has announced positive results of the Phase II study with this patient-friendly technology.

"3M hMTS may provide valuable differentiation for drug products intended for dexterity-challenged patients while offering the capability for intradermal delivery of liquid formulations over a range of viscosities."

3M microneedle technologies address the need for consistent delivery of biologics, including proteins and peptides. "Studies have demonstrated that microneedle technology is easy to use and can be considered less intimidating to physicians and patients than other injectable methods," she says. "Microneedle technology may offer potential for faster absorption and higher bioavailability for some drugs, along with other benefits. For instance, there could be pharmacoeconomic benefits for certain therapeutics if switching from intravenously administered formulation with a clinician to intradermal delivery in the comfort of a patient's home."

3M Drug Delivery Systems partners with pharmaceutical and biotech companies to develop and manufacture pharmaceutical products using 3M's inhalation, transdermal or microneedle drug delivery technology. 3M offers a full range of feasibility, development and manufacturing capabilities to help bring products to market. Regulatory expertise, quality assurance, operations, extractables/leachables expertise, marketed product support and other in-house resources are available for each step of the development and commercialization process.

4P THERAPEUTICS—APPLYING NEW TECHNOLOGY TO EXISTING THERAPEUTICS

4P develops patches to deliver large molecules, biologics and difficult-to-deliver small molecules. The company is also developing simple, passive, and still commercially valuable transdermal products.

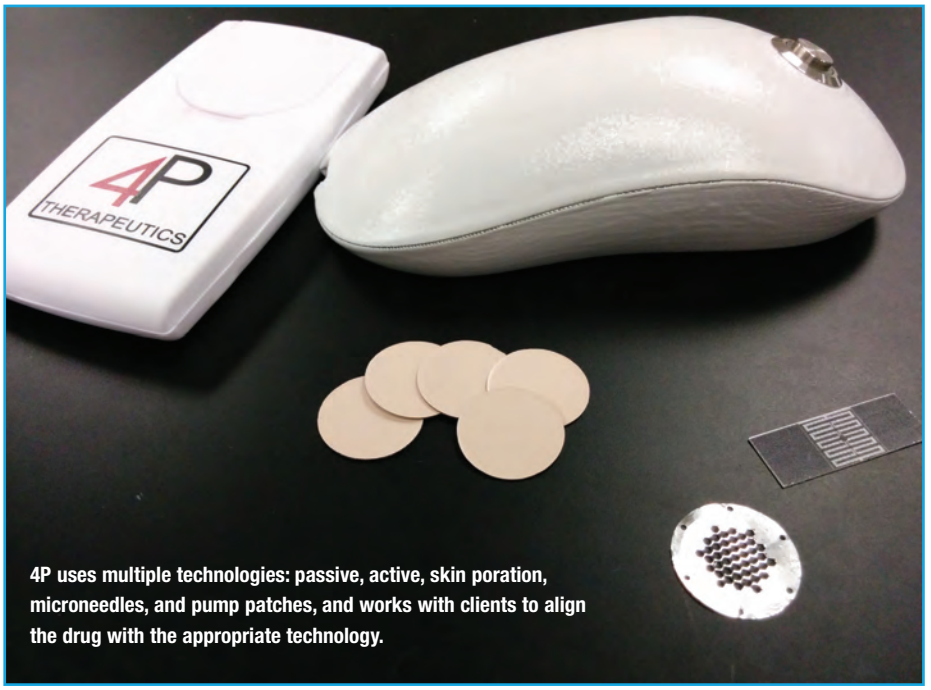
"We are seeing trends toward simpler transdermal products that have commercial value but may not be a major advancement in

clinical outcome," says Steven P. Damon, President & CEO of 4P Therapeutics. "Rethinking what is already available in terms of technology and applying it to the appropriate therapeutic can lead to valuable product opportunities. Taking an older transdermal therapeutic product and reformulating slightly using some of the advancement in chemistry that we have made can produce a better generic and potentially some new IP."

Mr. Damon continues: "In addition, we can take a basic patch technology that uses one or a few needles and a liquid reservoir with a driving force (mechanical, electronic or even chemical) to deliver the therapeutic and potentially create a new transdermal product that replaces an IV and keeps a patient out of the hospital."

4P uses multiple technologies: passive, active, skin poration, microneedles, and pump patches, and works with clients to align the drug with the appropriate technology. This involves a series of preclinical studies with several technologies. The patient, provider, and payer are all considered, along with the therapeutic indication. Then, clinical studies commence with what has been determined to be the best transdermal product for the indication in terms of clinical success and commercial success.

4P Therapeutics has entered into multiple partnerships with companies, ranging from a global healthcare conglomerate to small biotech companies and academic institutions. In the case of specialty pharma Medicure International,



4P uses multiple technologies: passive, active, skin poration, microneedles, and pump patches, and works with clients to align the drug with the appropriate technology.

Inc., the partnership with Medicure initially focused on developing a transdermal patch for Aggrastat® (tirofiban HCl injection for intravenoususe), Medicure's lead product currently marketed for the treatment of acute coronary syndrome. 4P Therapeutics initially partnered with Medicure to demonstrate the preclinical feasibility of delivering tirofiban transdermally as an alternative to its current IV delivery. After successfully completing the feasibility studies, 4P Therapeutics and Medicure entered into a product development and commercialization partnership. This approach allowed Medicure to assess the preclinical feasibility of delivering tirofiban transdermally and offered the flexibility to generate valuable data before entering into a broader partnership with 4P Therapeutics and committing additional resources to the project.

"This development program presents an important lifecycle management strategy for Aggrastat. Drugs in the Glycoprotein IIb/IIIa inhibitor class (GPI), including tirofiban, are currently only available for IV delivery," explains Mr. Damon. "Transdermal delivery of a GPI promises to offer several benefits over IV delivery, including ease of administration using a transdermal patch that can potentially be self-administered, possible reduce in hospital length-of-stay to lower healthcare costs, and the potential for new indications that could lead to additional market penetration."

4P Therapeutics and Medicure demonstrated *in vivo* proof-of-concept for transdermal tirofiban delivery. The development program is now focusing on refining the transdermal tirofiban delivery system in preparation for initial human studies. ◆

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

Mark Your Calendars

2014 AAPS Annual Meeting and Exposition
November 2–6, 2014
San Diego Convention Center
San Diego

Mark Your Calendar for the Meeting that Extends Your Boundaries:

- Widen Your Personal Network with Scientists from all Fields Related to Pharmaceutical Scientists;
- Explore Programming Covering Both Large and Small Pharma;
- Find the Latest Advances with over 2,500 Contributed Papers;
- Find Your Supplier Solutions in San Diego

2014 Keynote Speaker Announced
Daniel Kraft, M.D.

aaps® American Association of Pharmaceutical Scientists

aaps.org/annualmeeting

IDENTITY HUB

Leveraging Identity Hubs to Speed the Drug Development & Delivery Process & Maximize Revenue Opportunities

By: Vijay Takanti, MS, MBA

INTRODUCTION

The life sciences industry is in the midst of significant change, driven by a number of factors, including globalization, demographic shifts, emerging markets, increased healthcare delivery costs, and the introduction and maturity of disruptive technologies, such as cloud, mobile, social, and big data. These factors are possible contributors to another industry trend - highly centralized research and development (R&D) centers are no longer yielding as many blockbuster drugs as they once did.

In fact, the IMS Institute for Healthcare Informatics anticipates that "spending on most therapies will grow at slower rates - or even decline - through 2015." At the same time, $120 billion in revenue is threatened by the number of drugs coming off patent, while productivity in R&D continues to decline.*

To survive in this increasingly competitive landscape, life sciences companies are turning to new sources of innovation. They are engaged with unprecedented intensity in collaborative efforts with external partners that lie beyond their virtual four walls. This decentralized collaborative environment encourages specialization and focus, which in turn accelerates innovation - speeding the drug development and delivery process so companies can take full advantage of revenue opportunities.

LIFE SCIENCES COLLABORATION DRIVERS & REQUIREMENTS

Changing market conditions may be intensifying the need for multi-party collaboration, but the disruptive technologies are facilitating it. Mobility, in the form of 4G/LTE wireless networks and powerful smartphones, tablets, and laptops, allows individuals to work productively anytime, anyplace, anywhere. Cloud computing lets partners share data, processes, research, applications, and more. With a single connection to the cloud, an organization and its users, assuming valid permissions, can access the applications and data of all other organizations connected to the cloud. Cloud architectures are designed to scale and maintain high performance as new organizations and applications are connected, saving time and cost for all participants.

Life sciences companies are looking to leverage collaboration to help them meet a host of business requirements, among them:

- Improve information sharing and accountability
- Reduce costs by sharing infrastructure and minimizing outsourcing overhead
- Adopt common policies and tools
- Adapt to changing security policies
- Adjust to dynamic operating models
- Comply with regulatory mandates

Ultimately, the goal is to gain competitive advantage by using collaboration to streamline the time and cost of the drug development and delivery process.

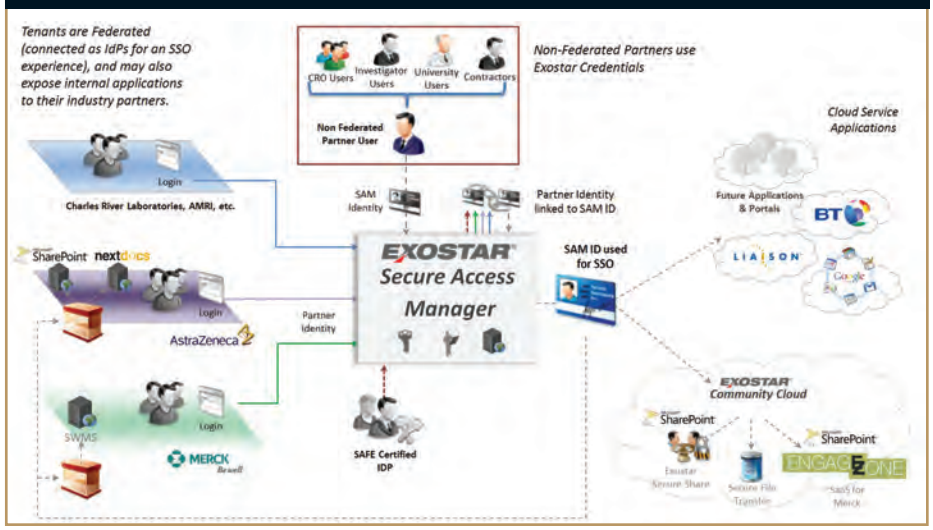
COLLABORATION RAISES THE SECURITY STAKES

Collaboration is loaded with upside potential, but it's not without its downside. By adopting collaborative technologies and working together in a community that includes manufacturers, investigators, laboratories, academic institutions, contract research organizations, and others, life sciences companies expose themselves to increased security risks. More participants in the drug development and delivery process means more points of vulnerability and the potential for compromise of sensitive information or intellectual property.

As companies make their systems, applications, and data available to more organizations and users beyond the enterprise's boundaries, they must manage a growing number of user accounts, privileges, and access channels. While they do so, they not only must protect their assets, but they also must ensure they properly address the compliance requirements that are the foundation of this highly regulated industry.

Historically, life sciences companies granted access to their external partners by creating virtual private networks over the web; otherwise, they would directly provision each partner and its employees to each shared application. Either approach is acceptable

FIGURE 1



with a limited number of partners. Neither approach works well with today's collaborative communities, where scale, performance, and cost concerns quickly become overwhelming.

BRINGING PARTIES TOGETHER THROUGH TRUST

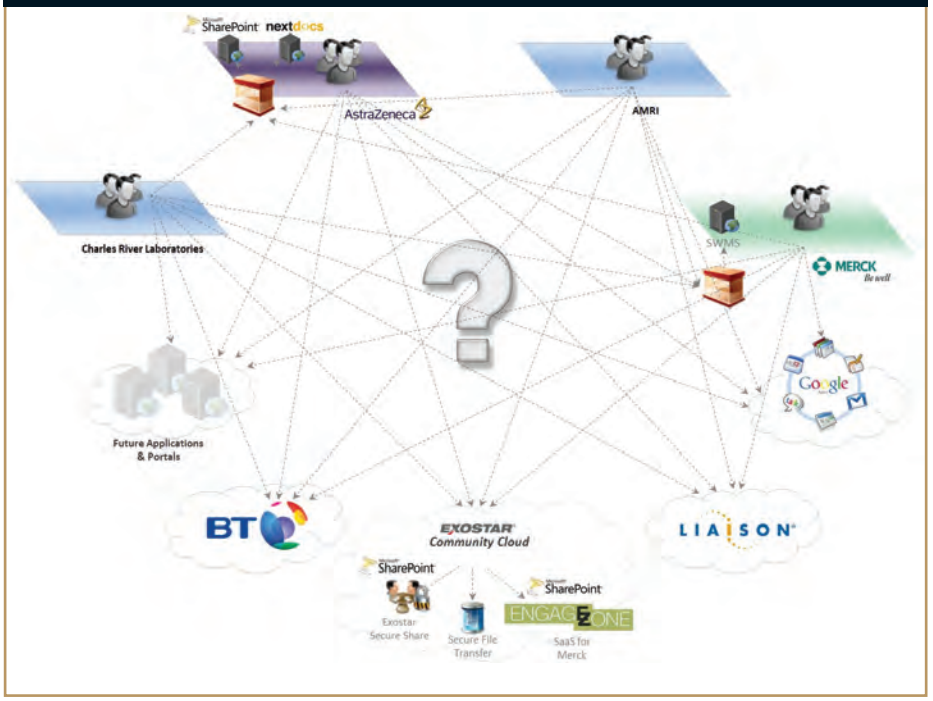
Trust allows life sciences companies to take full advantage of the power of collaboration while mitigating security risks. Rather than each application owner building a database of validated users and permissions from across the partner community (which places an enormous burden on IT to maintain), organizations can establish trusted relationships with their partners. With the advent of identity federation, application owners rely on their partners to manage user identities internally, and allow application access when partner users request it.

