Leading the way with integrated containment and delivery solutions

West
By your side for a healthier world™

SMARTDOSE®

PRECISE. RELIABLE. READY TO GO.

FDA Approved

- The first combination product that incorporates the SmartDose platform technology was recently approved by the US Food and Drug Administration (FDA)
- Thousands of doses have been administered using the SmartDose platform
- Proven engineering, manufacturing and regulatory expertise to support your needs

Wearable Injector

- Subcutaneous self-administration
- Ability to deliver high volume and high viscosity drug products

Patient-Centric

- User-centered design
- Connectivity to a variety of software platforms
- Able to link with adherence solutions
- Onboarding and training solutions available

Flexible Technology

- Address a variety of delivery times through adaptable, pre-programmable technology
- Maximize patient comfort through pre-programmable delivery times

West Pharmaceutical Services, Inc. | 530 Herman O. West Drive, Exton, PA 19341 | www.smartdose.com | North America +1 800-345-9800 | Europe +49 2403 7960 | Asia Pacific +65 6860 5879

West seeks partners for its SmartDose platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company.

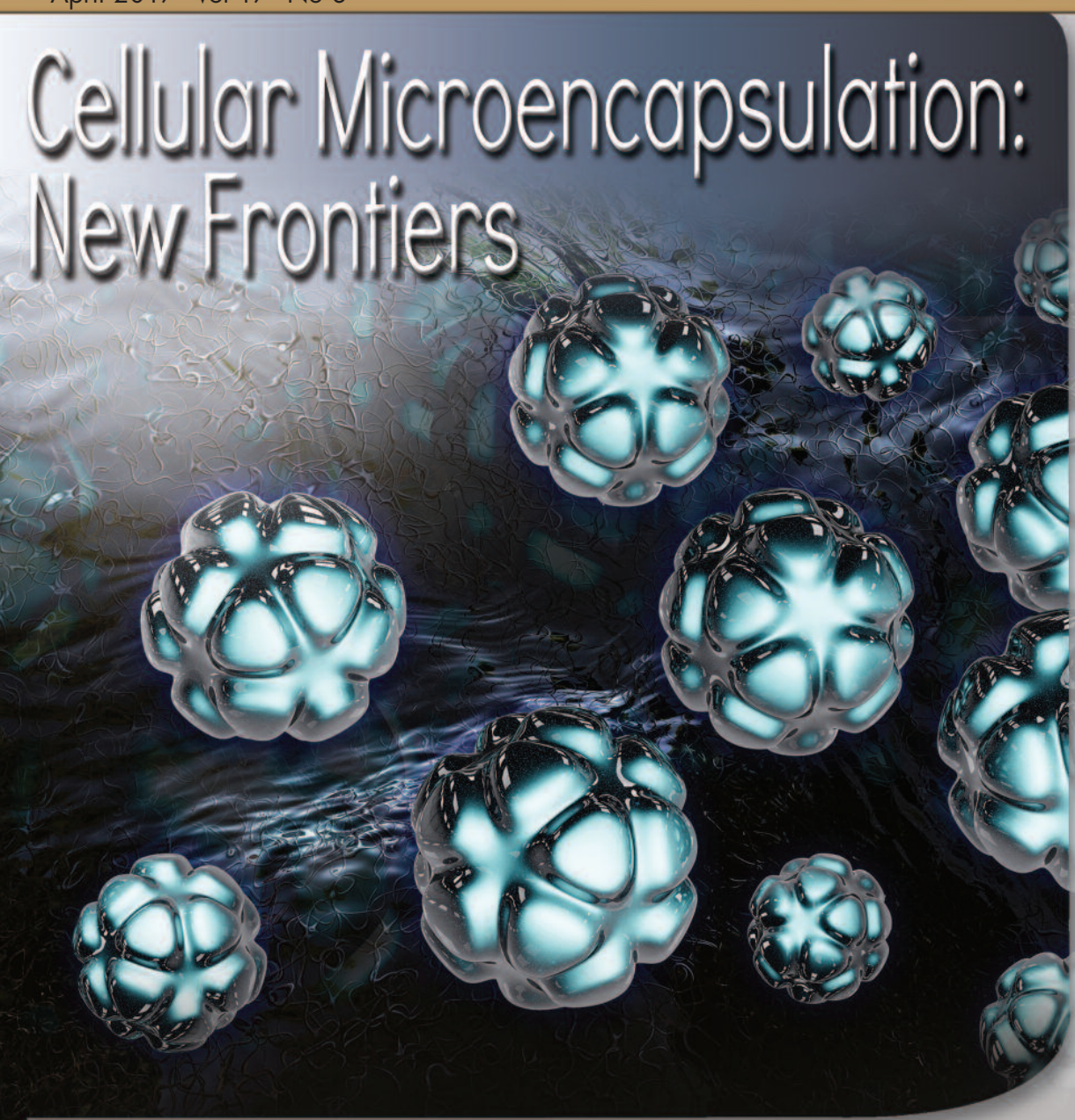
For more information visit www.westpharma.com

#10224 0317

Drug Development® & Delivery

April 2017 Vol 17 No 3 www.drug-dev.com

Cellular Microencapsulation: New Frontiers



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

Detlev Haack, PhD
Improving the Palatability of User-Friendly Dosage Forms Using an Electronic Tongue

Gerald Crabtree, PhD
Cell Encapsulation for Drug Delivery & DiseaseTreatment

Cindy Dubin
CDMOs Offer Speed, Advanced Technologies & the Ability to Handle More Potent APIs

IN THIS ISSUE

INTERVIEW WITH **VETTER DEVELOPMENT SERVICES'** PRESIDENT SUSANNE RESATZ, PHD

WWW.CAPSUGEL.COM

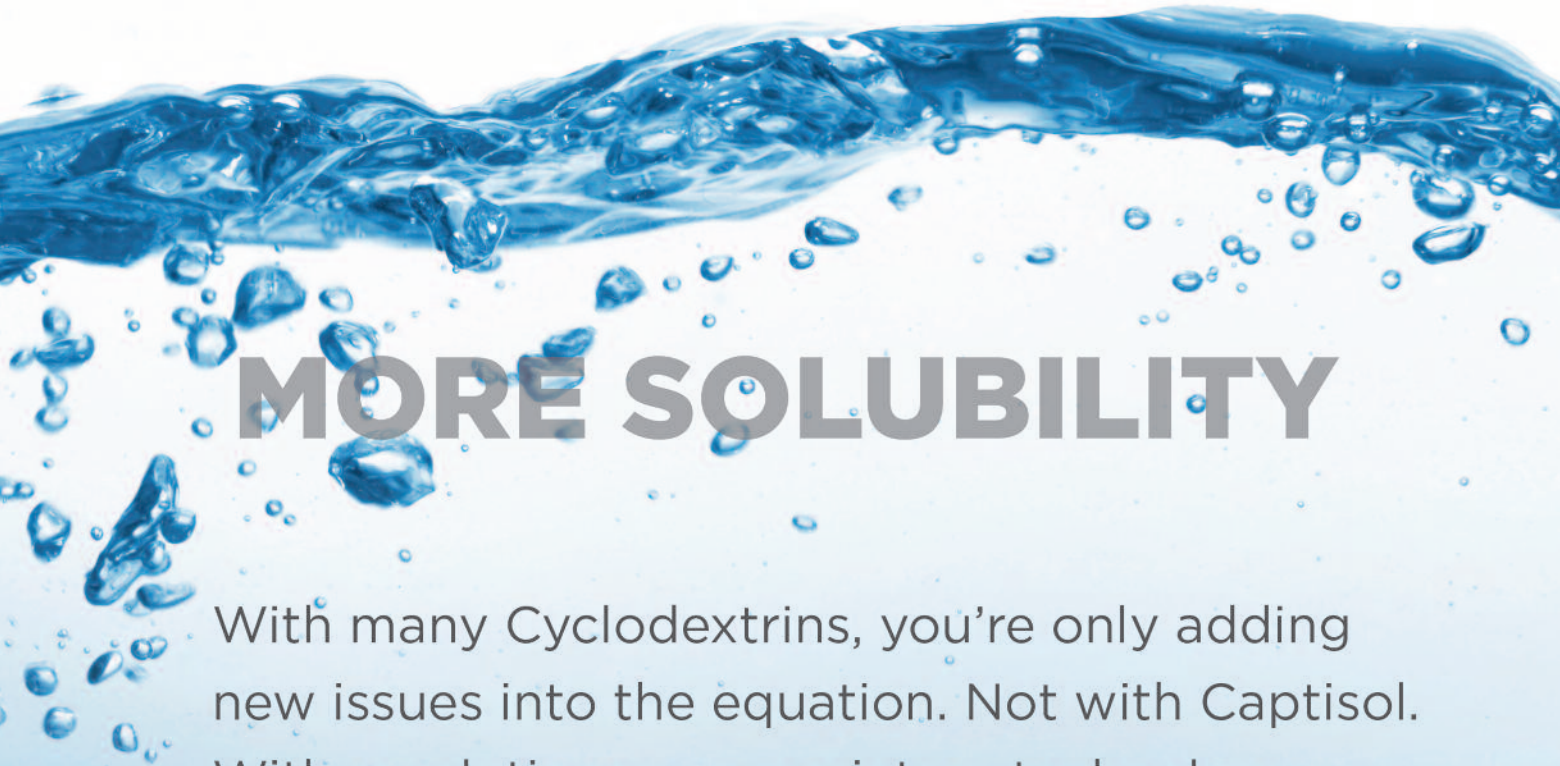
ENGINEERING MEDICINES TO LIFE

Capsugel®

DRIVING PULMONARY DELIVERY FORWARD

Capsugel's unique capabilities and expertise in product design and particle engineering can prove crucial for enhancing the bioperformance of inhaled therapeutics. We design and optimize formulations using an array of specialized tools, including micronization, spray dry processing and nanocrystal technologies. Combined with formulation expertise for both small and large molecules, specialized DPI capsules, and finished product manufacturing capabilities to commercial scale, Capsugel is the right partner to bring your product from concept to market.

MORE TECHNOLOGY.



MORE SOLUBILITY

With many Cyclodextrins, you're only adding new issues into the equation. Not with Captisol. With revolutionary, proprietary technology, Captisol is rationally engineered to significantly improve solubility, stability, bioavailability and dosing of active pharmaceutical ingredients.