Identity federation in its most basic form puts a premium on vetting the partners who will be trusted. Applications owners are ceding access control with little insight into the dynamics present within partner organizations. External personnel may come, go, or change roles, with no guarantee that this information will be reported by the partner in a timely or accurate manner. Because partners are privy to scientific breakthroughs, pricing, and other sensitive information, risk of compromise remains high.

Another shortcoming of the traditional approach to identity management is that it only allows point-to-point collaboration between two parties. As the size of the collaborative community grows, so does the number of unique connections and identity credentials that must be created. Basic identity federation leads to the development of a trusted bi-lateral mesh of point-to-point connections, relationships, and legal agreements - each of which requires care, feeding, governance, and audit.

The more partners in the mix, the larger the mesh becomes. Not only does each connection take a significant amount of time and effort to establish and maintain, but the mesh produces a massively redundant

FIGURE 2



infrastructure. While a small amount of redundancy may make sense, excessive overlap results in unnecessary capital and operating expenditures. Collaboration is supposed to reduce the time and cost of the drug development and delivery process, not extend it.

DELIVERING ON THE PROMISE OF IDENTITY FEDERATION WITH THE IDENTITY HUB

Fortunately, there is another approach to identity federation that enables trust amongst collaborating parties without the cost, scalability, and time/maintenance shortfalls. Other industries, such as aerospace and defense and retail/financial services, have moved to an identity hub federation model. The identity hub's connect-once, hub-and-spoke architecture allows parties to communicate and collaborate by accessing one another's applications and data, yet eliminates the requirement for a bi-lateral mesh of point-to-point connections whose design inherently is inefficient and vulnerable to threats that cause compliance and security failures.

Credit cards issued by financial institutions and used by consumers at retail/e-tail establishments clearly demonstrate why the move from basic identity federation with a bi-lateral mesh to the identity hub is critical. Maintaining all of the unique connections of a bi-lateral mesh is equivalent to asking consumers to obtain a unique credit card for every store or online site at which they shop. The overhead for all parties is far too high, and the risk of a stolen or lost credit card rises significantly with the number of cards an individual carries.

Credit card companies have been successful by creating a hub-and-spoke architecture that brings everyone together. The credit card company serves as the hub, with consumers, businesses, and financial institutions as the spokes. As the hub, the credit card company works with its constituents to define the rules of engagement, including how to connect and how to confirm identities through authentication, to which all parties agree. The credit card company manages the network, and all participants trust it. Transactions take place quicker and more efficiently, and the resulting environment is more scalable, easier to monitor, and mitigates risk by concentrating higher security measures on a single entry point with strong, multi-factor authentication.

Aerospace and defense companies have relied on the identity hub to bring collaborating organizations together with trust for almost a decade. The identity hub lets companies leverage an existing community of interest to connect to applications and provide a single pathway to internal applications. With a single connection, an organization and its users, with appropriate permissions, can access the applications and information of all other connected organizations, and vice versa - even when new organizations and applications are added to the community, saving time and cost for everyone. Individuals no longer need keep track of a dozen or more passwords; in many cases, a single credential to access local applications and all applications connected to the identity hub will suffice.

DEPLOYING AN IDENTITY HUB

The identity hub's proven performance and benefits for industries with stringent security and compliance requirements, sensitive information, and diverse collaborating parties makes it a compelling option for life sciences companies. Organizations considering the identity hub model first must decide how to implement it.

To build and maintain an identity hub, a life sciences company must possess significant identity management expertise. The do-it-yourself approach also means the company must invest the necessary resources and budget, as well as obtain the cooperation of other parties in the drug development and delivery process, including its peers. In other words, the company's commitment must be intense and unwavering.

As the number of partners in the proposed community rises, the time, cost, and risk associated with managing external identities in the identity hub becomes prohibitive. Affected groups include IT personnel, who must create and maintain user accounts; customer care, which must respond to issues, such as lost credentials and the inability to successfully access applications connected to the identity hub; and business stakeholders throughout the enterprise who are caught in the middle, coordinating with IT and customer care internally, and partner personnel externally instead of collaborating on research.

The maturation of the cloud presents another alternative - outsourcing the identity management function. The beauty of the cloud-based, outsourced identity hub is that a single third-party provider can deliver federation services for all members of the partner network, or community. All members of the community connect once to the provider's identity hub, which becomes the single point of entry to all applications throughout the community. Participants enjoy reduced upfront and ongoing resource commitments, a neutral central authority with whom they can develop the rules of engagement and enforcement, and the opportunity to focus on research and development activities instead of identity management.

When companies choose the outsourced option, they are entrusting a third-party provider to help them achieve their collaboration objectives, including rapid on-boarding of new partners, efficient establishment of dynamic working groups on R&D projects, and secure information exchange. Selecting a provider that truly understands the identity hub delivery model is essential.

THE EXOSTAR LIFE SCIENCES IDENTITY HUB

The Exostar Life Sciences Identity Hub is a cloud-based, software-as-a-service (SaaS) solution that delivers identity and access management to life sciences partner applications and data. It also provides trust-based federation between parties while separating authentication (identity verification) from authorization (access control). Organizations connect once to the Exostar Life Sciences Identity Hub, creating a secure community of participants that allows partners, and even competitors, to leverage resources across the industry for greater utility of information, applications, and regulatory compliance.

The SaaS model eliminates the pain enterprises previously faced establishing point-to-point connections with each of their partners, as well as on-boarding and provisioning organizations and individuals. Exostar assumes responsibility for those tasks, along with training, customer care, reporting, and functional maintenance and upgrades - all while offering service level agreements for performance, availability, response time, and other metrics.

Exostar also issues credentials as an identity provider so users can be authenticated before being granted access to applications connected to the Life Sciences Identity Hub. With delegated administration, application and data owners follow processes implemented by Exostar to quickly and easily make credentialing and access decisions and assignments, which Exostar in turn executes.

Exostar's Secure Access Manager (SAM) is the gatekeeper to the Life Sciences Identity Hub. SAM authenticates users by verifying the credentials a user presents. Credentials may be Exostar's, a third-party identity provider's, or come from the user's enterprise. These credentials can be as basic as

username/password, or stronger, for enhanced security. Examples of stronger authentication SAM accepts include hardware token- or phone-based one-time passwords or public key infrastructure certificates cross-certified with the SAFE-BioPharma certificate authority. SAFE credentials allow life sciences users to comply with second-factor authentication requirements for electronic/digital signatures and for managing controlled substances.

The Enterprise Access Gateway (EAG) is an optional SAM function. With EAG, individuals can access any application connected to the Life Sciences Identity Hub, assuming the asset owner has granted authorization, with the same credential they use to logon locally. As a result, individuals receive a true web-based single sign-on experience, which improves productivity and reduces the risk that a credential is lost or stolen.

WHY CONSIDER THE EXOSTAR LIFE SCIENCES IDENTITY HUB?

The Exostar Life Sciences Identity Hub is a proven implementation of the identity hub concept that provides the trust necessary for enterprises and individuals to collaborate with confidence. Today, more than 550 life sciences companies - including three major pharmaceutical manufacturers, over 100 contract research organizations, and approximately 50 universities - and over 10,000 individuals in nearly 50 countries on 6 continents count on the Life Sciences Identity Hub to help them collaborate securely. These entities have established more than 2,000 distinct mini-communities to work together, leveraging nearly two dozen connected applications or portals. The overall community is growing by an average of ten percent per month.

Companies connected to the Life Sciences Identity Hub are saving millions of dollars annually by eliminating infrastructure, reducing on-boarding and provisioning times by an order of magnitude, enhancing customer care, and redeploying IT resources to focus more intently on the needs of business stakeholders in the drug development and delivery process.

At a February 2014 BioPharma Research Council webinar, Andrea Kirby, Merck's External Partner Program Director, said, "What used to routinely take months to start collaborating on projects now takes an average of three days - a time that would have been unheard of by Merck employees in the recent past. We blow people's minds internally here at Merck."

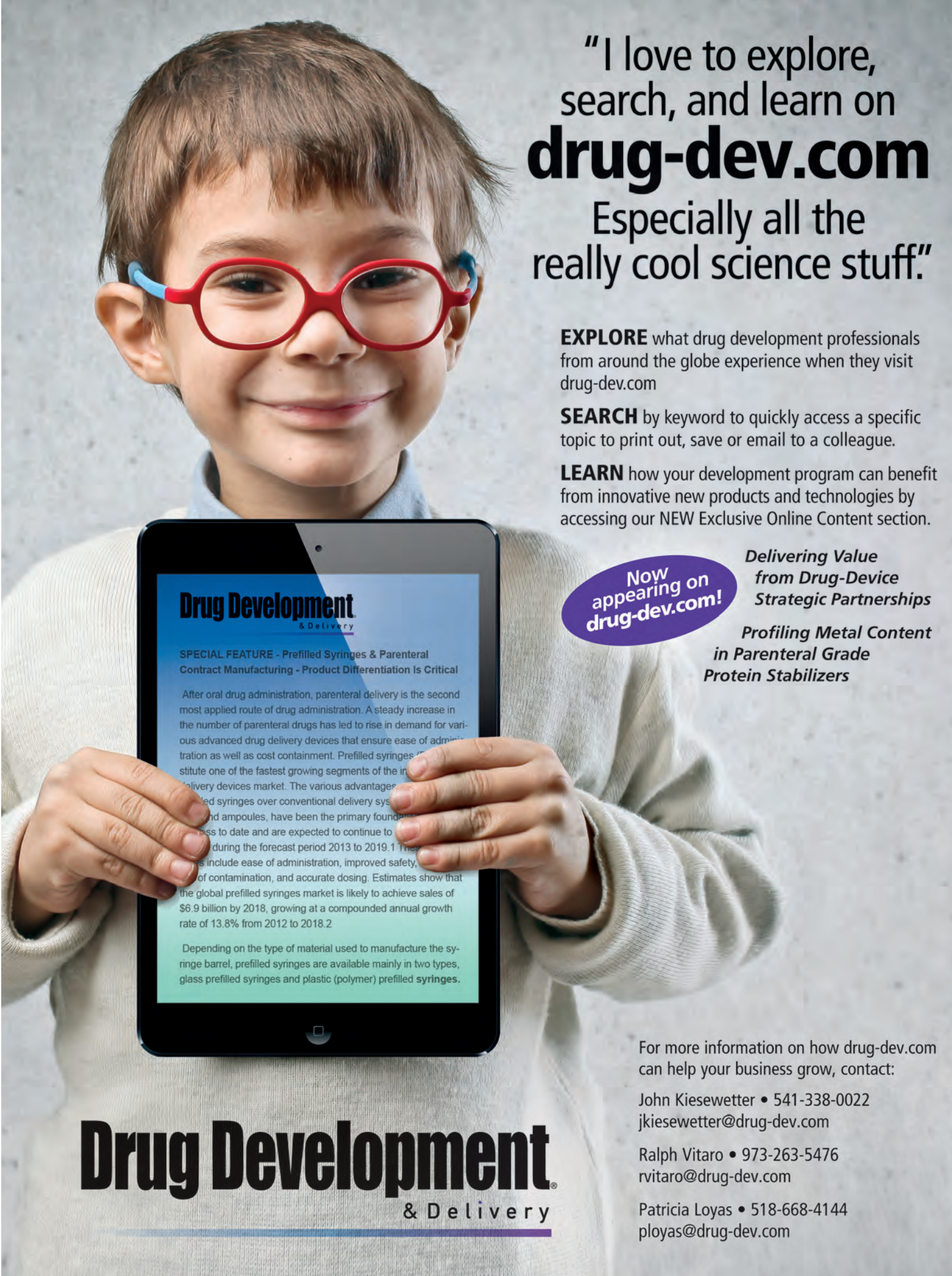
These benefits are just the tip of the iceberg, because collectively, they are speeding collaboration while strengthening security. Life sciences companies will realize an even bigger payoff by bringing new drugs and therapies to market more quickly so they can take full advantage of patent exclusivity to maximize revenues. In that scenario, everyone wins.◆

*IMS Institute for Healthcare Informatics The Global Use of Medicines: Outlook Through 2015

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

BIOGRAPHY

Vijay Takanti is Vice President, Security & Collaboration services at Exostar. As such, he is responsible for the strategy and product road map, design, development, and customer delivery of these solutions. Since taking his role, he has grown the Exostar Security Solutions business. He has over 20 years of experience in electronic data processing, application design and development, and information security solutions. He joined Exostar through the acquisition of Evincible® Software in 2004, where he was the founder and CEO. At Evincible, he developed solutions that bridge the integration chasm between business applications and security components, such as Public Key Infrastructure (PKI). Prior to founding Evincible Software, Mr. Takanti served as CTO at Society of Worldwide Interbank Telecommunication (SWIFT) where he architected the Next Generation of the SWIFT Net architecture. He is recognized as an authority on the emerging and evolving technologies related to electronic signatures and digital identity management; and has consulted to a variety of enterprises on these topics. He earned his Bachelors in Electronics and Communications from JNTU in Hyderabad, India; a Masters in Computer Sciences from the Indian Institute of Technology in Khargpur; and a Masters in Business Administration from George Mason University, Virginia.