SOLVE PROBLEMS WITH CAPTISOL SOLUTIONS.

CAPTISOL®
A Ligand TECHNOLOGY

CAPTISOL.com

Drug Development & Delivery

April 2017 Vol 17 No 3

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

CORDENPHARMA

EXPERTS TAKING CARE

FULL-SERVICE CDMO > FOR A GLOBAL MARKET

CordenPharma is your full-service CDMO for a global market. Through our network of technology platforms and cGMP facilities for the manufacture of APIs, Drug Products and pharmaceutical Packing, CordenPharma experts translate your complex processes, ideas and projects at any stage of development into high-value products.

www.cordenpharma.com

TECHNOLOGY PLATFORMS

- PEPTIDES, OLIGONUCLEOTIDES, LIPIDS & CARBOHYDRATES
- HIGHLY POTENT & ONCOLOGY
- INJECTABLES
- SMALL MOLECULES
- ANTIBIOTICS

VISIT US AT

OutsourcedPharma
Boston > Booth 121
April 26–27, Boston, MA

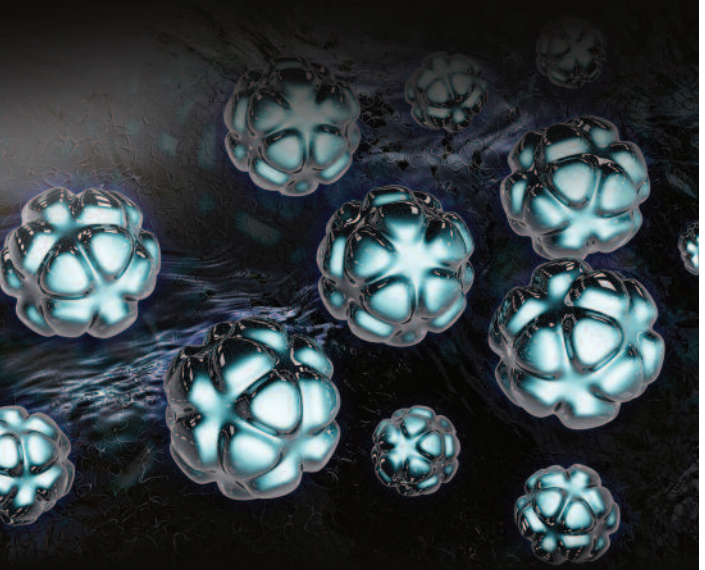
Tides 2017 > Booth 302
April 30–May 3, San Diego, CA

Innovation Networking
May 4–5, Parsippany, NJ

CPhI North America > Booth 2160
May 16–18, Philadelphia, PA

Cellular Microencapsulation

"Although type 1 diabetes can begin at an early age, as our population ages, chronic and age-related conditions, such as various cancers, are increasing in frequency. Until now, managing them has been the only medical option. Drug or treatment delivery that employs microencapsulation, one of many promising developments in the field of regenerative medicine, offers not only treatments but also potential cures for a wide variety of maladies, from diabetes to cancers to neurological problems."



p.26

Table of Contents

Leading the way with integrated containment and delivery solutions

West
By your side for a healthier world™

SMARTDOSE®

PRECISE. RELIABLE. READY TO GO.

FDA Approved

- The first combination product that incorporates the SmartDose platform technology was recently approved by the US Food and Drug Administration (FDA)
- Thousands of doses have been administered using the SmartDose platform
- Proven engineering, manufacturing and regulatory expertise to support your needs

Wearable Injector

- Subcutaneous self-administration
- Ability to deliver high volume and high viscosity drug products

Patient-Centric

- User-centered design
- Connectivity to a variety of software platforms
- Able to link with adherence solutions
- Onboarding and training solutions available

Flexible Technology

- Address a variety of delivery times through adaptable, pre-programmable technology
- Maximize patient comfort through pre-programmable delivery times

West Pharmaceutical Services, Inc. | 530 Herman O. West Drive, Exton, PA 19341 | www.smartdose.com | North America +1 800-345-9800 | Europe +49 2403 7960 | Asia Pacific +65 6860 5879

West seeks partners for its SmartDose platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company.

For more information visit www.westpharma.com

#10224 0317

Formulation Development & Manufacturing

"Despite significant focus on biologics, small molecules still represent more than half of the total market. For instance, tyrosine kinase inhibitors and poly ADP-ribose polymerase inhibitors are among the small-molecule targeted therapies. These products are also driving the need for oral solid dose highly potent manufacturing. Some estimates predict oral oncolytics to be 25%-30% of the market, double the figures from 10 years ago."

Table of Contents

FILLED WITH EXPERTISE

Richard's Unique Expertise Meets Your Demanding Biologics Fill and Finish Needs.

Richard is one of the many manufacturing technicians at Althea that deliver the highest quality drug product to our clients on a daily basis. At Althea, we are aware of the innate properties of biologics and we have a strong understanding of how fill finish processes and equipment can affect quality and stability. Our technical experience, combined with an impeccable regulatory track record, enable Richard and the Althea team to meet your most demanding biologics fill and finish needs.

Learn more. Visit AltheaCMO.com

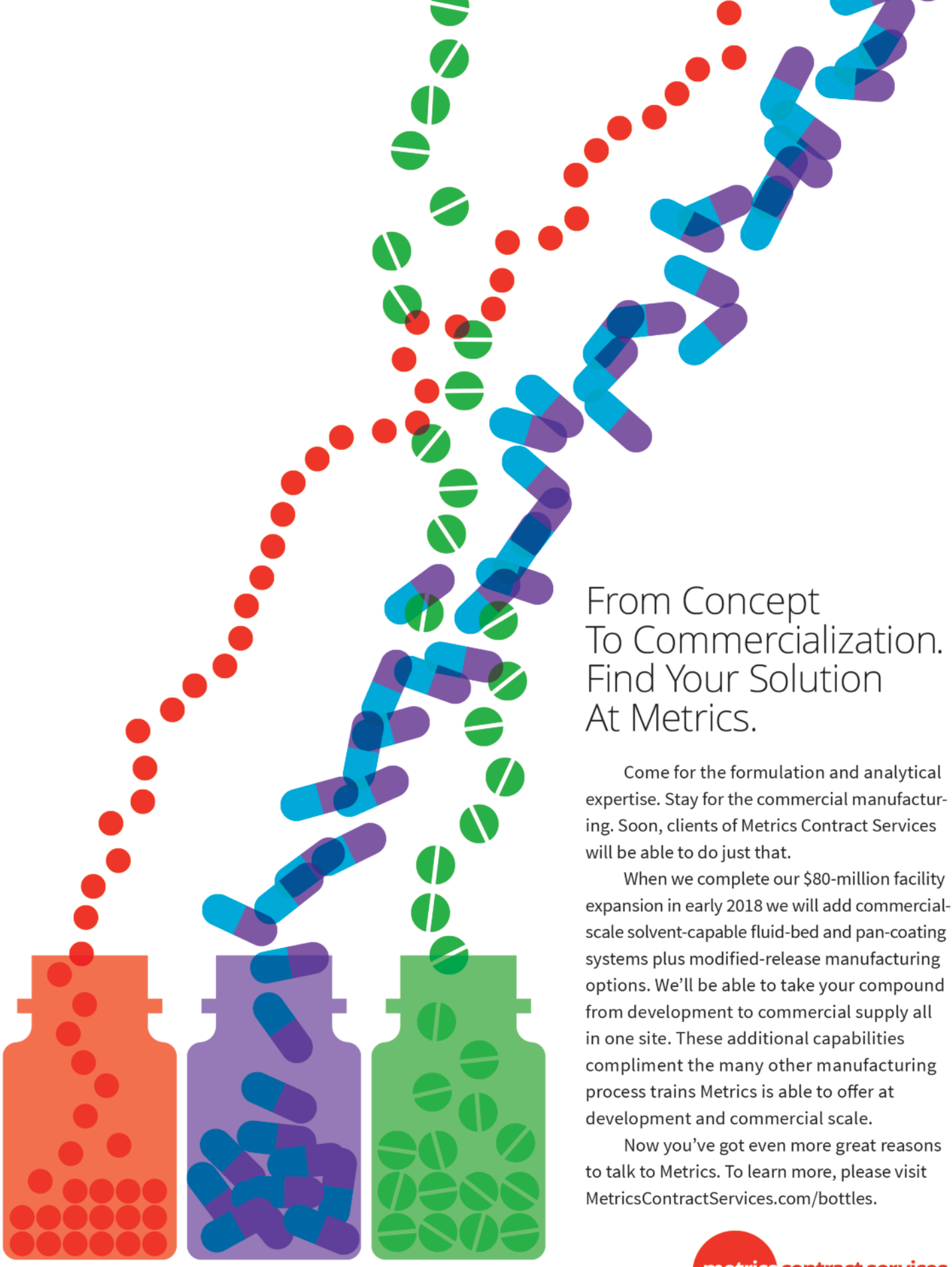
ALTHEA | THE POWER TO MAKE®

A MEMBER OF THE AJINOMOTO GROUP

11040 Roselle Street, San Diego, CA 92121 | 1.888.425.8432 | 858.882.0123

PROCESS DEVELOPMENT • DRUG SUBSTANCE MANUFACTURING • DRUG PRODUCT MANUFACTURING • ANALYTICS • HPAPI & ADC

The Editorial Advisory Board



From Concept To Commercialization. Find Your Solution At Metrics.

Come for the formulation and analytical expertise. Stay for the commercial manufacturing. Soon, clients of Metrics Contract Services will be able to do just that.

When we complete our $80-million facility expansion in early 2018 we will add commercial-scale solvent-capable fluid-bed and pan-coating systems plus modified-release manufacturing options. We'll be able to take your compound from development to commercial supply all in one site. These additional capabilities compliment the many other manufacturing process trains Metrics is able to offer at development and commercial scale.

Now you've got even more great reasons to talk to Metrics. To learn more, please visit MetricsContractServices.com/bottles.

metrics contract services

Pharmaceutical Development • Analytical Testing • Commercial Manufacturing

Greenville, NC, 252-752-3800, www.metricscontractservices.com

ZIOPHARM Announces Successful End-of-Phase II Meeting With FDA

ZIOPHARM Oncology, Inc. recently announced the receipt of positive guidance from an End-of-Phase II meeting with the US FDA for its lead gene therapy product candidate, Ad-RTS-hIL-12 plus orally administered veledimex (V), to harness and control IL-12 production for the investigational treatment of recurrent glioblastoma (GBM), an aggressive form of brain cancer with few treatment options.