"I love to explore, search, and learn on **drug-dev.com** Especially all the really cool science stuff."

EXPLORE what drug development professionals from around the globe experience when they visit drug-dev.com

SEARCH by keyword to quickly access a specific topic to print out, save or email to a colleague.

LEARN how your development program can benefit from innovative new products and technologies by accessing our NEW Exclusive Online Content section.

Now appearing on drug-dev.com!

Delivering Value from Drug-Device Strategic Partnerships

Profiling Metal Content in Parenteral Grade Protein Stabilizers

Drug Development®
& Delivery

For more information on how drug-dev.com can help your business grow, contact:

John Kiesewetter • 541-338-0022
jkiesewetter@drug-dev.com

Ralph Vitaro • 973-263-5476
rvitaro@drug-dev.com

Patricia Loyas • 518-668-4144
ployas@drug-dev.com

Peptides in Antibody & Peptide Drug Conjugates

By: Archana Gangakhedkar, MS, and Jyothi Thundimadathil, PhD

INTRODUCTION

Antibody drug conjugates (ADCs) are known to be strong and powerful tumor- killing agents with targeted therapy and minimal side effects for cancer patients. ADCs are capable of optimizing the best features of the cell-killing potential and higher tumor selectivity, thus increasing the tolerability by limiting the systemic exposure. ADCs are monoclonal antibodies (mAbs) attached to therapeutically active drugs by chemical linkers that can be cleaved easily in vivo in the tumor cell.[1] The combination of the unique targeting of mAbs with the cancer-killing ability of cytotoxic drugs allows ADCs to discriminate between normal healthy and disease-affected cell or tissue.[2]

ADCs can be custom designed to target antigens that are expressed on the cell surface, with multiple mechanisms of action involving cytotoxic anti-cancer activity toward targeted delivery. The mAb component can prevent cell signaling in cancer cells, or induce apoptosis. To date, two ADCs have secured market approval from regulatory agencies. Brentuximab vedotin/Adcetris is used in relapsed or refractory Hodgkin's lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma. This ADC was developed by Seattle Genetics and targets the cell membrane protein CD30. It has valine-citrulline cleavable linker and cytotoxic anti-mitotic monomethyl auristatin E (MMAE). The MMAE unit is connected to an antibody through the peptide linker, which provides stability to the ADC by not letting the drug cleave under physiological conditions and thus prevents the healthy cells from being exposed to toxic drugs. The peptide antibody drug bond is rapidly cleaved inside the tumor cells to release the cytotoxic drug. The second ADC approved by FDA is Trastuzumab emtansine/Kadcyla, marketed by Genentech and Roche.

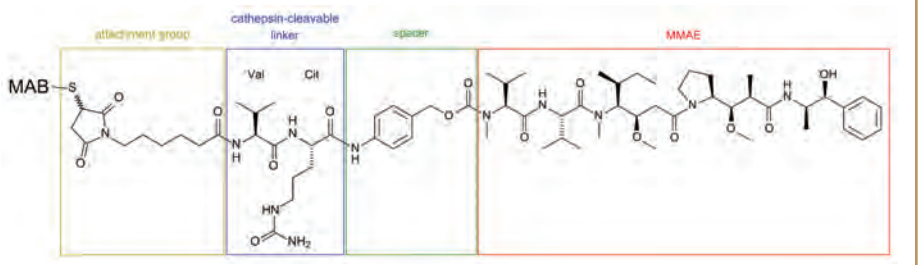
DESIGN & DEVELOPMENT OF ADCS

The first step towards successful development of an ADC is a comprehensive understanding of the cancer biology and the identification of the proper target antigen for the tumor type. The development of an ADC is a design-driven and continual process. First-generation ADCs were targeting selectivity with traditional chemotherapeutic agents, such as vinca alkaloids and doxorubicin and linking them to mAbs with limitations of linker stability, resulting in low potency with reduced efficacy. Insufficient internalization and insufficient serum concentrations were also attributed toward unstable linkers. Failure to choose an appropriate target antigen that was sufficiently overexpressed on the target cell surface led to low concentrations of the ADC inside the tumor cell.[3] Linkers are designed to prevent the release of the cytotoxic drugs into circulation. Linker stability in circulation is critical because it controls the distribution and delivery of the cytotoxic drug to the target cell. Studies suggest that the selection of a linker should depend on the tumor type, the cytotoxic drug selected, linker stability in circulation, and the ability

of the linker to be cleaved within target cells.[4] These ADC linkers are designed in the form of peptidyl linkers to be cleaved by enzymes, such as cathepsins and matrix metalloproteinases (MMPs), expressed in the tumor, or linkers that would release drug by hydrolysis at the slightly acidic pH observed in many solid tumors. It was observed that the non-internalizing ADCs did not show significant antigen-specific activity and thus unable to improve the therapeutic index relative to that of the free drug. Therefore, to be effective, ADCs must internalize, selectively bind, and deliver intracellular concentration of cytotoxic drug for diseased cell death.

Keeping these things in mind, next-generation ADCs were designed to deliver potent chemotherapeutic agents to tumors in a targeted manner to limit systemic exposure. The therapeutic success of an ADC is dependent upon the linker component and therefore, linker technology impacts ADC potency, specificity, and safety. Linkers generally fall into one of two categories: cleavable (peptide, hydrazone, or disulfide) or non-cleavable (thioether). Early ADC linkers were derived from cleavable acid and peptidase-labile hydrazones designed to cleave inside target tumor cells, but they cleaved at non-target sites instead, which

FIGURE 1



Structure of a MMAE-MAB-conjugate. The linker, consisting of the amino acids valine (Val) and citrulline (Cit), is cleaved by cathepsin inside tumor cells.

increased systemic toxicity. Next, disulfide linkers were developed, which achieved greater in vivo stability but were recently found to be inefficient.

Peptide linkers have the potential to be selectively cleaved by lysosomal proteases (eg, cathepsin-B) and have demonstrated increased serum stability and improved anti-tumor effects compared to hydrazone linkers. Valine-citruline (Val-Cit) pairs are the most commonly used peptide linkers and are ideally suited to work with the auristatin family of drugs, such as monomethyl auristatin E (MMAE). MMAE is totally synthetic, stable, very potent, and ideally suited for chemical modification.[5]

A typical linker, mostly a peptide derivative, links the potent drug to the large-molecule antibody, targeting the antigens on a specific cell. The release of this toxic potent molecule into the cancer cells depends on the lysosomal abundance into the cell. Therefore, it is important for the antibody to reach the target cell to get complete efficacy of the drug. The linker has an important role to control the release of cytotoxic drug into the target cell to ensure the efficacy and safety of the ADC. Generally, degradable linkers as mentioned earlier can be chemically and enzymatically degraded. So the linker design is targeted to be chemically stable and can be enzymatically cleaved from the antibody by the enzymes present in the lysosome low pH matrix like the proteases or esterases. According to Seattle Genetics, there needs to be a spacer for enzyme site recognition between the antibody and peptide linker. The chemistry that is used to attach the linker to the antibody and the sites within the antibody to which the linker are bound both affect the performance of an ADC. It is most common to connect the linker to the antibody via reaction with amino acids, with cysteine being the most common, followed by the lysine. Greater degree of uniformity has been noticed in cysteine-

FIGURE 2

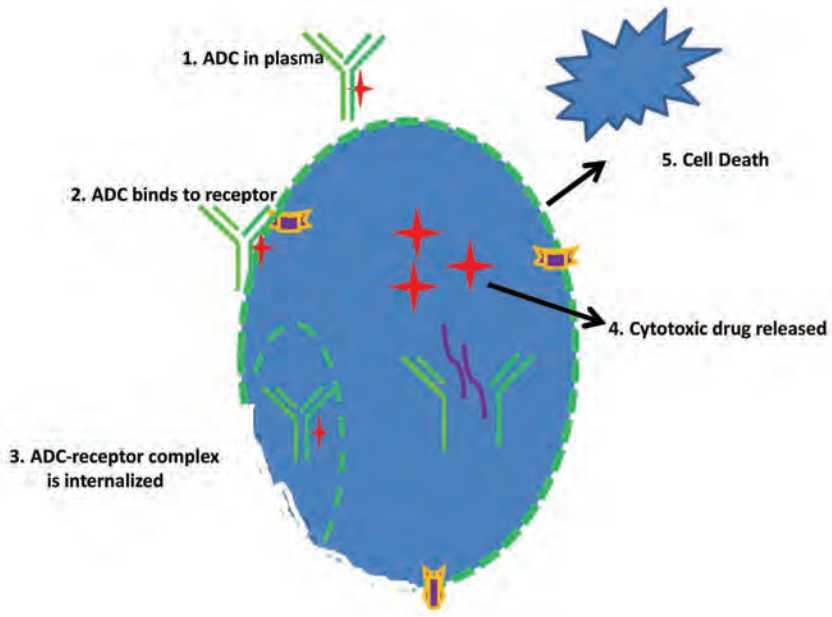


Image created at APC; Antibody Drug Conjugate pathway in tumor cell.

based conjugates compared to lysine-based conjugates. In recombinant methods where cysteins are introduced to the backbone of the antibody at specific sites has shown higher degree of uniformity. Incorporating highly potent cytotoxic moieties, such as maytansinoids, auristatins, and duocarmycins, resulted in a major advancement into ADC development.[6] Although it is difficult to ensure, the general observation is that the location of the conjugated drug moiety is not as important as the stoichiometry of the drug attachment. Drug-loading stoichiometry varies, and it is difficult to control the regioselectivity of conjugated drug moieties. ADCs with two or four drugs per antibody are of higher efficacy than heavily loaded conjugates that tend to be flushed out from the circulation faster. These cytotoxic moieties are 10- to 1000-fold more efficacious than the drugs used in clinics and lacked therapeutic index when used alone. ADCs can clinically exploit the cytotoxic potency of these moieties and can also reduce the systemic toxicities.

PEPTIDE DRUG CONJUGATES

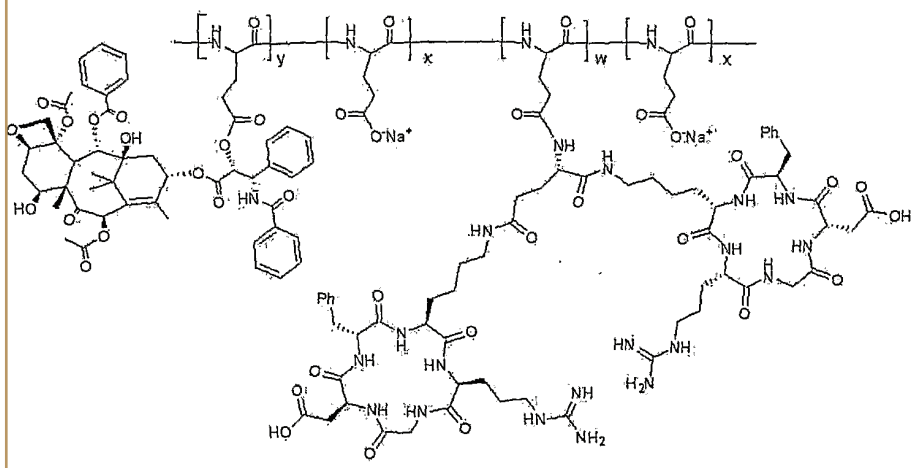
Another popular topic in therapeutic industry is peptide drug conjugates (PDCs) where peptides are exclusively is used in place of antibodies for targeted therapy.[7] PDCs are equivalent to ADCs in terms of potency, but have better tissue penetration and efficacy in animal and clinical studies. In comparison to the bulk weight or size of mAb carriers, the peptide carriers have the advantage of overcoming the interstitial tumor pressure in reaching the tumor interior. Peptides as carriers may offer advantages over mAbs as they (mAbs) need antigenic targets and do not target tumor-specific antigens, whereas PDCs do not need an antigenic target and can be generated through a DNA and RNA peptide library phage. The molecular structure of antibodies is standard - antibody unit with different immunoglobulin isotypes, whereas peptides can be linear or cyclic. Pharmacokinetics and pharmacodynamics of antibodies depends on many variables and is difficult to predict, whereas peptides have lower molecular mass, larger formulation base, and a defined outline for PK-PD. Antibody applications are somewhat limited in solid tumors, and peptides have enhanced application in therapeutic industry. ADC structures are heterogeneous with a high cost of development; PDCs have significantly lower cost of production and increased product reproducibility. Researchers are confident about providing PDCs with precise carrier stoichiometry, high loading efficiency, and potent anti-cancer efficacy as efficient drug delivery vehicles.[8]

Many PDCs are in the developmental

phase of preclinical and clinical studies, and PDCs have yet to get marketing approval from regulatory agencies. GRN1005, a angiopeptin-2-paclitaxol PDC targeting lipoprotein receptor protein-1, is over expressed on solid tumor cell surface. This conjugate is in clinical trials for the treatment of advanced solid tumors in patients with brain metastases. The important requirement for using peptides as carrier molecules is selective binding of the peptide to the cell surface receptors on the targeted cells. The receptor expression should be higher on the targeted cells than on the non-targeted cells. The peptide carrier should be stable enough in systemic circulation to reach the target cell in an effective concentration.