"We are pleased with our productive interactions with the FDA and the valuable direction we received at the End-of-Phase II meeting. Our controlled approach utilizing the RheoSwitch platform represents the next-generation of gene therapy enabling IL-12 to be regulated through a transcriptional switch. We appreciate the FDA's feedback surrounding our plans to advance Ad-RTS-hIL-12-based therapy to a pivotal registration study for patients with recurrent GBM in 2017 and look forward to establishing the benefits of this novel therapeutic approach," said Laurence Cooper, MD, PhD, Chief Executive Officer of ZIOPHARM.

"The median overall survival remains very promising and continues to be greater than 12 months for these heavily compromised patients," added Francois Lebel, MD, Chief Medical Officer of ZIOPHARM. "After positive meetings with both FDA and European regulators, the company is working toward finalization of the optimal pathway for our pivotal trial for Ad-RTS-hIL-12 + veledimex."

In collaboration with its investigators and regulators, the company is currently assessing its protocol design options for the pivotal trial, including the potential for a single-arm study comparing Ad-RTS-hIL-12 + V to historical controls in a subpopulation of patients with recurrent GBM. Details of the pivotal Phase III trial will be made available following evaluation and completion of discussions with clinical advisors as well as regulators.

GBM represents approximately 15% of all primary brain tumors and remains a high unmet clinical need that affects roughly 74,000 people worldwide annually. GBM is an aggressive form of brain cancer with recurrence rates near 90%, and prognosis for patients is poor with treatment often combining multiple approaches including surgery, radiation, and chemotherapy. Median overall survival (OS) is only 6 to 7 months in patients who have experienced multiple recurrences, and the prognosis is even poorer for patients who have failed temozolomide and bevacizumab, or equivalent salvage chemotherapy with a median OS of approximately 3 to 5 months.

ZIOPHARM Oncology is employing novel gene expression, control, and cell technologies to deliver safe, effective, and scalable cell- and viral-based therapies for the treatment of cancer and graft-versus-host-disease. The company's immuno-oncology programs, in collaboration with Intrexon Corporation and the MD Anderson Cancer Center, include chimeric antigen receptor T cell (CAR-T) and other adoptive cell-based approaches that use non-viral gene transfer methods for broad scalability. The company is advancing programs in multiple stages of development with Intrexon Corporation's RTS technology, a switch to turn on and off, and precisely modulate, gene expression to improve therapeutic index.

Calithera to Receive $12-Million Milestone Payment From Incyte

Calithera Biosciences, Inc. recently announced it has achieved pharmacokinetic and pharmacodynamic goals for CB-1158 which, under its agreement with Incyte Corporation, entitles the company to receive a $12-million payment from Incyte.

"We are very excited to achieve this early milestone under our collaboration with Incyte as CB-1158 has demonstrated the desired pharmacologic activity in humans, with a corresponding elevation in plasma arginine levels to those achieved with efficacious doses in preclinical models of cancer. Through our collaboration with Incyte, we will continue to evaluate the role of arginase inhibition in the immuno-oncology setting with CB-1158, and we expect to present additional clinical data mid-2017," said Susan Molineaux, President and Chief Executive Officer of Calithera Biosciences.

In January 2017, Calithera and Incyte established a global collaboration and license agreement for the research, development, and commercialization of Calithera's first-in-class, small molecule arginase inhibitor CB-1158 in hematology and oncology. CB-1158 is currently being studied in a monotherapy dose escalation clinical trial and also in combination with anti-PD-1 therapy. Additional studies are expected to evaluate CB-1158 in combination with other immuno-oncology agents.

Arginase is an enzyme produced by immunosuppressive myeloid cells, including myeloid-derived suppressor cells (MDSCs) and neutrophils, which prevents T-cell and natural killer (NK) cell activation in tumors. Arginase exerts its immunosuppressive effect by depleting the amino acid arginine in the tumor microenvironment, which subsequently prevents activation and proliferation of the immune system's cytotoxic T-cells and NK-cells. Inhibition of arginase activity reverses this immunosuppressive block and restores T-cell function. In preclinical models, arginase inhibition has been shown to enhance anti-tumor immunity and inhibit tumor growth.

Calithera Biosciences, Inc. is a clinical-stage pharmaceutical company focused on discovering and developing novel small molecule drugs directed against tumor metabolism and tumor immunology targets for the treatment of cancer. Calithera's lead product candidate, CB-839, is a potent, selective, reversible, and orally bioavailable inhibitor of glutaminase. CB-839 takes advantage of the pronounced dependency many cancers have on the nutrient glutamine for growth and survival. It is currently being evaluated in Phase I/II clinical trials in combination with standard of care agents. CB-1158 is a first-in-class immuno-oncology metabolic checkpoint inhibitor targeting arginase, a critical immunosuppressive enzyme responsible for T-cell suppression by myeloid-derived suppressor cells. Arginase depletes arginine, a nutrient that is critical for the activation, growth and survival of the body's cancer-fighting immune cells, known as cytotoxic T-cells. CB-1158 is currently in a Phase I clinical trial. Calithera is headquartered in South San Francisco, CA. For more information, visit www.calithera.com.

Apeiron Biologics Receives Green Light for Marketing Approval

Apeiron Biologics recently announced the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending the approval of dinutuximab beta (ch14.18/CHO; APN311) for immunotherapy of high-risk neuroblastoma.

Dinutuximab beta has been generated and profiled by European academic institutions originating at the Clinical Cancer Research Institute in Vienna (St. Anna Children's Hospital), initiated by Prof. Ladenstein. The development was extended to multiple clinical trials across Europe and abroad, performed by the SIOPEN neuroblastoma study group and the German group at the University Children's Hospital Greifswald led by Prof. Lode. In 2011, Apeiron and SIOPEN joined forces and Apeiron took over the lead for commercialization. More than 1,000 patients have been treated, and the results served as basis for Marketing Authorization Application (MAA) in the EU in 2015. In September 2016, EUSA Pharma acquired an exclusive license to the global commercial rights to dinutuximab beta.

Based on the CHMP's opinion published on March 24), the European Commission within 2 months will issue a formal decision on the approval of dinutuximab beta, which is indicated for use in children aged 12 months and older with high-risk neuroblastoma who have achieved a complete or partial response to prior therapy and those with a history of relapsed or refractory disease.

"We are delighted with the CHMP positive opinion for approval of dinutuximab beta for immunotherapy of high-risk neuroblastoma, an area of significant unmet medical need," said Dr. Hans Loibner, Apeiron's Chief Executive Officer. "We regard this as key step in the successful development of our company."

"This was a complex but highly rewarding collaborative effort over several years between academic institutions and support companies), coordinated and led by a dedicated group at Apeiron," added Dr. Oliver Mutschlechner, Apeiron's VP Regulatory Affairs.

"This positive CHMP opinion is an important milestone for EUSA as we work to bring dinutuximab beta to children suffering from the high-risk form of the devastating disease, neuroblastoma. Following this positive opinion in Europe, as next step we plan to submit dinutuximab beta for approval in the United States," said Lee Morley, EUSA Pharma's Chief Executive Officer.

Neuroblastoma is an orphan oncology condition with significant unmet medical need. It accounts for up to 10% of childhood tumors and affects approximately 1,200 children in the EU5 and US each year. Dinutuximab beta is currently used across Europe and abroad under a managed access scheme and is included in a number of treatment protocols for high-risk neuroblastoma.

Dinutuximab beta (ch14.18/CHO; APN311) is a mouse-human chimeric anti-GD2 monoclonal antibody produced in a state-of-the art process in Chinese Hamster Ovary (CHO) cells that significantly improves event-free and overall survival in children with high-risk neuroblastoma, with a favorable safety profile compared to other antibody-based neuroblastoma immunotherapies. Dinutuximab beta forms an important part of treatment regimens for high-risk neuroblastoma. Its features offer the potential for further development in other malignancies to expand its current role. Dinutuximab beta has orphan drug designation for neuroblastoma treatment in the US and EU, and EUSA plans to file the product for approval in the US in 2017.

Apeiron is a private biotech company based in Vienna, Austria, engaged in innovative projects in immuno-oncology. Its most advanced project, APN311 (ch14.18/CHO, dinutuximab beta), a MAA has been submitted to the EMA in May 2015, the CHMP adopted a positive opinion on March 24, 2017. APN301 is a humanized anti-GD2 antibody-IL-2 fusion protein in clinical stage. Focus of clinical development presently is on melanoma by unique intratumoral application. A broad program is pursued to develop therapies aiming at stimulation of the immune system via novel checkpoint blockade mechanisms to fight cancer: APN411 is a preclinical project for orally available drugs, performed together with Sanofi and Evotec. APN401 is a novel individual cellular immunotherapy targeting the intracellular checkpoint cbl-b. A Phase I study in advanced cancer patients was successfully performed in the US (Wake Forest University, NC), Phase II is in planning stage.For more information visit www.apeiron-biologics.com.

Opiant Pharmaceuticals Announces Results of PET Study of Nasal Spray

Opiant Pharmaceuticals, Inc. recently announced the completion of a study evaluating two doses of a naloxone nasal spray on the occupation of brain opiate receptors using PET imaging. The study was commissioned by the National Institute for Health and Welfare of Finland and was carried out by researchers at Clinical Research Services Turku (CRST) and Turku PET Centre, a leading international PET center.

The purpose of the study was to determine the extent and time course of brain mu opioid receptor occupancy following the administration of two doses (4 mg and 2 mg) in healthy volunteers. Mu opioid receptors mediate the actions of both prescription opioids and illicit drugs such as heroin, and high occupancy of these receptors by opioids is responsible for the clinical symptoms of overdose, such as respiratory depression that can often be fatal.

"We are highly encouraged by the results of this study, which support the potential advantages of the 4-mg dose of nasal naloxone," said Dr. Roger Crystal, Chief Executive Officer of Opiant. "With the precision of PET imaging, we were able to assess for the first time the mu opioid receptor occupancy of naloxone in many different regions of the brain. The study demonstrates that the 4-mg dose results in a greater and more rapid occupancy of mu opioid receptors than the lower 2-mg dose. With increasing numbers of opioid overdose deaths due to more potent opioids, such as fentanyl and carfentanil, this higher dose may be even more relevant. This study attests to Opiant's ongoing commitment to innovation in the addiction and opioid overdose space, and these data may have relevance to our broader pipeline."