There are two main strategies for the synthesis of PDCs: end-to-end and convergent. Both of these approaches have proven effective, with the convergent approach employed for faster results. A convergent approach was used to assemble the RGD paclitaxel conjugate (Figure 2). Paclitaxel is first coupled to its succinic acid linker, which is subsequently coupled to the RGD peptide. Fatty acid RGD peptide (Arginine-Glycine-Aspartic Acid) if

FIGURE 3



RGD peptide with Taxol warhead used for targeted delivery.

conjugated to the small molecules warhead can be used for targeted delivery against various types of cancers.[9] Pegylated RGD peptides with ADA (adenosine deaminase) linkers form stable micelles, and when conjugated to paclitaxel, are effective against ovarian, breast, and lung cancer. Peptide delivery vectors are being investigated in other diseases like viral infections and psoriasis and are in at early developmental stage. In designing these peptide drugs or warhead conjugates, it is important to identify peptide conjugation sites, the length of the linker between peptide, and drug or warhead without interfering with their activity. This will ensure excellent cellular targeting and deliverability toward the diseased cells, the efficacy of the drug, and its reduced penetration into neighboring tissues. Apart from end-to-end and convergent methods, application of orthogonal methods to synthesize these conjugates mimics the bond formation in the cell environment, and hence, can be termed as bio-orthogonal reactions. Click chemistry provides orthogonality in its reactions and is widely used for cycloadditons using alkynes and alkenes. A notable example is CPP Tat conjugation to oligonucleotide moiety. In spite of some limitations, copper catalyzed click reactions are useful in bioconjugation of peptides to drugs and can deliver them to target cells.

Manufacturing these conjugates are challenging due to multiple molecular components. Peptide API conjugates must be of higher purity with good yields and low bioburden. Many technical advances in peptide chemistry offer solutions to overcome problems like reduced half-life and stability issues. These advances in peptide technology

make peptides a strong alternative to antibodies as drug carriers.[10]

SUMMARY

In summary, peptide-based linkers are promising counterparts in ADCs, providing tumor-specific cleavable and stable circulating linkers. A new emerging class of PDCs is proving to be useful towards a broad spectrum of indications when compared to ADCs. These two approaches are paving a new pathway in cancer treatment and their clinical outcomes are yielding some encouraging results for cancer patients.◆

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

REFERENCES

1. Carter PJ, Senter PD. Antibody-drug conjugates for cancer therapy. Cancer J. 2008;14:154-169.
2. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Molec Cell Biol. 2001;2:127-137.
3. Nolting B. Linker technologies for antibody-drug conjugates. Methods Mol Biol. 2013;1045:71-100.
4. Flygare JA, Pillow TH, Aristoff P. Antibody-drug conjugates for the treatment of cancer. Chem Biol Drug Des. 2013Jan;81(1):113-121.
5. Galush WJ, Wakankar AA. Antibody drug conjugates. Methods Mol Biol. 2013;1045Z:217-233.
6. Trail PA. Antibody drug conjugates as cancer therapeutics. Antibodies. 201;2(1):113-129.
7. Firer MA, Gellerman G. Targeted drug delivery for cancer therapy: the other side of antibodies. J Hematol Oncol. 2012;5:70.
8. Yang M, Xu D, Jiang L, Zhang L, Dustin D, Lund R, Liu L, Dong H. Filamentous supramolecular peptide-drug conjugates as highly efficient drug delivery vehicles. Chemical Comm. 2014;50:4827-4830.
9. Javali NM, Raj A, Saraf P, Li X, Jasti B. Fatty acid-RGD peptide amphiphile micelles as potential paclitaxel delivery carriers to alphavbeta3Integrin overexpressing tumors pharmaceutical research. 2012;29(12):3347-3361.
10. Majumdar S, Siahaan TJ. Peptide-mediated targeted drug delivery. Medic Res Rev. 2012;32(3):637-658.

BIOGRAPHIES

Archana Gangakhedkar earned her MS in Organic Chemistry and is a certificate holder in Regulatory Affairs from UCSC. She has more than 10 years of pharmaceutical research experience as a scientist and has worked on various complex diseases. She is inventor of many new chemical entities and has many patents and publications to her credit. She joined the marketing department at American Peptide Company in March 2013, where she investigates the possible application of peptides in the pharmaceutical and diagnostic fields to promote the peptide business.

Dr. Jyothi Thudimadathil is currently working as an Associate Director of Marketing at American Peptide Company. During his 14 years of career in peptide science, he has served in different roles in industry, including R&D positions. After earning his PhD in Applied Chemistry from CUSAT (India), he worked as Post-Doctoral fellow at Ben Gurion University (Israel), IUPUI (USA) and Purdue University (USA). He has authored several articles and reviews on peptides in different magazines and journals.

ADAPTIVE FOUCUSED ACOUSTICS

Scalability of Adaptive Focused Acoustics™ (AFA) in Nanoemulsions: From Microliters to Continuous Flow

By: Laura E. Forte and Srikanth Kakumanu, PhD

INTRODUCTION

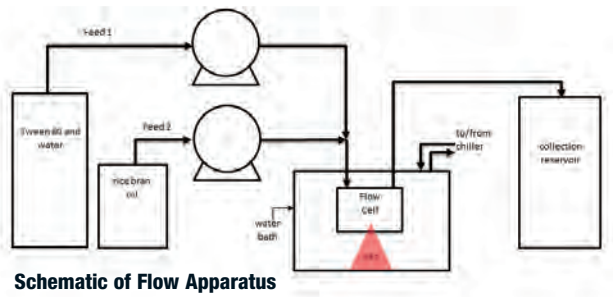
Emulsification is a key step in a vast array of processes, whether pharmaceutical, nutraceutical, or cosmetic. Within the pharmaceutical industry in particular, applications include injectable medications and nutrition supplements, topical creams, and oral formulations. Emulsifying oils in water enables drugs with a low solubility to be easily incorporated into a water-based formula, improves the palatability of oral drug formulations, and allows for careful control of the absorption of formulations by different organs, among other benefits.[1]

Emulsions are fine mixtures of two immiscible phases, most commonly oil and water, with droplets of one phase, the dispersed or discontinuous phase, distributed throughout the other, continuous, phase. Given sufficient time, however, the dispersed phase of an emulsion will undergo Oswald ripening and coalescence in order to minimize its surface area, eventually producing two distinct layers.[1,2]

The use of surfactants can be used as emulsifying agents to facilitate the formation of kinetically stable emulsions. Good emulsifying agents tend to be preferentially soluble in the continuous phase and act to decrease the interfacial tension by surrounding the dispersed phase droplets.[2] The suitability of a particular emulsifying agent can be evaluated using its hydrophilic-lipophilic balance (HLB), a ratio of the relative hydrophilicity and lipophilicity of a molecule. For an oil-in-water emulsion (O/W), an HLB of between 8 and 15 is required for a substance to be an effective emulsifying agent. The specific ratio of components used has a bearing on droplet size; increasing surfactant concentration relative to dispersed phase concentration has been shown to decrease the average particle size.[3-5] The viscosities of the dispersed phase also affect the particle size. Low viscosity phases have lower interfacial tensions, facilitating shearing of the fluid into smaller droplets.[6] As a result, less viscous discontinuous phases produce smaller particles.[7] These variables also impact the overall stability and shelf-life of commercial emulsion products.

Current methods of emulsion production include high shear mechanical stirring, homogenization, microfluidization, and sonication. Mechanical mixing occurs in vessels equipped with turbines, propellers, or impellers. These methods utilize pressure gradients in the fluid to create bubbles that forcefully implode in a process called

FIGURE 1

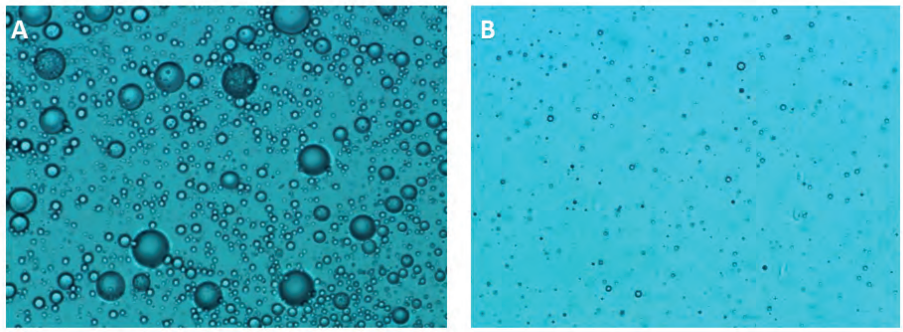


Schematic of Flow Apparatus

cavitation.[6] Using a valve and valve seat setup, homogenizers push components through a very thin opening at high pressure.[1] Microfluidizers pump components through micro-channels at extremely high pressures. Stream collisions generate the shearing force necessary to produce nanometer-size particles. These setups tend to have minimum batch sizes of at least 15 mL, and often require multiple passes to produce homogeneous emulsions.[8] Typical sonication processes, including bath sonication and probe sonication, use unfocused acoustic energy. These methods have various technical flaws that make them less suitable for emulsion formulation. Bath sonication is inefficient, while probe sonication may contaminate the sample with titanium eroded from the probe.[9] Unfocused acoustic processing requires high energy input into the sample in order to generate a significant amount of cavitation. The excessive input energy eventually converts to heat, which can thermally damage the sample.

Covaris' patented Adaptive Focused AcousticsTM (AFA) technology is a non-contact, highly efficient, isothermal, focused-energy processing method. AFA technology, like other ultrasonic processes, generates cavitation in the sample, but in a highly controlled fashion. This energy causes micron-sized vapor bubbles to form, which oscillate with the acoustic waves.

FIGURE 2



The Effect of AFA on Particle Size
A. 40x magnification of unprocessed sample
B. 40x magnification after 5 min of processing

Bubbles implode when they reach critical size.[5] The collapse of the bubbles also generates microjets and shock waves, which are likely the driving force for disruption of the droplets nearby. The combination of the acoustic streaming of the bulk fluid and the microstreaming caused by bubble collapse improves the mixing of the sample and produces a homogeneous emulsion.

In this study, rice bran oil-in-water (O/W) emulsions were prepared in single vessels ranging in size from 300 microliters to 22 mL, utilizing vessels made out of both glass and stainless steel (SST). Emulsions were also prepared using continuous processing in 2-mL and 22-mL SST flow cells. Tween-80, a surfactant having a HLB value of 15.0, was used.[1,3,4] In this article, we describe the successful use of the AFA technology to produce different volumes of O/W emulsions in single vessels, and O/W emulsions in a continuous flow format.