This study was the first use of PET imaging to assess nasal naloxone on opioid receptor dynamics. The 4-mg dose resulted in a larger degree of receptor occupancy in the brain than the 2-mg, and receptor occupancy was also achieved more rapidly with the 4-mg dose. Nasal naloxone was safe and well tolerated at both dose levels. Opiant participated in the funding of this study with an unrestricted academic grant. The study results will soon be independently published in a scientific journal.

Opiant Pharmaceuticals, Inc., is a specialty pharmaceutical company developing pharmacological treatments for addictions and eating disorders. The National Institute on Drug Abuse (NIDA), a division of the National Institutes of Health (NIH), describes these disorders as chronic relapsing brain diseases, which burden society at both the individual and community levels. With its innovative opioid antagonist nasal delivery technology, Opiant is positioned to become a leader in these treatment markets. Its first product, NARCAN Nasal Spray, is approved for marketing in the US and Canada by the company's partner, Adapt Pharma Limited. For more information, visit www.opiant.com.

Cellect Announces Successful First Cancer Patient Stem Cell Transplant

Cellect Biotechnology Ltd. recently announced that the first stem cell transplant procedure has been successfully performed using its ApoGraft technology in the company's Phase I/II clinical trial in a blood cancer patient.

Up to 50% of stem cell transplant procedures, such as bone marrow transplants, result in life-threatening rejection disease, known as Graft-versus-Host-Disease (GvHD). Cellect's ApoGraft technology is aiming to turn stem cell transplants into a simple, safe, and cost-effective process, reducing the associated severe side effects, such as rejection and many other risks.

"After 15 years of research, this is the first time we have used our technology on a cancer patient suffering from life-threatening conditions. It is a first good step on a road that we hope will lead to stem cell-based regenerative medicine becoming a safe commodity treatment at every hospital in the world," said Dr. Shai Yarkoni, Cellect's CEO.

Based on the successful transplantation results, the independent Data and Safety Monitoring Board (DSMB) approved the enrollment of two additional patients for ApoGraft treatment to complete the first study cohort as planned.

Despite improved prophylactic regimens, acute GvHD disease still occurs in 25% to 50% of recipients of allogeneic stem cell transplantation. The incidence of GvHD in recipients of allogeneic stem cells transplantation is increasing due to the increased number of allogeneic transplantations survivors, older recipient age, use of alternative donor grafts, and use of peripheral blood stem cells. GvHD accounts for 15% of deaths after allogeneic stem cell transplantation and is considered the leading cause of non-relapse mortality after allogeneic stem cell transplantation.

The ApoGraft01 study (Clinicaltrails.gov identifier: NCT02828878), is an open label, staggered four-cohort, Phase I/II, safety and proof-of-concept study of ApoGraft process in the prevention of acute GvHD. The study, which will enroll 12 patients, aims to evaluate the safety, tolerability, and efficacy of the ApoGraft process in patients suffering from hematological malignancies undergoing allogeneic stem cell transplantation from a matched related donor.

Cellect Biotechnology has developed a breakthrough technology for the isolation of stem cells from any given tissue that aims to improve a variety of stem cell applications. The company's technology is expected to provide pharma companies, medical research centers, and hospitals with the tools to rapidly isolate stem cells in quantity and quality that will allow stem cell-related treatments and procedures. Cellect's technology is applicable to a wide variety of stem cell-related treatments in regenerative medicine and that current clinical trials are aimed at the cancer treatment of bone marrow transplantations. For more information, visit www.cellect.co.

Neothetics Announces Last Subject Enrolled in Phase II Trial

Neothetics, Inc. recently announced completion of subject enrollment for its Phase II proof-of-concept trial, LIPO-202-CL-31, for the reduction of submental subcutaneous fat.

"We are excited to announce the conclusion of enrollment in our first trial with LIPO-202 for the reduction of submental fat. We are encouraged by the strong investigator interest and rapid subject enrollment," said Kim Kamdar, PhD, a member of Neothetics' Operating Committee and Board of Directors. "This is a robust clinical trial design based on both our significant experience with LIPO-202 and extensive feedback from key opinion leaders and investigators on submental fat reduction."

LIPO-202-CL-31 is a multi-center, randomized, double-blind, placebo-controlled Phase II proof-of-concept trial to evaluate the safety and efficacy of two doses of LIPO-202 versus placebo for the reduction of submental bulging due to subcutaneous fat. The trial has enrolled approximately 150 subjects at 12 sites across the US. Subjects will be randomized 1:1:1 and receive up to either 0.3 mcg, or 3.0 mcg dose of LIPO-202, or placebo. Subjects will receive up to 30 subcutaneous injections of LIPO-202 or placebo once a week for 8 weeks and follow up visits to assess safety and efficacy will occur 1 week and 4 weeks post the last treatment.

The study endpoints include both safety and efficacy measurements. Efficacy measures will assess improvement in the subject's submental region as evaluated by both the patient and clinician, covering overall subject satisfaction and evaluation of submental fat thickness by calipers. The company expects to report top-line data in June 2017.

LIPO-202 is a proprietary, first-in-class injectable formulation of the well-known long-acting ß2-adrenergic receptor agonist, salmeterol xinafoate, which is an active ingredient of FDA-approved inhaled products such as SEREVENT DISKUS, ADVAIR HFA, and ADVAIR DISKUS. Our studies suggest that salmeterol xinafoate activates ß2 -adrenergic receptors on fat cells, triggering the body's natural process of metabolizing stored triglycerides (fat) resulting in a reduction in size and volume of the fat cells in the treatment area without damage of nearby tissues. LIPO-202 has an extremely favorable safety profile, with little to no adverse post treatment effects. LIPO-202 is being evaluated for the reduction of submental fat commonly referred to as a double-chin.

Neothetics is a San Diego-based clinical-stage specialty pharmaceutical company developing therapeutics for the aesthetic market. Our initial focus is on localized fat reduction and body contouring. Our lead product candidate, LIPO-202, is a first-in-class injectable formulation of the long-acting ß2-adrenergic receptor agonist, salmeterol xinafoate, which is an active ingredient in the US FDA approved inhaled products SEREVENT DISKUS, ADVAIR HFA, and ADVAIR DISKUS. For more information, visit www.neothetics.com.

ONLY THREE WEEKS LEFT

REGISTER NOW!

Drug-DevConference.com

2ND ANNUAL

Innovation Networking Summit &

TABLE-TOP EXHIBITION

MAY 4-5, 2017

HILTON HOTEL

PARSIPPANY, NJ

For more details and to reserve your table-top and sponsorship, contact:

John Kiesewetter
T: 541-338-0022
E: jkiesewetter@drug-dev.com

Ralph Vitaro
T: 973-263-5476
E: rvitaro@drug-dev.com

Drug Development®
& Delivery

CONFERENCE SPEAKERS

Keynote Speaker
Donald Sebastian, PhD
President & CEO, New Jersey Innovation Institute & Senior Vice President, Technology & Business Development, New Jersey Institute of Technology

Keith Horspool, PhD
VP of Material & Analytical Sciences, Boehringer Ingelheim

Jeffrey Bacha, MBA
Chairman & CEO, DelMar Pharmaceuticals

Finn Bauer, PhD
Director of R&D & Head of Solid Formulations, MilliporeSigma

Scott Brown, MS
Executive Director, Device Development, Merck

Nila Das, PhD
Senior Research Investigator, Bristol-Myers Squibb

Martin Eastgate, PhD
Director, Chemical & Synthetic Development, Bristol-Myers Squibb

Mahen Gundecha, MBA
Head of Alliance Management, Sandoz Inc. (Novartis Group)

Tom Johnson
Senior Director, Life Science Solutions, Exostar

Conrad F. Mir
President & CEO, Calmare Therapeutics

Kurt Nielsen, PhD
President, Lupin

Peter Pekos, MSc
President & CEO, Dalton Pharma Services

Mathias Romacker, MA
Senior Director, Device Strategy, Pfizer

Laurie Smaldone, MD
COO & CSO, NDA Group AB

Ronald L. Smith, PhD
Scientific Assoc. VP, Pharmaceutical Sciences, Merck Research Laboratories

Cornell Stamoran, PhD
Vice President, Strategy for Catalent, Inc., & Co-Chair, Catalent Applied Drug Delivery Institute

Lilli Zakarija MSME, MBA
Co-Founder/ President, EdgeOne Medical

GOLD SPONSORS

ADARE Pharmaceuticals™

Catalent APPLIED DRUG DELIVERY INSTITUTE

Catalent®

GATTEFOSSÉ

PharmaCircle™ The Information You Need At Your Fingertips

SGW | Pharma MARKETING

SILVER SPONSORS

LifeSciencePR

BRONZE SPONSORS

CRODA

EVONIK POWER TO CREATE

ASCENDIA PHARMA

TABLE-TOP EXHIBITORS

Adare Pharmaceuticals
Ascendia Pharma
Captisol
Catalent
CordenPharma
Croda
DPT Labs
EdgeOne Medical
EG-GILERO
Eutech Scientific Services
Evonik
Fareva
Fuji Chemical Industries
Gattefosse
InKemia Green Chemicals
LifeSciencePR
Lyophilization Technology, Inc.
Metrics Contract Services
MonoSol Rx
Nitto Avecia Pharma Services
Pace Analytical Services
PharmaCircle
SGS Life Sciences
SGW Pharma B2B
Siegfried
SiO2 Medical Products
SMI
Transdermal Specialties
UPM Pharmaceuticals
URSATEC
Yonwood Packaging
Yukon Medical

CONTRACT MANUFACTURING

Flexibility in an Evolving Market

By: Matthew Moorcroft, PhD

INTRODUCTION

In the fast-moving pharmaceutical industry, change is the only constant. To keep up with market developments, small molecule manufacturers must first understand the trends. The past 2 decades have been a period of major change in the pharmaceutical manufacturing sector. The end of the traditional blockbuster model, the patent cliff, the burgeoning biologics sector, and the shift to niche patient populations as the move begins toward more targeted therapies, have all contributed to the drive for change among drug makers, and in the contract manufacturing sector in particular.

Determining how to react to these trends and create a business model that is flexible enough to adjust to whatever the next few years may bring is one of the challenges faced by many global contract manufacturing organizations (CMOs), and Cambrex was no exception.