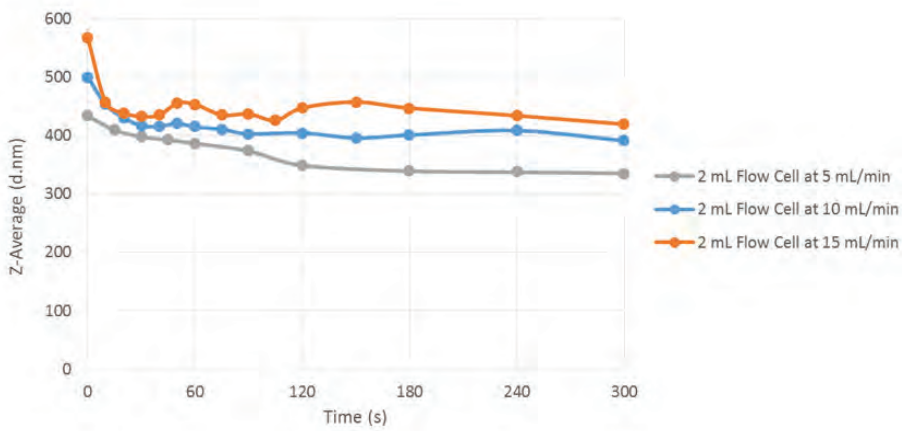
MATERIALS

All materials were used as received: Tween-80 from Sigma Aldrich (St. Louis, MO) and rice bran oil from Select Origins (Southampton, NY). A focused ultrasonicator S220x, equipped with an intensifier from Covaris, Inc. (Woburn, MA) was used to produce the emulsions. Batch mode samples were processed in 2-mL, 4-mL, and 8-mL glass vials, and 300-microliter and 2-mL SST vessels (with respective sample holders). Continuous flow emulsions were generated in 2-mL and 22-mL SST flow cells.

METHODS

Single-vessel samples were prepared in glass vials and SST vessels, such that the overall composition of the mixture was 4.25% rice bran oil, 8.5% Tween-80, and 87.25% deionized water. A schematic of the continuous flow experiment setup is shown

FIGURE 3



Equilibration of Continuous Flow Emulsions

in Figure 1. Feed 1 was formed by preparing an 8.5:87.25 Tween-80-to-water solution, while Feed 2 was composed purely of rice bran oil. The flow rates of the pumps were set such that the total feed composition would be 4.25% rice bran oil (qin), and 95.75% Tween-80 and deionized water mixture (qin). The two pumps were started simultaneously, and when the chamber had filled, AFA processing began. The flow rate of the system was determined by the volume of the outflow (qout). Samples were then exposed to AFA using an S220x instrument with acoustic treatment parameters listed in Table 1. All samples were tested at 50% duty factor and 1000 cycles per burst, and batch experiments were repeated three times. These parameters were chosen as a result of previous internal research.

PARTICLE SIZE DETERMINATION

To determine the size of the oil droplets in the O/W emulsion, portions of the AFA-processed samples from each single vessel or each continuous flow time point were examined using a Malvern Zetasizer ZS-90 (Worcestershire, UK) at 25°C, and three measurements were made per sample. Additionally, an Olympus DX53 microscope (Center Valley, PA) at 40x magnification was used to view the droplets.

RESULTS & DISCUSSION

Comparisons were made of the sample before and after AFA treatment using a 2-mL glass vessel (Figure 2). The mean particle size was significantly reduced following AFA processing; within 5 minutes, particle size had decreased more than 30-fold.

Further experiments showed that vessels can repeatedly produce particles on the scale of 500 nm. Based on the same acoustic energy consumptions per unit volume (kJ/ml), different sizes of glass vials produced average particle sizes within 20 nm of each other. The sample variation, however, was somewhat broader, with standard deviation among samples as large as 90 nm (for the 4 mL vessels). Regardless, all of the z-average values (mean particle size) fell well within the expected range of sizes (400 nm to 600 nm). In contrast, the SST vessels produced smaller particles with significantly less sample variation using less acoustic energy per unit volume than the glass vessels. Unlike the disposable glass vessels, in which the precision may be limited by the process of glass manufacturing, the emulsion yields from SST vessels are more reproducible because of the highly engineered vessel design. This, combined with the higher transmission of acoustic energy through the Kapton film on the bottom of the vessel and greater dissipation of the heat, makes Covaris' SST vessels more efficient, requiring lower energy densities than glass vessels. As a result, these SST vessels produced highly reproducible results.

AFA technology can be easily adapted to continuous flow processes. The 2-mL flow cell was used to examine the effect of flow rate on particle size. It was found that

droplet size increased fairly linearly with flow rate, and by altering the flow rate, the particle size can be tailored as needed. These observations agree with results in the literature, whereby increasing the ultrasonic processing time for a sample decreases the particle size.[2,5] As shown in Figure 3, different flow rates from 5 mL/min to 15 mL/min were tested, creating particles ranging in mean size from 340 nm to 450 nm after equilibrium. Increasing the flow rate decreased the mean residence time. As a result, the mixture remained in the vessel for less time on average, so the particle size increased because the processing time for any portion of the mixture decreased. The mean particles after equilibrium produced using continuous flow were, in fact, smaller than those produced in individual vessels, which was likely due to the improved mixing introduced by the bulk fluid motion in the flow cell. In this way, it was possible to tailor the droplet size and produce particles that matched the size of those produced in glass vials.

It should be noted that the equilibration times of the continuous flow processes were quite brief - within 2 minutes - and the particle size stabilized for all tested flow rates (Figure 3). Having a short equilibration time is economically advantageous, especially where precious components are concerned, as waste is minimized. As was seen in these experiments, it was possible to produce O/W emulsions by continuous flow at relatively high rates; for instance, in an 8-hour shift, up to 7.2 L of emulsion was produced using a single 2-mL flow cell. With multiple units set up in parallel, the production rate can be scaled up significantly. Additionally, unlike microfluidizers and homogenizers, the use of AFA for processing only necessitates one pass to create uniform emulsions.[11]

Scalability of AFA in production of O/W emulsions was demonstrated across many vessel sizes and types without adversely affecting size distribution (Figure 4). By adjusting the acoustic parameters of the experiments, consistent particle size distributions can be obtained both in single-cell and continuous flow processes. As the vessel size was increased, the required power input was increased, as was the time required to obtain the same average size.

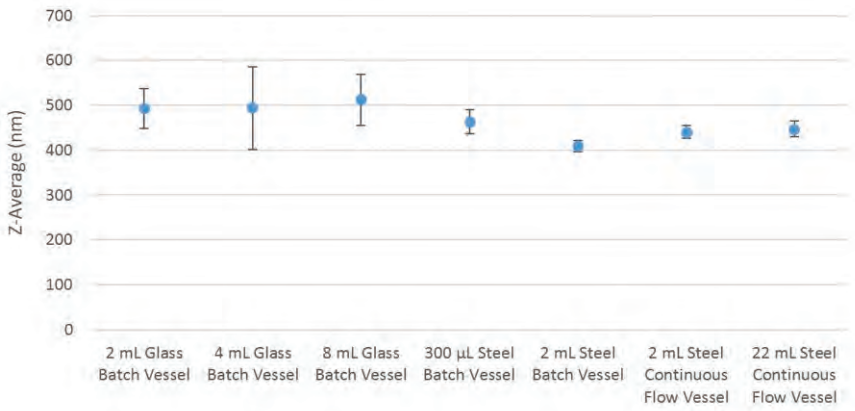
In addition to the acoustic parameters, the temperature of the sample also affects the mean particle size of the emulsion. Cavitation and viscosity, which influence particle size, are both affected by temperature. The strength of cavitation bubble collapse is reduced with increased sample temperature.[5,6,10] As the temperature of the sample increases, the vapor pressure within each cavitation bubble increases, reducing the force upon implosion, which reduces the shear force applied to the particle.[10] However, the incidence of the bubble collapse tends to increase at higher sample temperatures. The higher temperatures reduce the viscous force, which also reduces the strength of the bubble collapse. Meanwhile, as viscous forces become weaker at higher temperatures, the ease of mixing increases, facilitating the formation of small particles. Increasing the bath temperature decreases the average particle size and makes the process more repeatable. As a result, 10°C and 20°C were determined to be the optimal processing temperatures for creating 500-nm particles in SST and glass vessels, respectively, yet with further tuning, the particle size could be even more finely controlled.

TABLE 1

Vessel Type	Vessel Size	Peak Acoustic Power	Time of Process/Flow Rate	Chiller Temperature
Glass Batch	2 mL	150 W	10 min	20°C
	4 mL	150, 300 W	20, 10 min	20°C
	8 mL	200 W	30 min	20°C
SST Batch	300 µL	100 W	10 s - 1 min	10°C
	2 mL	300 W	2 min	10°C
SST Continuous Flow	2 mL	500 W	5, 10, 15 mL/min	10°C
	22 mL	500 W	10 mL/min	10°C

Processing Conditions

FIGURE 4



Comparing Droplet Size across Vessel Types

Additionally, AFA is able to produce homogeneous O/W emulsions from as little as 300 microliters up to continuous flow in both glass and SST vessels in a consistent manner (Figure 4).

CONCLUSION

The current study demonstrates that Covaris' Adaptive Focused Acoustics can quickly and easily produce nanoemulsions on sample scales varying from 300 microliters to continuous flow. By adjusting bath temperature, acoustic power, and processing time, it is possible to control the particle size of the O/W emulsion using AFA processes. In addition, the production rate of the sample in continuous flow can be increased simply by connecting multiple AFA processors. ◆

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

REFERENCES

1. Crowley MM. Solutions, Emulsions, Suspensions, and Extracts. In: Beringer P, ed. The Science and Practice of Pharmacy. 21st ed. Philadelphia: Lippincott Williams & Wilkins; 2006:759-766.
2. Abismaïl B, Canselier JP, Wilhelm AM, Delmas H, Gourdon C. Emulsificiation by ultrasound: drop size distribution and stability. Ultrasonics Sonochemistry. March, 1999;6:75-83.
3. Mathiowitz E, Kreitz MR, Brannon-Peppas L. Microencapsulation. Encyclopedia of Controlled Drug Delivery. New York: John Wiley & Sons, Inc.; 1999:497-499.
4. Pichot R, Spyropoulos F, Norton IT. O/W emulsions stabilized by both low molecular weight surfactants and colloidal particles: The effect of surfactant type and concentration. Journal of Colloid and Interface Science. December 2010;352:128-135.
5. Canselier JP, Delmas H, Wilhelm AM, Abismaïl B. Ultrasound Emulsification – An Overview. Journal of Dispersion Science and Technology. 2002;23:333-349.
6. Suslick KS. The Chemical Effects of Ultrasound. Scientific American. February 1989:80-86.
7. Freitas S, Hielscher G, Merkle HP, Gander B. Continuous contact- and contamination-free ultrasonic emulsification – a useful tool for pharmaceutical development and production. Ultrasonics Sonochemistry. January 2006;13:76-85.
8. How It Works: Particle Size Reduction Video. The Microfluidics Web site. http://www.microfluidicscorp.com/images/system.mp4. Published in 2012. Accessed July 8, 2013.
9. Lasch J, Weissig V, Brandl M. Preparation of liposomes. In: Torchilin VP, Weissig V, eds. Liposomes. 2nd ed. Oxford: Oxford University Press; 2007:7-8.10.
10. Lorimer JP, Mason TJ. Sonochemistry Part 1 – The Physical Aspects. Chemical Society Reviews. January 1, 1987;16:239-274.
11. Corixa Study Shows Microfluidizer® Processor Results Superior to those of Leading Homogenizer. The Microfluidics Web site. http://www.microfluidicscorp.com/images/stories/pdf/corixa.pdf. Published in 2009. Accessed July 8, 2013.

BIOGRAPHIES

Laura E. Forte is an undergraduate at Massachusetts Institute of Technology working toward a BS in Chemical Engineering. She was working at Covaris, Inc. as an intern, where her research focused on the scale-up and continuous flow processing of formulations. In previous research, Ms. Forte has done work with crystallization and drug formulation.

Dr. Srikanth Kakumanu earned his PhD from the Department of Biomedical Engineering and Biotechnology at University of Massachusetts in 2010. Since June 2010, he has been working as Research Scientist at Covaris Incorporated, where he heads the research in the application of Adaptive Focused Acoustics in formulations (dissolution, micronization, nano-suspension (tops down milling and sonocrystallization), drug delivery systems (polymer nano-particles, nano-emulsions, and liposomes). His major focus of research is scaling the AFA process to pilot-scal.e and continuous flow sample volumes.

Addressing HPV-Related Cancers in HIV/HPV Co-Infected Population

By: Eyal Talor, PhD

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), about 90% of genital warts begin with infection by the human papilloma virus (HPV). HPV is a sexually transmitted infection (STI.) Transmission of HPV may occur even if the warts are not visible. It usually spreads by direct contact with the anus, mouth, penis, or vagina of an infected person. Intercourse is not necessary to spread the infection. It can also be transmitted by skin-to-skin contact. In general, genital warts are known to spread relatively easily among partners.