REGULATORY APPROVAL

As a first step, the company undertook an extensive research program throughout 2016 to assess what was happening in the small molecule market, particularly in terms of volume demand, FDA approvals, and product lifecycles. Once it had established the dominant trends, Cambrex could tailor its investment strategy to give it the necessary flexibility in both capacity and capabilities.

The first thing the research showed was that although biologics may be making the headlines, small molecule drugs continue to form the backbone of the pharmaceutical industry. Not only is innovation in the small molecule sector at an all-time high, the level of US FDA approvals for new molecular entities (NMEs) in 2015 was at its highest since 1999 (Figure 1). And of the 45 NMEs approved this past year, by far the largest proportion (33 out of 45) were small molecules, while only 12 were biologics. Furthermore, there are more small molecules in every phase of drug development than at any point in the past 15 years (Figure 2).

Analysis of the 2015 NME approvals clearly showed an increasing focus on rare diseases: 21 of the novel drugs approved (just under half of the total) were for rare or orphan diseases that affect 200,000 or fewer Americans and for which there are limited or no treatment options available. Whereas once small molecule development was looking for the classic blockbuster, used to treat millions of patients with chronic conditions, the versatility of the products allow the model to evolve toward more targeted therapies. This is especially relevant for orphan indications, or in the specific oncology sectors. The data generated by the Cambrex research indicates how significant this change has been. In 1999-2000, the average patient population targeted was 13 million, representing indications such as obesity, diabetes, conjunctivitis, gastro-esophageal reflux disease (GERD), and hyperlipidemia, but by 2014/15, this had fallen to just 6 million as the drugs are being used for conditions such as multiple myeloma, cystic fibrosis, and thyroid cancer.

VOLUME DEMAND

To track the evolution of APIs by volume demand, Cambrex looked at the 408 small molecule drugs launched in the US throughout the past 15 years. An interval period of 5 years was chosen to give enough data points for a quantitative study. To avoid any annual anomalies, the data from two consecutive years was combined, giving a final data set of 209 small molecules

"Taking all these factors into account, there are still plenty of growth opportunities in the small molecule market, but key to contract manufacturers remaining competitive will be the ability to be flexible enough to be able to produce APIs in a range from kilograms to hundreds of metric tons to satisfy the wide variety of demand from customers. The trend highlighted in the research toward concentration of average volume requirements actually is a great opportunity for CMOs, as service companies are used to handling multiple customer projects with varying volume requirements and chemistries."

(around half the total number of approvals), which the company believed would be sufficient to identify any emerging trends.

The study was also limited to the US market to exclude potentially misleading data arising from differences in disease prevalence/epidemiology in more populous markets, such as India and China, that can result in large uptake of some products. However, it can be assumed that volumes for the five major European markets and Japan would be similar to those recorded in the US. It is also important to note that the research looked at NCEs (New Chemical Entities) only, and did not take into account reformulations, Abbreviated New Drug Applications (ANDAs), or line extensions.

The trend in volume evolution showed a clear decline in the numbers of NCEs with volume ranges above 10 metric tons (mt) and below 10 kg, while those reaching their peak volumes in the ranges 10 kg to 1 mt and 1 to 10 mt are stable or increasing. Of the 27 NCEs launched in 2014/2015, 12 are forecast to reach volumes of 1 mt at their peak. The research

FIGURE 1

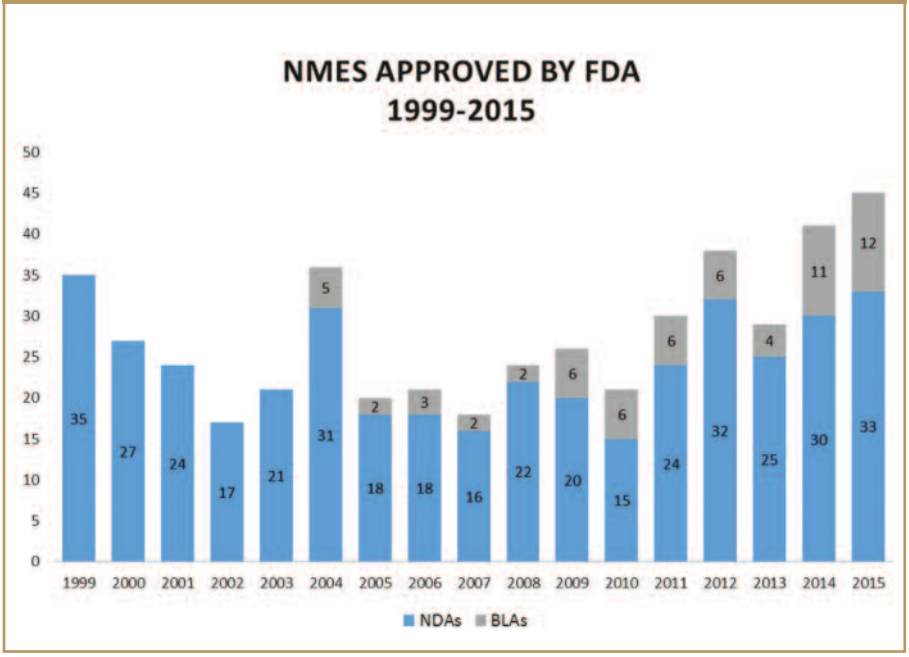


FIGURE 2

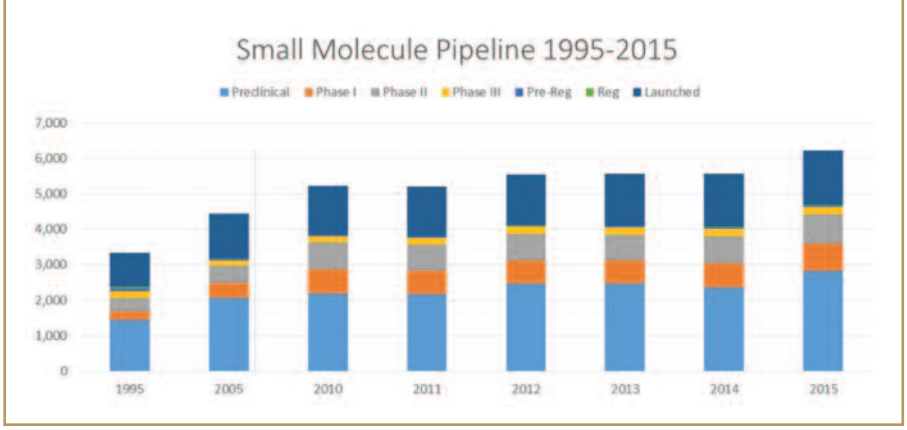
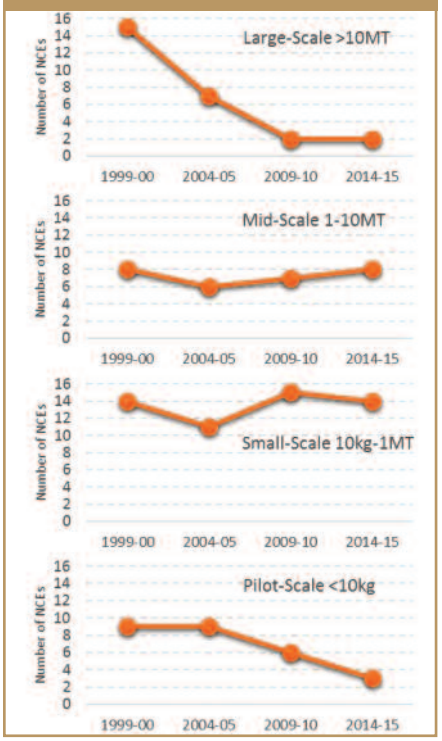


FIGURE 3



shows that the spread of volumes is becoming narrower and that there is more clustering around the middle volume range now compared with 15 years ago (Figure 3).

One conclusion that can be drawn from this is that the peak volume demand (at least within the US market) seems to be in the range of 1 to a few tens of metric tons of API. The numbers of drugs with a peak demand greater than 100 mt has dropped, as have those below 10 kg.

However, it would be wrong to assume that a small patient population means a small annual volume of the API; sometimes it means exactly the opposite. Small molecule drugs that are in the region of 1- to 10-mt volumes can be blockbusters in the sense they can command in excess of $500 million in sales. This is especially true for drugs used in oncology indications, where the pricing per pill is orders of magnitude higher than drugs used in more chronic indications, such as hyperlipidemia and diabetes. Similarly, not all orphan drugs are low volumes; some are taken in high doses and consumed daily.

TRENDS IN PATIENT DOSE REQUIREMENTS

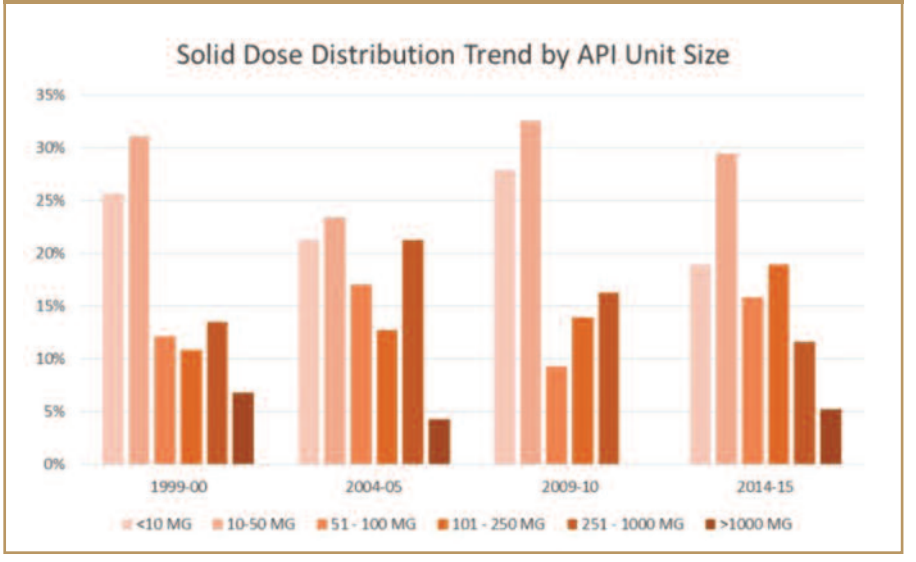
There were no findings from the research that showed significant changes in the potency of the APIs nor in the size of the dosage. The majority of drugs are still in the 1 to 100 g per patient per year range, although there was a slight increase in the number of lower dose NCEs below 1 g per patient per year, according to the study (Figure 4). The data does not show any real trends in reduced dosages to patients, and although often spoken about in the industry, the trend to targeted medicines does not show up in the data yet with respect to the dose that patients are actually taking.