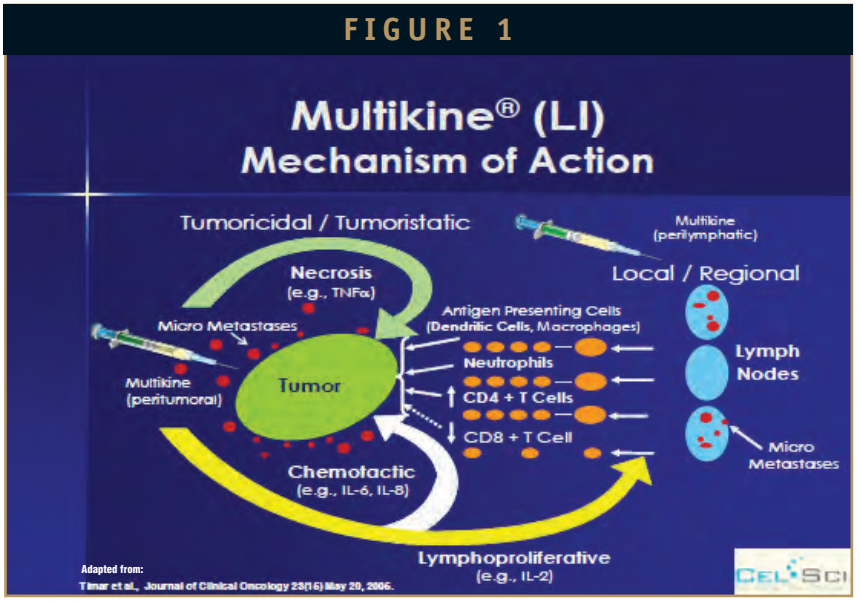
The National Institute of Allergy and Infectious Diseases (NIAID) warns that as many as two thirds of those who have had intimate contact with an infected sexual partner could develop warts within about 3 months of the initial contact (NIAID). Men and women with a history of anogenital warts have approximately a 30-fold increased risk of developing anal cancer, and persistent HPV infection in the anal region is thought to be responsible for up to 80% of anal cancers. HPV is now recognized as a significant health problem in the HIV(Human Immunodeficiency Virus)-infected population because, although today HIV infected individuals live longer as a result of greatly improved HIV treatments, their immune systems still remain compromised.

Usually, HPV infection can be eliminated in a healthy individual by their immune system within about 2 years of infection, without treatment. However, certain high-risk human papilloma virus strains may cause persistent infection that can lead to local abnormal changes in the infected and surrounding tissues, which if untreated, can develop into a cancerous lesion, particularly in immune-compromised individuals. Men and women who have HIV are therefore at a higher risk of developing cancer, which may include cancers of the cervix, vulva, vagina, penis, and anus. It is now accepted by the scientific community that some head and neck cancers are also associated with HPV infection.

Much attention has been focused on diagnosing and following the development of cervical intraepithelial neoplasia (CIN) following HPV infection. Efforts have been made by the scientific and medical communities to better understand and treat CIN with the aim of curbing its progression to cervical cancer. With the advent of cervical Pap smear and HPV testing and screening in various regions in the world, the incidence of cervical cancer has declined.

In the same way that persistent HPV infection is understood to be linked to development of CIN, the precursor of cervical cancer, persistent HPV infection has also been implicated in the development of anal intraepithelial neoplasia (AIN), the precursor to anal

FIGURE 1



cancer. As stated previously, HPV infection is thought to be responsible for up to 80% of anal cancers.

In general, there are marked similarities in the biological and pathological profiles of cervical cancer and anal cancer, which suggests that the incidence of anal cancer may be reduced - by developing strategies that can curb the progression of AIN to cancer.

ESTIMATING THE PREVALENCE OF HIGH-GRADE AIN IN THE HIV/HPV- INFECTED US POPULATION

It should be noted that there is a scarcity of literature with which to try to accurately estimate the prevalence of HPV in HIV-infected individuals and by extension, to accurately estimate the prevalence of high-grade AIN in both men and women who are HIV/HPV co-infected in the US.

It is estimated that there are currently approximately 1,148,200 HIV-infected adults (men and women) in the US (CDC; http://www.cdc.gov/hiv/resources/factsheets/us.htm). To try to estimate the range of individuals with high-grade AIN in the HIV/HPV-infected adult population (in the US), the following methodology was employed:

- The target patient population began with the total number of HIV-infected men and women in the US.
- Next, the HIV-infected population was split into three groups (MSM, women, and all others).
- Then each group was broken down into the percentages that are co-infected with HPV.
- Finally, each group that was determined to be co-infected was broken down into the percentages that were diagnosed with AIN.

Of the total HIV-infected population, about 597,064 are MSM (men sleeping with men) and about 287,050 are women. About 23% or 264,086 represent all others. Taking into consideration the variable estimations of different infected populations and using the aforementioned methodology, this leads to a calculated range of 94,594 to 372,086 individuals (both men and women) in the US who are likely to have high-grade AIN in the co-infected HIV/HPV population.

HIV treatment has now progressed to the point that it could be considered a "manageable" disease in most patients (ie, patients can live with the disease for a long period of time with relatively good quality of life). As a result, HPV infection is surfacing as a rapidly growing problem in the HIV-infected population. The prevalence of AIN can only be estimated from surveying the available scientific literature (see above) because there seemingly is no comprehensive source(s) of information for estimating the prevalence of HIV/HPV co-infected individuals. The incidence of anal warts in HIV/HPV co-infected patients is likely to be larger than the estimated incidence of high-grade AIN, but apparently at present there is insufficient literature to accurately document this estimate.

ENTER IMMUNOTHERAPY

The Naval Medical Center San Diego, a referral center of excellence for HIV/AIDS care of active duty, family members, and retired individuals since the start of the HIV epidemic in the 1980s, is investigating the use of an immunotherapy against AIN in HIV/HPV co-infected individuals, specifically, Leukocyte Interleukin, Injection (LI) [Multikine®], an investigational new drug product that is produced by CEL-SCI Corporation.

A Cooperative Research and Development Agreement (CRADA) between the US Naval Medical Center, San Diego, and CEL-SCI will involve a Human Subjects Institutional Review Board approved Phase I dose escalation study of Multikine in HIV/HPV co-infected men and women with peri-anal warts. Multikine is currently being investigated for the neoadjuvant/adjuvant treatment of previously untreated (Treatment Naïve) cancer patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck. Phase I clinical trials have also been performed with Multikine in male and female HIV-infected subject volunteers and in women volunteers with cervical dysplasia who were infected with both HIV and HPV. The results of the Phase I Study of females who were HIV/HPV co-infected led by Dr. Edmund Tramont, currently an Associate Director for Special Projects for DCR/NIAID/NIH, suggest that the Multikine treatment regimen might be useful in clearing HPV- and HPV-infected tissue and lesions of the cervix, which if not treated, could lead to cancer of the cervix.

HOW DOES IT WORK?

Multikine (LI), is a complex biologic product that contains a mixture of naturally derived and naturally occurring human pro-inflammatory cytokines (including IL-2, IL-1-beta, GM-CSF, TNF-alpha and IFN-gamma, and other small biological molecules) with

immunomodulatory activity. Each cytokine in this mixture has a distinct effect on the host and the tumor, and the sum of all of these effects are thought to affect solid tumor destruction in cancer patients. The pro-inflammatory cytokines in Multikine also have the potential to activate an array of anti-infective responses in treated individuals, which are thought to be required in order to be able to clear infections. The therapy is administered locally, percutaneously (peritumorally and perilymphatically to cancer patients) and aims to elicit a maximal immune response. In the studies of peri-anal warts that are currently being considered, Multikine would be injected perilesionally at the base of the anal-wart. The hope is that a strong local specific immune response would develop that will result in the elimination of the anal-wart and impact the underlying cause of disease, the HPV persistent viral infection, while at the same time, it may also have an impact on the AIN status of the subject volunteers.

The purported mechanism of action of Multikine (Figure 1) has been published by Timar J et al, 2005, in the Journal of Clinical Oncology (JCO). It describes how the local/regional injection percutaneously (peritumorally and perilymphatically injection) of "mixed interleukins" overcomes local immune suppression (induced by the tumor), is thought to break- tumor-tolerance to tumor antigens, changes tumor cellular immune infiltrate, and affects the tumor microenvironment, allowing for an effective and sustainable local anti-tumor immune response.

HOW MULTIKINE TREATMENT MIGHT LEAD TO THE "KILLING" OF HPV-INFECTED CELLS? (A HYPOTHESIS)

The pro-inflammatory cytokines, such as TNF-alpha (in Multikine) may also activate transcriptional factors (such as NF-kB). A critical downstream target of NF-kB gene encoding for IL-6 (a cytokine also known to be present in Multikine), which stimulates an array of anti-infection processes, including the synthesis of acute phase protein (CRP), proliferation of B cells, neutrophil production, and differentiation of Th17 helper T cells, all of which are thought to be necessary to bring about an anti-infective response. In addition, IFN-gamma (also present in Multikine) has been shown to have specific anti-viral activity (including anti-HPV activity), where studies conducted (by others) with the administration of purified or recombinant IFN-gamma directly to or in the vicinity of HPV-warts have shown lesion regression accompanied by activation of T-cell mediated immune response, with influx of activated T lymphocytes. This same/similar clinical and histological manifestation has already been shown previously with the administration of Multikine in the HIV/HPV CIN population.

CONCLUSION

Many agree that the goal of HIV care is empowering people to live well (long and productive lives) with the virus. When it comes to the risk of developing HPV-related cancers, HIV positive individuals need expanded arsenals that will be able to address their specific needs. The various clinical trials conducted aim to provide answers for those needs. ◆

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

BIOGRAPHY

Dr. Eyal Talor joined CEL-SCI in October 1993 as Senior VP for Research and Manufacturing. In October 2009, Dr. Talor was promoted to CSO. He is a Clinical Immunologist with over 19 years of hands-on management of clinical research and drug development for immunotherapy application; preclinical to Phase III, in the biopharmaceutical industry. His expertise includes biopharmaceutical R&D and biologics product development, GMP manufacture, quality control testing, and the design and building of GMP manufacturing and testing facilities. He served as Director of Clinical Laboratories (certified by the State of Maryland) and has experience in the design of clinical trials (Phase I-III) and GCP requirements. He also has broad experience in the different aspects of biological assay development, analytical methods validation, raw material specifications, and QC tests development under FDA/GMP, USP, and ICH guidelines. He has extensive experience in the preparation of documentation for IND and other regulatory submissions. His scientific area of expertise encompasses immune response assessment. He is the author of over 25 publications and has published a number of reviews on immune regulations in relation to clinical immunology. Before coming to CEL-SCI, he was Director of R&D and Clinical Development at CBL, Inc., Principal Scientist - Project Director, and Clinical Laboratory Director at SRA Technologies, Inc. Prior to that, he was a full-time faculty member at The Johns Hopkins University, Medical Intuitions; School of Public Health. He has invented technologies covered by 2 US patents; one on Multikine's composition of matter and method of use in cancer, and one on a platform peptide technology (Adapt) for the treatment of autoimmune diseases, asthma, allergy, and transplantation rejection. He has patents issued on Multikine in the EU, Japan, and China. He also is responsible for numerous product and process inventions as well as a number of pending US and PCT patent applications. He earned his PhD in Microbiology and Immunology from the University of Ottawa, Ottawa, Ontario, Canada, and had post-doctoral training in clinical and cellular immunology at The John Hopkins University. He holds an Adjunct Associate post-graduate teaching position at the Johns Hopkins University Medical Institutions.

Powered by

partneringONE®

PartneringONE®, the most successful and highly regarded partnering tool in the market will be at Drug Delivery Partnerships Europe

DRUG DELIVERY PARTNERSHIPS™ EUROPE

17 – 18 September 2014
Radisson Blu Hotel Hamburg | Hamburg | Germany

Collaborating to drive innovation in drug delivery

- ✓ **Creating sustainable innovation and value in drug delivery**
- ✓ **Overcoming small molecule delivery challenges**
- ✓ **Advancing the delivery of biologics**
- ✓ **One-to-one networking powered by partneringONE®, the leading conference networking solution for the life sciences**

partneringONE®

FEATURING REPRESENTATIVES FROM:

- **Pfizer**
- **Novartis**
- **Bayer**
- **F. Hoffmann La Roche AG**
- **Medimmune**
- **Lundbeck**
- **Fresenius Kabi**
- **Ipsen**
- **Merck**
- **GlaxoSmithKline**
- **Boehringer Ingelheim Pharma GmbH & Co. KG**

KEY SPEAKERS:

Anand Subramony, Vice President Drug Delivery & Device Development, **Medimmune,** USA

Keith Horspool, PhD Vice President, Pharmaceutical Development, **Boehringer Ingelheim,** USA

Mark McAllister, Research Fellow, **Pfizer** Deputy Project Co-ordinator, **OrBiTo,** UK

Andy Lewis, Director Novel Delivery Technologies, **Ipsen,** France

Prof. Dr. Claus-Michael Lehr, Head, Dept. of Drug Delivery (DDEL), **Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS),** Germany

Sponsored by

Aptar pharma | HOVIONE | VISCOGEL | APTALIS Pharmaceutical Technologies

In Association with CRS Leading Delivery Science and Technology

Partnered by ON drugDELIVERY

www.informa-ls.com/DDP

Please quote VIP Code CQ5233DRUG when registering

DRUG DEVELOPMENT
3M Executive

3M Drug Delivery Systems Division: A Partner to Tackle Market Complexities

Cindy R. Kent, MBA
VP & General Manager
3M DDSD

"Given all of this, my hope and vision for our business is that we are the trusted developer and manufacturing partner of choice. There are reasons that partners come to us and want our help in bringing their products to market. Our core capabilities - product development, commercial manufacturing, global regulatory expertise, and our technological and innovation savvy - are resonating very strongly with customers."

3M Drug Delivery Systems Division (DDSD) applies its 50-plus year history of global pharmaceutical development and manufacturing services to give customers proven expertise in inhalation, transdermal, oral, and topical solutions. In 2012, Drug Development & Delivery interviewed James D. Ingebrand, then Vice President and General Manager of 3M DDSD, who spoke about the challenges of globalization, technologies like the microstructured transdermal system and nasal MDI, and how 3M partners with pharmaceutical companies to help them control costs while bringing products successfully to market. Cindy R. Kent has recently succeeded Ingebrand as Vice President and General Manager of the division, transitioning from a role as Vice President of Strategy, Business Development and US Medical Key Accounts for 3M Health Care. Before she joined 3M, she spent time at both Medtronic and Eli Lilly, giving her broad expertise in both pharmaceuticals and medical devices. *Drug Development & Delivery* recently interviewed Ms. Kent to learn about her vision for the company and how developing trends are impacting the players in the pharmaceutical industry.

Q: Congratulations on your appointment. With a background in both pharmaceutical and medical device fields, how are you planning to utilize your experience and insight to help grow the division?

A: One of the things I'll be the first to admit is that the healthcare marketplace today is radically different than the one I entered into 24 years ago. Part of what's exciting to me, having transitioned through pharma, to devices and supplies, and now contract manufacturing and development, is that the marketplace in the past has changed significantly every 5 years on average, but of late, we are seeing significant changes every single year. However, what I believe is consistent - and the value that my background brings to this - is that I'm able to look at news and decipher what's meaningful to us and what it suggests in terms of where the puck is going.

As a healthcare business within an industrial company, 3M Drug Delivery Systems has some unique advantages. For instance, 3M has its background in industrial adhesives and tapes, so

our corporate scientists may be able to connect the dots when there's a new polymer that impacts adhesive capabilities. In our case, this polymer change might impact our skin adhesive products, enabling changes like gentler adhesives for transdermal products. Given my background, I can look at a piece of news and be able to say, "This opens up an entire field of play for drug delivery."

Q: What is your vision for the 3M Drug Delivery Systems Division and how do you plan to position the company to meet the needs of its partners?

A: One of the first things I did when I arrived here was to work with my team to come up with Drug Delivery Systems vision cards, outlining who we are, what we do, and where we drive value. I'm fortunate in that it's not just me looking through old strategic plans and coming up with a new one; we recently conducted a customer survey that has given us data from approximately 150 of our customers. So we have their insights on what works well, and what are they looking for in an R&D and contract manufacturing partner. With that information, we are able to base our vision on aligning our core capabilities with what customers are asking for. This initial round of research was based on US customers; however, we have plans for the remainder of the year to do similar research in all of our major regions. Based on what we learned in the US, customers - not surprisingly - are saying they choose to partner with 3M Drug Delivery Systems based on our quality, our expertise with approval bodies and agencies around the world, and our technical expertise, both in manufacturing as well as in early stage development. Customers tell us that they recognize our technical expertise not only in drug delivery, but within the larger 3M, which gives us the backing of 3M's innovation and rigorous scientific competence.

Given all of this, my hope and vision for our business is that we are the trusted developer and manufacturing partner of choice. There are reasons that partners come to us and want our help in bringing their products to market. Our core capabilities - product development, commercial manufacturing, global regulatory expertise, and our technological and innovation savvy - are resonating very strongly with customers.

Q: What general trends are you seeing in the healthcare industry, and how are these helping to shape the pharmaceutical market?

A: Among the big trends driving shifts in pharma is an increased focus on outcomes. It's not a simple matter of being at parity anymore. When I was in pharma, we had some pretty defined development archetypes. A new product could be novel, second-and-better, or perhaps an additional entrant into a crowded market. We defined our value proposition within the boundaries of those archetypes. Frequently, in the case of a product that was a new entrant into a crowded market, we would design clinical studies to be non-inferiority studies, as opposed to superiority studies to dethrone the market leader. But I believe the bar has been raised, and the standard is now better outcomes at lower costs. It is a completely different game. I believe there will be fewer blockbuster drugs being developed, and the focus will shift to how to take cost out of the system - not just in terms of having a lower price point, but how one product might be able to eliminate the need for two to three others.

We are also in a time when pharmaceutical companies are facing a high number of patent cliffs, which is forcing consolidation. In this climate, it doesn't seem applicable to label companies as friends or foes anymore; companies that are partnering together in one area may be competitors in other areas. It used to be that there were very clear lines of demarcation between branded pharma companies and generic pharma companies. But at this point, that's no longer the case. Many companies are diversifying their own portfolios with a mix of branded and generic products, because if you're only branded, you really leave no room for a situation like a government entity asking for volume discounts. In this situation, having a market laggard or a generic in the mix might give you the leverage you need.

And thus a lot of companies are becoming their own generic providers, which is unheard of historically in the pharma universe.

Finally, the increased focus on emerging and developing markets means that we're no longer only thinking about how we launch products in developed markets. We have to figure out quite quickly how to compete in international situations where a local company may receive preferred or accelerated approval status from the ministry of health and local regulatory agencies. When granting approvals for multinational companies, these ministries maintain the quality standards seen in developed markets, but they want price points for developing markets. We just don't develop products that way, so this means that we must change our process to take costs out, or think about a pyramid of products and develop products at various tiers. This is simply a much different universe than we've ever been in as an industry.

Q: What main factors in the healthcare industry are influencing the innovations in drug delivery?

A: Some of the factors I see driving changes are the large and untapped opportunities as they relate to new therapeutic areas. For example, cancer continues to have devastating impacts on the health of people around the world. And yet, limited therapeutic solutions exist, depending on what type of cancer we're talking about of course. So companies are considering what the therapeutic areas are that do not have a "gold standard," and drug delivery can offer tremendous opportunity in these areas. Combining a marketplace need like that with our capabilities is an area that is very promising.

Furthermore, for therapeutic areas that we are already involved in, such as asthma or COPD, the trends toward minimizing waste and being patient-friendly are having important impacts. One of the factors currently driving increased demand for our products is that we have an innovative dose counter that helps assure patients of exactly how much drug has been dispensed, and also helps them stay on top of their remaining supply. We're seeing increased requests for dose counters on actuators, so this is an innovation we are continually working to optimize.

Q: What advice do you have for pharmaceutical companies looking to become competitive in the generics marketplace?

A: The easy answer is to work with a reliable partner. That sounds self-serving, but it's not as glib as it may seem. There's evidence all around that the bar for generics is increasing. Companies in the past haven't necessarily thought about generics as an "easy play," but the point is that standards around generics are ever changing. At the end of the day, it's becoming clearer that generic simply means, "yes, it's off patent." It's a cheaper price point, but the regulatory pathway is as robust and rigorous as the initial branded innovator product.

Combine that insight with the reality of the market today. As companies become increasingly cognizant of cost at every point in the value chain, it becomes clear that not everyone can master every point in that value continuum. Given this, the best thing a company can do is to think about where its greatest area of expertise is and concentrate in that area. Then, when it comes to overall maximization of the value chain, companies should find a credible and competent partner that can handle other aspects. It's in everyone's best interest to maximize the value chain and help get high-quality products on the market faster. So I encourage companies, instead of trying to be all things to all people, to really consider working with a partner like 3M DDSD, with whom they can partner to navigate these new market realities. ◆

Technology & Services Showcase

Solid Oral Dosage Forms

Agere Pharmaceuticals' services include solubilization formulation design and development, cGMP analytical, and solid oral dosage forms. Solid dosage forms supported include tablets, capsules, powder for inhalation, and alternative dosage forms. Our capabilities include excipients selection, drug excipient ratios, and process development. We also support clients by preparing immediate and sustained-release forms for the clinic. In addition to characterization of unit operations, Agere offers a broad spectrum of analytical and physical measurement capabilities. Formulation development leverages our Quadrant 2™ solubilization platform, and all Agere services follow QbD guidelines. For more information, contact Agere at (541) 318-7115 or visit **www.agerepharma.com**.

Search Firm

If you're looking to build your workforce, Altitude Staffing will get you the right people, every time. We are a premier full-service search firm. With over 20 years of experience, we have helped small, medium, and large organizations attract the best talent. We offer a wide array of services, including Temporary, Temp-to-Perm, and Full-Time placements on a retained as well as contingency basis. Our approach is to engage in each SEARCH as a unique opportunity, and it all begins with the clients' needs first. Businesses we serve: Pharmaceutical/Biotechnology/Drug Delivery/Specialty Pharma, Device Designers/Developers/Manufacturers, Pharmaceutical Software Development, Clinical Research, Contract Research, Clinical Trial & Development Services, etc. For more information, contact Altitude Staffing at (908) 228-5999 or visit **www.altitudestaffing.com**.

HPMC Capsules

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

Biologics Development

Catalent's proprietary Gene Product Expression Technology (GPEx®) sets the standards in mammalian cell line engineering. GPEx allows rapid selection of the best clinical candidate from a group of potential molecules, providing a stable Master Cell Bank to rapidly generate proteins for clinical trials. GPEx technology can ensure genetically stable cell lines are produced 100% of the time. The advanced mammalian cell line technology in GPEx accelerates timelines, increases reliability and yield, and provides superior cell stability compared to any other method, with flexibility and unmatched versatility. Catalent provides a faster path from gene to clinic and offers high-performance cell line biologics development and biomanufacturing. Catalent boasts a new, state-of-the-art, biologics manufacturing facility in Madison, WI, allowing for batch sizes from 10-1,000 L. To learn more about Catalent's global Biologics capabilities, call (877) 587-1835 or visit **http://www.catalent.com/index.php/development/biologics/overview.**

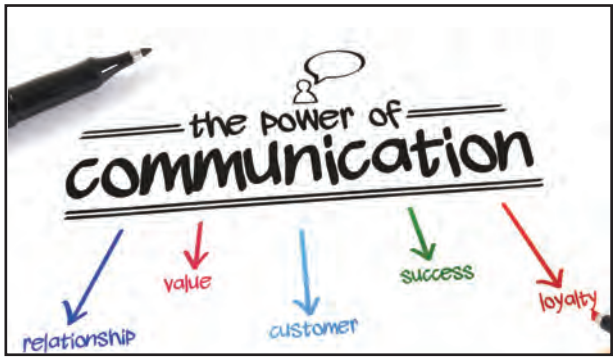
Technology & Services Showcase

Development & Manufacturing

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

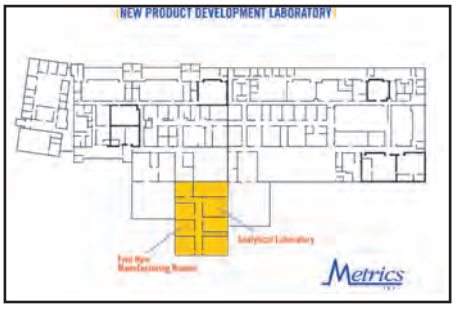
Insulin Management Systems

Marketing & Communications



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

Product Development Lab



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

Technology & Services Showcase

Knowledge Management

PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (920) 850-3056 or visit **www.pharmacircle.com.**

Intranasal Vaccine Delivery

Teleflex Medical is a global provider of medical devices with over 20 years' experience servicing OEM partners with bespoke device requirements. The Teleflex VaxINator™ is an easy-to-use and cost-effective solution for intranasal drug delivery. The droplet size output of the VaxINator allows for drug coverage across the anterior and posterior areas of the nasal cavity, thereby facilitating rapid adsorption. The VaxINator is a syringe-and-atomizer-based system, and a range of accessory items are available to meet your intranasal drug delivery needs. At Teleflex, we are committed to investing significant time and effort into demand planning and risk mitigation to ensure high-quality product supply when you need it and where you need it. For more information, including contact details, visit Teleflex Medical at **www.vaxinator.com.**

Development Services

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

CDMO Services

Xcelience offers a suite of services from preformulation and development through manufacturing and clinical distribution and logistics. Entrust all your clinical outsourcing needs by partnering with a single CDMO. Services include preformulation development, analytical services, formulation development, GMP manufacturing, and clinical supplies packaging and distribution. Xcelience's responsibility is delivering the best science and service with our commitment to quality, cost, and speed. Since 1997, Xcelience has been known for reliably expediting drug product development and clinical manufacturing for oral solid, semi-solid, and liquid dosage forms. In the past few years, Xcelience has grown exponentially, opening a facility in 2012 dedicated to clinical packaging and logistics, and in 2013, opening its first international facility in the UK. For more information, contact Xcelience at (813) 286-0404 or info@xcelience.com, or visit **www.xcelience.com.**

DRUG DEVELOPMENT Executive

PAREXEL®
YOUR JOURNEY. OUR MISSION.™

PAREXEL: Simplifying the Journey to Market

Carol Collins
Corporate VP, Strategic Partnerships
PAREXEL

Pressures from rising operating costs and decreasing economic returns have forced biopharmaceutical companies to rethink their approach to developing drug compounds. One approach is strategic outsourcing of clinical research to increase R&D productivity and cut overall operational costs. Research has demonstrated that Strategic Partnerships are changing the way biopharmaceutical companies meet the challenges of today's drug development environment. *Drug Development & Delivery* recently spoke with Carol Collins, Corporate Vice President, Strategic Partnerships, PAREXEL, to clarify how Strategic Partnerships differ from other outsourcing approaches - and what makes them more effective.