Similarly, there has also been little change in tablet unit sizes: 10 to 50 mg continues to be the most frequent dose size, although the 50- to 250-mg size range is gradually increasing in popularity. This highlights one of the reasons for the continued prevalence of small molecule drugs is their ability to be taken orally, which is clearly the preferred method of administration from the patient's point of view.

Patient centricity and compliance are currently important areas of focus in the pharmaceutical industry, and the flexibility and versatility of small molecules can be key to both. Drug formulators have a long familiarity with small molecules (since the 19th century), and technologies developed over the many years have afforded a number of dosage types from which patients can benefit, such as tablets, capsules, and inhalation through devices. Recent developments in oral dosing allow for innovations, such as delayed, controlled, and modified release to ensure that patients' ease of consumption is maximized. Drug developers are acutely aware that the lesser the burden on the patient to take a dose, the greater the chance of ongoing compliance.

For biologic-based drug development, although progress is being made with product development, there is some way to go before products can have the same "ease of use." Currently, the route of administration is typically injection, and products need to be kept refrigerated, which adds logistical considerations for both shipping and storage. The cost of dose manufacture for biological medicine is still disproportionately high with respect to small molecules, not just for the API itself, but the costs of vials and prefilled syringes

FIGURE 4



dwarf those of blister packs and pill bottles used to package small molecule-based products.

OPPORTUNITIES FOR CMO GROWTH

Taking all these factors into account, there are still plenty of growth opportunities in the small molecule market, but key to contract manufacturers remaining competitive will be the ability to be flexible enough to be able to produce APIs in a range from kilograms to hundreds of metric tons to satisfy the wide variety of demand from customers. The trend highlighted in the research toward concentration of average volume requirements actually is a great opportunity for CMOs, as service companies are used to handling multiple customer projects with varying volume requirements and chemistries. Unlike captive manufacturing at big pharma, CMOs have to be flexible and adapt to ever-changing demands of the marketplace.

The trend for pharmaceutical companies to close captive API facilities is poised to continue due to historic reliance on blockbusters, which were 100-mt products and now lack the correct scale of manufacturing capabilities. CMOs will continue to see more outsourcing opportunities as they are better placed to manufacture the coming pipeline of small molecule APIs. However, it will become more important for CMOs to offer a range of manufacturing options to cover the life cycle of the drug on the market – from introduction to maturity, as well as the option to manufacture key late-stage intermediates and starting materials, should security of supply or regulation be a prerequisite of customer demand.

The reformulation of existing drugs is also a key growth area that deserves particular attention. Supply of APIs into repurposed or reformulated drugs requires CMOs to act quickly and responsively. This may be the rapid supply of small volumes of API for product development and launch purposes or the technical and regulatory expertise to support the customer during registration and commercial supply.

Throughout the past 5 years, Cambrex has invested $150 million in small molecule capacity and infrastructure. By evaluating the market demands through this research, it has expanded its large-scale API facility in Charles City, IA, and is also planning to add 300-gallon and 500-gallon reactors to its small-scale plant in 2017.

This investment closely follows the trend seen in the industry and by establishing the right capacity and capabilities demanded by the market, allows the company to handle a variety of projects and chemistries while having the ability to be flexible in the supply chain and counter any volume fluctuations.

Flexible assets with the ability to manufacture multiple products at multiple scales in the same facility is crucial to win customer projects from the increasing commercial and clinical pipeline. Continually investing in manufacturing capacity is critical to plan ahead for the next generation of small molecule drugs. Pilot-scale, mid-scale, all the way to large-scale to cover APIs and advanced intermediates will enable security of supply and cover the fluctuations in demand.

In the constantly changing world, a CMO must be flexible to match these changes. Far from the rise of biologics and monoclonal antibody therapies signing the death knell to small molecule medicines, the market is flourishing. In oncology, pioneering drug classes, such as protein kinase inhibitors, have revitalized the existence and importance to modern medicine, and the challenge is to predict the changes and have the ability to respond. ◆

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

BIOGRAPHY

Dr. Matthew Moorcroft is the Vice President of Global Marketing and Communications for Cambrex. Prior to joining Cambrex, he worked for Lonza and held a number of roles, including Head of Global Marketing, VP Generics and Biosimilars, and Head of Strategy, Pharmaceuticals and Biologics. After gaining experience in the custom development and manufacturing business, he developed models for biosimilars and generic drug products. He has 15 years of commercial and scientific experience in the pharmaceutical, biotechnology, and chemical industry covering both innovative and generic medicines. Dr. Moorcroft earned his PhD in Chemistry from the University of Oxford.

Pharma Business Intelligence & Prospecting At Your Fingertips

PharmaCircle Business Class Solutions deliver a comprehensive view into drug, biologics and combination product development and innovation worldwide, and a combined scientific, regulatory and commercial perspective of the competitive landscape.

Business Class Professional

With an intuitive search interface and easy-to-use business prospecting and watch list apps, Professional examines more than 140,000 pipeline programs and marketed products and the business portfolios and transactions of 15,000 public and private companies.

Professional's integrated view and in depth analysis of pipelines and products includes:

- Molecule pharmacokinetic data and physical chemical structures
- Development summaries
- Insights into clinical trials worldwide
- Administration and dosing details
- Formulation and excipient information
- Global regulatory data with links to filings and monographs
- Patent exclusivity information
- Key product sales and forecasts
- Strategic partnerships and deals by country/region.

Business Class Elite

Elite builds upon and expands the core content and capabilities of Professional, adding more easy-to-use apps and search capabilities.

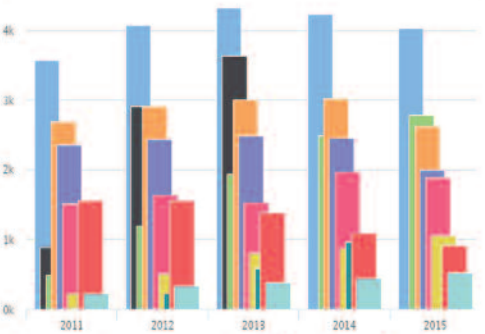
Elite's powerful research tools include: Patent exclusivity tracker for USA and EU, API source/manufacturer finder, Paragraph IV filing and case tracker, and drug delivery technology analyzer, which compares 5,800+ drug delivery technologies and delivery devices in more than 300 drug delivery categories.

Elite also incorporates management details and contact information into the company capabilities profiles, and adds four apps that streamline research and provide instant analytics: TimeScape, Reconnaissance, Label Comparison and Merge Simulator.

Elite equips you with the layered analytics and actionable insights needed to make strategic business decisions.

BUSINESS APPLICATIONS

- Research new therapeutic areas, and identify market gaps
- Uncover emerging science and evaluate new and promising technologies
- Target potential partners in a specific country or region, and screen potential licensing and investment opportunities
- Review comparable deals, acquisitions and financings
- Find and compare contract manufacturers and other outsourced services
- Assess competitive landscapes around an indication and research competitor pipelines
- Track generics and biosimilars, and identify Rx to OTC switch opportunities



Dynamic, customizable data display

Easy to Use Apps

Prospector
Search on industry sector, indication, route, most advanced phase and molecule/API type. Find companies within the search criteria in any region of the world by drawing a circle around the location of interest. Click for detailed information on companies within the selected search parameters and geographic area.

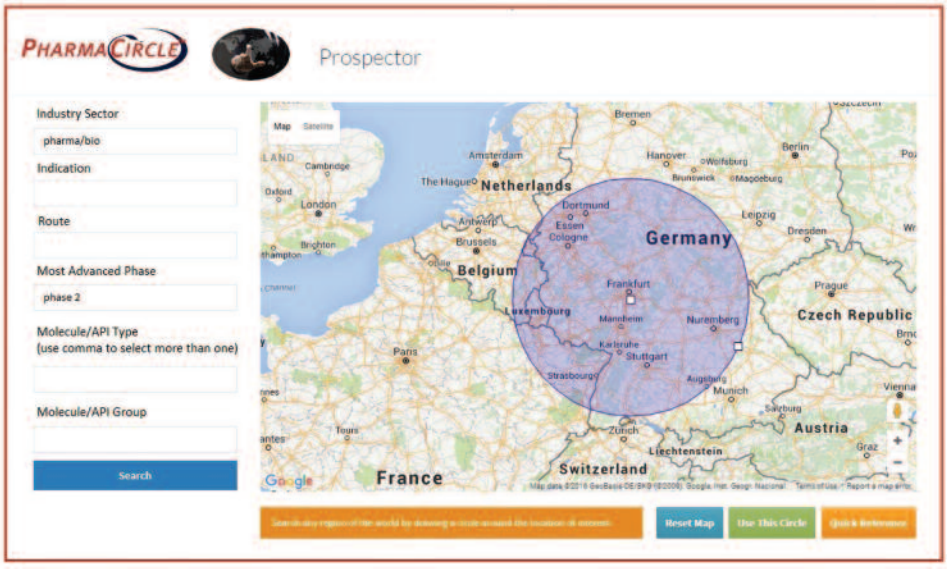
Spyglass
Create your personal watch list and track up to 30 indications, companies and products. Receive latest industry news with daily updates on your selections.

Timescape
View development timeline. Chart phase dates by region/country. Export chart as an image file and underlying data to an Excel spreadsheet.

Label Comparison
Compare current and previous versions of the label for the same product with changes highlighted, and view labels for different products side-by-side. Export comparisons to Excel and PDF.

Reconnaissance
Quick view and instant analytics on the competitive landscape around an indication, competitive intensity within an indication, and competitor pipelines across indications. Chart drugs and biologics by owner companies, highest development status within the indication, mechanism type, NME/ Generic/OTC, route, and dosage form. Programs/products are linked to development summaries.

Merge Simulator
Create a virtual company incorporating global assets of two business entities. Overlay and analyze pipeline/product, technology, operations, financial, deals and investments details to assist with initial due diligence on prospective acquisitions and mergers.



Be the first to recognize new opportunities and seize the competitive advantage.