"The model is considered particularly effective in enabling greater cost predictability, strategic management of the R&D portfolio, and management of capacity gaps. In addition, the report showed that among companies surveyed, more than half now use a Strategic Partnership model: 54% of North American biopharmaceutical companies engage in Strategic Partnerships, while 50% in Europe and 53% in Asia now use this approach."

Q: What is a Strategic Partnership? Does this description accurately reflect the industry's perspective?

A: As biopharmaceutical companies continue to seek opportunities to increase efficiencies, drive greater flexibility, extend expertise, reduce costs, and leverage limited resources, they are increasingly turning to outsourcing services offered by biopharmaceutical service providers. In particular, growing numbers of Sponsors are adopting a Strategic Partnership model. These multi-year, highly integrated engagements are proving to accelerate development cycles, create cost efficiencies, and ultimately enable important new treatments to reach patients more quickly. PAREXEL, a pioneer of the Strategic Partnership model between biopharmaceutical companies and service providers, continues to invest in revealing insights on the value this model delivers. Biopharmaceutical service providers and drug developers that leverage Strategic Partnerships have a compelling opportunity to collaborate effectively to make this possible. Our recent research reports, *Strategic Partnerships 2013 and Strategic Partnerships 2014*, confirm that this is how industry leaders define these integrated engagements.

Q: If the biopharmaceutical industry is embracing the Strategic Partnership model, then why did PAREXEL commission this research?

A: As one of the world's leading CROs and a leader in creating and implementing Strategic Partnerships, PAREXEL has made a major research investment to gain an independent understanding of how biopharmaceutical executives view Strategic Partnerships, the value alignment of these partnerships, including which drivers executives consider critical, and industry evolution trends. While PAREXEL's in-depth engagement with its current partners offers a rich source of information, there is also value in expanding our understanding beyond current clients via an independent third party who can probe areas that might otherwise be sensitive or difficult to explore.

Q: What value does a Strategic Partnership provide a biopharmaceutical company? Couldn't companies experience this value through a traditional transactional model?

A: The duration, depth, and mutual investments that characterize a Strategic Partnership create value opportunities that traditional transactional outsourcing cannot achieve. For example, mutual investments in aligned processes and systems, along with robust multi-level governance, significantly reduce required sponsor oversight while retaining quality. Furthermore, early pipeline visibility and awards associated with Strategic Partnerships enable timely expertise sharing to improve effectiveness and efficiency of development plans, protocols, and operational plans.

Lastly, incentive alignment, both de facto from the depth of the mutual commitment as well as direct commercial incentive alignment from appropriately structured master service agreements, is a hallmark of Strategic Partnerships that is not possible to create with transactional approaches. Among the industry executives interviewed in our research in 2013, the majority (85%) have seen that Strategic Partnerships improved the Sponsor-CRO relationship. These executives stated that the Strategic Partnership model reduces oversight level, decreases fixed costs, and provides access to capabilities not found internally. A traditional project-by-project agreement can help a biopharmaceutical company reduce fixed costs and improve flexibility to a limited degree, but cannot deliver the level of operational efficiencies needed to help the industry meet the challenges of a changing R&D landscape. We have seen that, in fully established Strategic Partnerships, time-to-market and development efficiency can be improved significantly relative to transactional outsourcing. These improvements can be driven by compound outsourcing, in which early engagement, study optimization, and reduction of down-time between phases generate cost and time savings. The internal cost for a sponsor to manage a CRO is also reduced through partnership-level processes and infrastructure. The internal cost for a sponsor to manage a CRO is also reduced through partnership-level processes and infrastructure. These investments decrease the average sponsor full-time employee (FTE) to CRO FTE oversight ratio from the 1:3 seen in transactional relationship to 1:8 or less. In more advanced partnerships, the oversight ratio can decrease further to levels of 1:15 or less - all while maintaining quality.

Q: PAREXEL recently launched a new report in 2014. Can you tell our readers more?

A: PAREXEL has released *Strategic Partnerships 2014: Driving Biopharmaceutical Outsourcing Effectiveness,* which provides compelling insights that highlight the value of these multi-year, highly integrated engagements between sponsors and CROs. In particular, the report reveals that the Strategic Partnership model is perceived as the most effective biopharmaceutical outsourcing approach in meeting key sponsor needs. The model is considered particularly effective in enabling greater cost predictability, strategic management of the R&D portfolio, and management of capacity gaps. In addition, the report showed that among companies surveyed, more than half now use a Strategic Partnership model: 54% of North American biopharmaceutical companies engage in Strategic Partnerships, while 50% in Europe and 53% in Asia now use this approach. The report also found that positive perceptions of outsourcing effectiveness within the biopharmaceutical industry have increased significantly in the past 3 years. This increase has occurred across all geographies and with sponsors of all sizes.

Q: What is the future vision of Strategic Partnerships, and how does that differ from where the model is today?

A: The 2014 Strategic Partnerships report reveals that the Strategic Partnership model holds untapped potential to yield additional value and meet future biopharmaceutical industry needs. Sponsors surveyed clearly believe the next generation of Strategic Partnerships has the potential to deliver additional value through several additional features.

Continuous study optimization is considered the top opportunity for added value, followed by additional focus on shared knowledge and greater integration among partners. Enhancements in these areas will continue to accelerate the industry's ongoing shift from in-house development and transactional outsourcing to Strategic Partnerships. For a full copy of the Strategic Partnerships 2014 report, please visit www.PAREXEL.com. ◆

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

July/August 2014
Advertiser Index

Company	Pg	Phone	Web Site
AAPS	43		www.aaps.com/annualmeeting
Altitude Staffing	73	908-228-5999	www.altitudestaffing.com
Catalent Pharma Solutions	76	1-888-SOLUTION	www.catalent.com
CPhI Worldwide	11		http://www.cphi.com/europe
DPT Laboratories	2		www.dptlabs.com
Drug Development & Delivery	49	973-263-5476	www.drug-dev.com
Drug Delivery Partnerships	63		www.informa-ls.com/event/DDP2014
Frost & Sullivan	13		www.frost.com
Insulet	3	866-941-4576	www.insulet.com
LifeSciencePR	75	800-724-2374	www.lifesciencepr.net
Metrics	5	252-752-3800	www.metricsinc.com
PDA	15		www.pda.org/prefilled2014
PharmaCircle	9	760-436-1199	www.pharmacircle.com
Teleflex	7	+353 (0) 1896-4961	www.vaxinator.com

If you're looking to build your workforce, Altitude Staffing will get you the right people, every time.

We are a premier full-service search firm. With over 20 years of experience, we have helped small, medium, and large organizations attract the best talent. We offer a wide array of services, including Temporary, Temp-to-Perm, and Full-Time placements on a retained as well as contingency basis. Our approach is to engage in each SEARCH as a unique opportunity, and it all begins with the clients' needs first.

Here are just some of the businesses we serve and positions we place:

- Pharmaceutical/ Biotechnology/Drug Delivery/ Specialty Pharma
- Device Designers/ Developers/Manufacturers
- Pharmaceutical Software Development
- Clinical Research
- Contract Research, Clinical Trial & Development Services
- Excipients & Specialty Ingredients
- Universities
- Consultants
- Financial
- Legal
- Government
- Sales/Marketing
- Business Development
- Corporate Management— Chairman, President, CEO, CFO, CSO, CTO

Visit us at altitudestaffing.com for a complete list of services we offer.

Altitude
STAFFING

1122 Route 22 • Suite 203 • Mountainside, NJ 07092 • P: (908) 228-5999
Ed.koch@altitudestaffing.com • www.altitudestaffing.com

Increasing Your Reach & Frequency

By: David F. Scelba, Associate Partner, LifeSciencePR

For several years, I've been preaching the benefits of re-purposing press releases and re-distributing content via video to social media networks and third-party websites and blogs. A few courageous clients have taken this advice. However, with the increased publicity and hype surrounding social media, many fence sitters are now ready to jump into these interactive communication waters. For those employing a PR strategy that includes writing and distributing press releases, I have a seven-step KISS program to offer.

Step 1: Establish a person or persons who will have a good on-screen camera presence and can articulate your company's message.

Step 2: Evaluate social networks, third-party websites, blogs, and databases that could be used for v-mail broadcasting. Your product or service will dictate which networks will communicate best to your audience. And remember, it's always better to walk before you run, so using proven socials like YouTube and Facebook would be a good start. The initial set-up is easy and doesn't require much time to execute.

Step 3: Create a virtual set to serve as the backdrop for each of your videos.

Step 4: Determine which press releases would be of interest to your audience and edit them into a short one – 3-minute video script. The writer of the original press release should be able to re-edit the content in less than an hour.

Step 5: Video the on-screen talent in front of a green screen, edit the footage in post- production, and convert the file to flash movies for distribution. Our people are cross trained and act as the director, videographer, and editor, so we're able to significantly reduce production costs.

Step 6: Videos are then distributed to the pre-selected socials, websites, and blogs by a dedicated staff.

Step 7: Analytics are available to monitor each of the social networks, and Google Analytics is used to measure your web and blog stats. For most clients, these tools satisfy all their measurement requirements and best of all, they're free.

By re-allocating a small portion of your annual marketing or advertising media budget to this activity, I guarantee you will increase your reach and frequency by numbers greater than you could ever imagine! ◆

BIOGRAPHY

David F. Scelba is the Founder & Chairman of SGW Integrated Marketing & Communications and is a Partner at LifeSciencePR. He is responsible for the development of the company's new interactive products and services and plays a key role as senior strategist for developing clients' integrated marketing communications programs. He is also involved in researching and investigating acquisition opportunities and for initiating negotiations on behalf of the company. His diversified B2B, consumer, and retail experience encompasses industries such as: automotive; biochemical; broadcast; education; healthcare; hospitals; life sciences; microwave; pharmaceutical (research/drug delivery); political; professional video/audio; medical; telecommunications; and more. He is a keynote motivational speaker whose audiences include marketing professionals, college professors, MBA graduate students, and undergraduates seeking careers in the marketing- and communications-related industries. He also mentors business and government leaders on the use of technologically innovative tools for better communication with their targeted audiences.

Smarter. Faster. Easier.

- Public Relations
- Media Relations
- Investor Relations
- Advertising and Design
- Media Planning and Placement
- Multimedia/Web Development
- Social Media Development/Management
- Search Engine Optimization/Marketing

Get Noticed. Get Funded. Grow Faster.

When you need to connect with investors, business partners and regulatory agencies, LifeSciencePR can make that happen. Our integrated communication strategies and well-established industry contacts will help your emerging life science company achieve its short and long-term corporate objectives.

We work seamlessly with your senior management team to develop the most effective communication initiatives to reach your prospective investors and partners.

LifeSciencePR will get you there smarter, faster and easier than any other marketing and communications firm in the industry.

Call us at 800.724.2372 or visit lifesciencepr.net.

LifeSciencePR
we'll get you there.

Catalent®
rp scherer softgel

inventors then.

1934 RP Scherer invents the rotary die encapsulation process, launching 80+ years of innovation

1940 First prescription softgel capsules

1955 In-line printing for softgel capsules

1960 Cough, cold and allergy softgel capsules

1993 OTC LiquiGels™ and topical twist-off capsules

2001 Vegicaps® natural, GMO-free, plant-based capsules

innovators now.

2012-2013 New, break-through technologies that help enable more molecules, convenient dosing and better treatments:

- OptiShell™ for semi-solid formulations
- OptiGel Lock™ for multi-level abuse deterrence
- OptiGel Bio™ for oral delivery of macromolecules
- OptiGel Mini™ for concentrated formulations in a smaller size
- OptiGel Micro™ delivers our smallest, micro-sized softgels
- Dual-action, multi-layer SoftDrop™ lozenges

DEVELOPMENT DELIVERY SUPPLY

Every molecule has a challenge. We have a softgel solution.

+1 888 SOLUTION (765-8846) solutions@catalent.com www.catalent.com/softgel