Content & Capabilities	Professional	Elite
Keyword Search Across All Datasets	✓	✓
Company Capabilities Profiles	✓	✓
Products & Pipeline Intelligence	✓	✓
Trial Landscape Explorer	✓	✓
Key Product Sales & Forecasts	✓	✓
Strategic Deals Analyzer	✓	✓
Venture Capital Investment Tracker	✓	✓
News & Insights	✓	✓
Prospector - Business Prospecting Application	✓	✓
Spyglass - Watch List Application	✓	✓
Drug Delivery Technology Analyzer		✓
Patent Exclusivity Trackers		✓
Paragraph IV Filings & Case Tracker		✓
API Source/Manufacturer Locator		✓
Drug Label Comparison Tools		✓
Timescape - Development Timeline Application		✓
Reconnaissance - Competitive Landscape Analysis		✓
Merge Simulator - Acquistion & Merger Simulation		✓
Management Details & Contact Information		✓

PHARMACIRCLE™

For more information or to schedule a demo:
Encinitas, CA 92024
T: +1.800.439.5130
E: contact@pharmacircle.com
www.pharmacircle.com

CELLULAR MICROENCAPSULATION

Cell Encapsulation for Drug Delivery & Disease Treatment

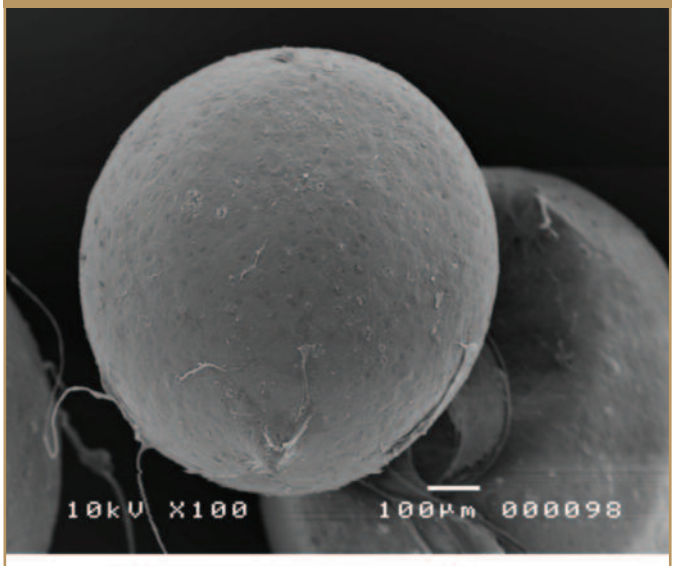
By: Gerald W. Crabtree, PhD

INTRODUCTION

Regenerative medicine is not all that new; tissue and organ transplants have been around for decades. However, the Mayo Clinic has said, "But advances in developmental and cell biology, immunology, and other fields have unlocked new opportunities to refine existing regenerative therapies and develop novel ones." It has also stated, "Regenerative medicine is a game-changing area of medicine with the potential to fully heal damaged tissues and organs, offering solutions and hope for people who have conditions that today are beyond repair. Within regenerative medicine, some of the most noteworthy developments are coming from the area of tissue engineering. Combining cells with scaffolding materials to generate functional tissue constructs describes tissue engineering at its most basic level."

The rejection of transplanted tissue has been one of the major stumbling blocks in the treatment of many chronic and age-related conditions. Immune suppressors are one avenue for dealing with rejection, but tissue engineering by way of cellular microencapsulation offers a different, and likely better, path.

FIGURE 1



Microscopic View of a Single Cell-in-a-Box® Capsule

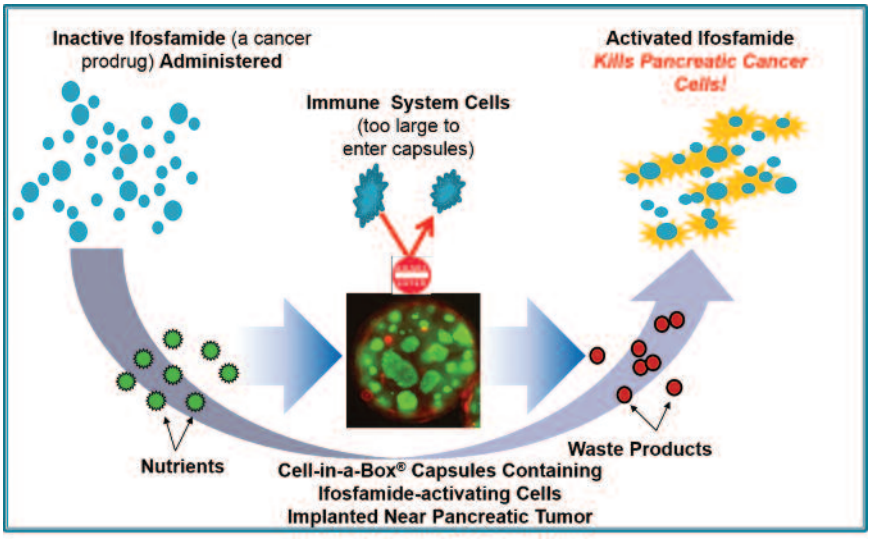
MICROENCAPSULATION: THE NEW FRONTIER IN DRUG DELIVERY

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. Most microcapsules have diameters between a few micrometers and a few millimeters. The idea was based on natural subcellular organelles, which contain proteins, growth factors, or enzymes. The first suggestion was made in 1964 that encapsulation could be used to replace cells or cell products lost due to genetic defects.

The polymeric material essentially creates a wall that protects the encapsulated cells from rejection by the body's immune system. This means that an organ could be grown in a bioreactor to replace a diseased organ, and the risk of rejection would be virtually eliminated. Harvard Apparatus has already grown and implanted an artificial trachea grown from the patient's own stem cells.

At the same time, microencapsulation offers various significant advantages as a drug or treatment delivery system, including: (i) an effective protection of the encapsulated active agent or encapsulated live cells against degradation or destruction by the immune system, (ii) the possibility to accurately control the release rate of an incorporated drug over periods of hours to months, (iii) an easy administration (compared to alternative parenteral controlled release dosage forms, such as macro-sized implants), and (iv) the provision of desired, pre-programmed drug-release profiles which match the therapeutic needs of the patient.

FIGURE 2



NEUROLOGICAL DISORDERS: MICROENCAPSULATION OVERCOMES THE BLOOD-BRAIN BARRIER

One of the areas in which this technology is most useful is in the treatment of neurological disorders. Many drugs to treat maladies of the brain and central nervous system are administered orally, but they cannot cross the blood-brain barrier readily. One of the main advantages of cell microencapsulation is for the treatment of neurological disorders in which some drugs have potential therapeutic possibilities, such as growth factors or peptides, however, only at low and constant concentrations. These microcapsules implants are able to secrete only the drug required by the damaged tissue, because the implants with microencapsulated cell are formed by live cells.

Bringing this technology out of the lab and into clinics is now underway. Living Cell Technologies Limited (LCT) is an Australasian biotechnology company, and its lead product, NTCELL®, is an alginate-coated capsule containing clusters of neonatal porcine choroid plexus cells. Following transplantation, NTCELL functions as a biological factory producing nerve growth factors to promote new central nervous system growth and repair disease induced nerve degeneration.

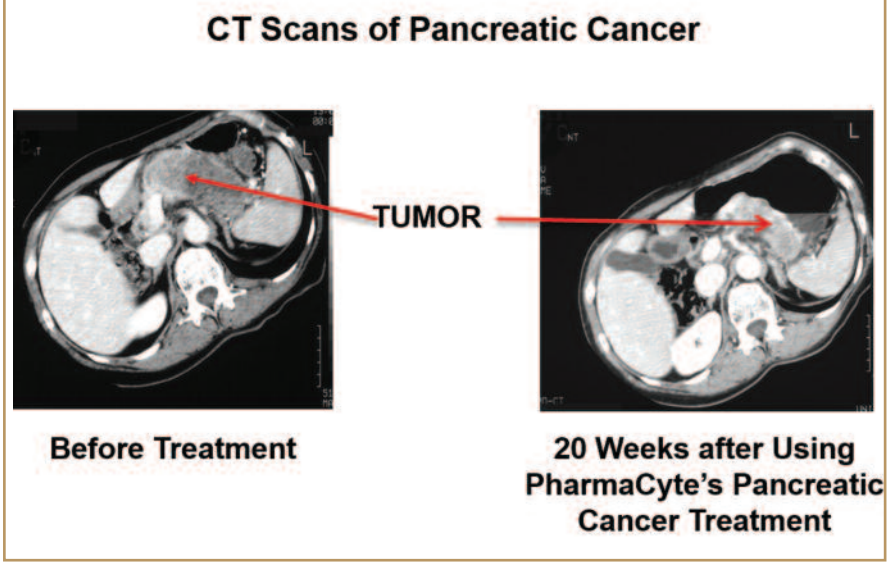
NTCELL is in Phase I/IIa clinical trial in New Zealand for the treatment of Parkinson's disease. It has the potential to be used in a number of other central nervous system indications, such as Huntington's, Alzheimer's, and motor neuron diseases.

DIABETES: ENCAPSULATED CELLS MAY BE THE PATH TO A CURE

Another condition microencapsulation can address is type 1 diabetes. In type 1 diabetics, their insulin-producing cells (beta islet cells of the pancreas) have been permanently destroyed by an autoimmune disease.

According to Novo Nordisk's 2014 annual report, there are two things needed to cure this condition: (i) a means to trigger stem cells to make unlimited quantities of insulin-producing cells, and (ii) a means to

FIGURE 3



encapsulate these cells so that the immune system doesn't destroy them while at the same time allowing the encapsulated cells to respond to glucose levels by producing insulin.

A research team at Harvard has found a solution to the first issue, and Astra Zeneca has recently linked up with that team to continue the work.

Living Cell Technologies has formed a joint venture with Japan's Otsuka Pharmaceutical Factory to develop LCT's DIABECELL. This product consists of encapsulated islet cells that produce insulin and that are sourced from pathogen-free pigs.

Another entrant into the type 1 diabetes cure sweepstakes is San Diego-based ViaCyte. In concert with the Juvenile Diabetes Research Foundation (JDRF), the leading research and advocacy organization funding type 1 diabetes research, ViaCyte filed an IND application with the FDA in the summer of 2014. ViaCyte wants to initiate a Phase I/II diabetes clinical trial to evaluate the safety and efficacy of its VC-01™ product candidate, a stem cell-derived, encapsulated cell replacement therapy. In a related development, ViaCyte submitted a Medical Device Master File (called MAF) to the FDA in support of the Encaptra® drug delivery system, the device component of the VC-01 product candidate.

A third contestant is the Cell-in-a-Box® live cell encapsulation technology. The Cell-in-a-Box technology is unique among all forms of cell encapsulation technologies. It differs from the types of live cell encapsulation used by others because those technologies use materials such as agarose (a derivative of seaweed) or chitosan. Cell-in-a-Box capsules are made largely of cellulose, a bio-inert material in the human body. Cellulose offers a number of advantages over other encapsulation materials because it is derived from a naturally occurring plant-sourced polymer that is relatively easy to obtain at reproducible quality and is free from impurities. The Cell-in-a-Box capsules are much more robust than capsules made from other materials and do not break down even after long periods in the body. Indeed, Cell-in-a-Box capsules have been shown in clinical trials to last for at least 2 years without being damaged or without causing damage to tissues that are nearby. Also, Cell-in-a-Box capsules can be stored frozen for years and when thawed, the cells inside the capsules are recovered with about 95% viability – a hint as to their having a long shelf-life.

PharmaCyte has obtained an exclusive worldwide license to use Melligen cells in developing a treatment for insulin-dependent diabetes. This line of cells was developed by Professor Ann Simpson and her colleagues at the University of Technology, Sydney (UTS) in Australia. Melligen cells were shown to be effective in reversing the diabetic condition in grossly diabetic mice whose immune systems were suppressed. PharmaCyte intends to use Melligen cells encapsulated using the Cell-in-a-Box technology in the pursuit of a treatment for insulin-dependent diabetes.

PANCREATIC CANCER: CELL-IN-A-BOX A NEW TREATMENT ALTERNATIVE

PharmaCyte is also looking into the treatment of pancreatic cancer using Cell-in-a-Box-encapsulated genetically engineered live cells designed to convert the well-known cancer prodrug ifosfamide into its cancer-killing form using only one-third of the "normal" dose of the chemotherapy drug. PharmaCyte Biotech's pancreatic cancer treatment was given the Orphan Drug designation by the FDA in December 2014. A similar designation has been granted by the European Medicines Agency (EMA) in the EU.

In a Phase I/II clinical trial, 14 elderly and very sick patients with advanced, inoperable pancreatic cancer were treated at a single study site in Germany with the combination of Cell-in-a-Box plus two courses of low dose ifosfamide. A single implantation (near the pancreatic cancer) of 300 Cell-in-a-Box capsules containing ifosfamide-activating cells was given to each patient.

The results from this trial showed that the Cell-in-a-Box plus low-dose ifosfamide combination increased the average lifespan of patients from about 5.7 months for gemcitabine (the "gold standard" for the treatment of pancreatic cancer at the time) to about 11 months with the combination therapy, and doubled the percentage of 1-year survivors from 18% to 36%, without any treatment-related side effects. The major conclusion was that the combination of Cell-in-a-Box plus low-dose ifosfamide was a safe and effective treatment for patients with advanced, inoperable pancreatic cancer.

A Phase II trial done with the Cell-in-a-Box plus ifosfamide combination was also a single-arm study. Here, 13 patients were treated at four study sites in Europe, but in this trial, the dose of ifosfamide was doubled to two-thirds of normal to see if there would be improved anti-tumor effects. Again, two courses of ifosfamide were given. The main conclusion was that the combination of Cell-in-a-Box plus one-third the normal dose of ifosfamide was the most appropriate combination to use in all future clinical trials for a safe and effective treatment of advanced, inoperable pancreatic cancer.

Now, a Phase IIb clinical trial is being planned for the U.S., Europe and Australia. This trial will be a multi-site, randomized study in which PharmaCyte Biotech's pancreatic cancer treatment will be compared head-to-head as a consolidation therapy with a currently used chemotherapy plus radiation treatment in patients with inoperable, nonmetastatic disease whose tumors have ceased to respond to 4-6 months of treatment with the current "gold standard" for pancreatic cancer treatment, the combination of the drugs gemcitabine plus Abraxane®. The two consilidation therapies will be compared for effects on patient survival, tumor size, whether they can change inoperable tumors into operable ones, on pain associated with the cancer, and on the safety of the treatments and their effects patients' quality of life.

A major problem associated with the development of abdominal cancers is their production of malignant ascites fluid that accumulates significantly in the abdominal cavity. This fluid contains cancer cells which can "seed" and form new tumors. Also, as ascites fluid accumulates, the abdomen becomes distended and painful and this accumulation can be lifethreatening.

As such, it must be removed on a periodic basis - a painful and costly procedure. A series of preclinical studies in mice bearing abdominal cancers is being done now in the US for PharmaCyte Biotech by Translational Drug Development (TD2) to determine the parameters under which PharmaCyte's pancreatic cancer treatment can slow the production and accumulation of this ascites fluid. Once these parameters are established, a Phase I/II clinical trial will be conducted by Translational Drug Development (TD2).

SUMMARY

Although type 1 diabetes can begin at an early age, as our population ages, chronic and age-related conditions, such as various cancers, are increasing in frequency. Until now, managing them has been the only medical option. Drug or treatment delivery that employs microencapsulation, one of many promising developments in the field of regenerative medicine, offers not only treatments but also potential cures for a wide variety of maladies, from diabetes to cancers to neurological problems. ◆

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

BIOGRAPHY

Dr. Gerald W. Crabtree is PharmaCyte's Biotech's Chief Operating Officer. For much of his 45-year career, he has been active in cancer research and cancer drug development. Since 1985, Dr. Crabtree has been involved with various biopharmaceutical and biotech companies, where he has participated in or coordinated the development of multiple drug candidates, assisted in the preparation of clinical protocols and investigator brochures, participated in clinical trials, prepared drug monographs, co-authored research and review articles, and served as project manager for development of a major oncologic agent. He is a member of the American Society of Clinical Oncology and the American Association for Cancer Research and is also is a past member of research grant review committees for the National Institute of Health and the American Cancer Society. Dr. Crabtree established and directed, from inception, a department that monitored and coordinated the development of oncologic and immunologic drugs from initial discovery through regulatory approval in a major pharmaceutical company and served as project manager for the development of the anticancer agent, Taxol®. He earned his PhD in Biochemistry from the University of Alberta, Edmonton, Alberta, Canada in 1970 and has published over 80 articles in peer-reviewed journals.

ELECTRONIC TONGUE INSTRUMENTATION

Improving the Palatability of User-Friendly Dosage Forms Using an Electronic Tongue

By: Detlev Haack, PhD

INTRODUCTION

User-friendly solid oral dosage forms are popular with patients and offer many benefits over conventional tablets. Rather than being swallowed whole, these dosage forms can be chewed, sucked, or dissolved in water and consumed as a drink. This makes them easy to swallow, even for children, elderly people, and those with dysphagia. As they tend to spend longer in the mouth and are tasted more thoroughly than traditional tablets and capsules, a pleasant taste is one of the key attributes that determines acceptability and patient compliance. However, even conventional tablets, which are normally considered by formulation scientists to taste neutral, are often perceived to taste unpleasant by patients and consumers, creating a potential barrier to uptake.

Given the inherently bitter taste of most active pharmaceutical ingredients (APIs), the challenge for the pharmaceutical industry is how best to use flavorings and taste-masking technologies to make oral dosage forms taste pleasant. Furthermore, the process of assessing taste raises both practical and ethical issues when relying on human tasting panels. One exciting alternative that is starting to gain traction in the industry is assessment via an electronic tongue to detect and analyze all the compounds responsible for taste within a sample. Electronic tongue instruments, methods, and data can be qualified and validated making this approach particularly suitable for pharmaceuticals. Electronic tongue analysis also means that taste evaluations can be incorporated into both stability studies and formulation development, potentially reducing drug development lead times and reducing costs accordingly.

THE CHALLENGE WITH CONVENTIONAL TABLETS & CAPSULES

While tablets and capsules remain a popular dosage form within the pharmaceutical industry, it is frequently underestimated how many people struggle to swallow them. In research recently conducted, it was discovered that more than half of the 2,000 people surveyed reported difficulty swallowing tablets and capsules, with around a third of these people describing the problem as serious.[1] There were a variety of reasons given for this with the most commonly cited being that tablets/capsules are too big,

FIGURE 1

User-friendly solid oral dosage forms offer an alternative to conventional tablets and capsules as they are easy to swallow – even for people with dysphagia and regardless of age. In addition, they are convenient and integrate well into daily routines.

Quality > It's how you get from formulation to the pharmacy.

With an outstanding compliance history, the CMC team at Frontage has extensive experience in:

- Formulation Development for IND, NDA & ANDA
- Analytical Method Development/Validation & Sample Testing
- GMP Manufacturing of CTM (Oral Solids, Topical, Sterile)
- Commercial Product Release & Stability Testing

FRONTAGE
YOUR DRUG DEVELOPMENT PARTNER

CONTACT US TODAY: sales@frontagelab.com
OR VISIT US AT: frontagelab.com

TABLE 1

ADVANTAGES	DISADVANTAGES
Ethical & Safe No pharmaceuticals are consumed by humans until the clinical trial stage.	**Liquids Only** Solids must be dissolved prior to measurement.
Sensitive At least as sensitive as human taste.	**Sample Preparation** Samples (including reference and calibration samples) need preparation.
Scientific Approach Formulation scientists can replace a trial-and-error approach with a more efficient, effective scientific approach. Knowledge of complementary excipients and flavorings remains an important aspect though.	**Taste Only** The electric tongue makes no assessment of smell or texture, which humans often find difficult to distinguish from taste.
Consistent Data Electric tongue data is consistent and objective, unlike that generated from human tasting panels.	**Data Analysis** Expertise required.
Validated Approach The ability to qualify and validate the instrument, method, and data makes the electric tongue ideally suited to the highly regulated pharmaceutical industry.	**Maintenance** The electric tongue requires ongoing maintenance, including replacement and recalibration of taste sensors.
Rapid Data is available much quicker than via a human tasting panel, which must receive regulatory approval to proceed. A range of drug formulations can be screened in a short time.	**Upfront Cost** Requires an investment in instrumentation, plus training.
Access All Patients By removing the ethical challenges associated with human tasting panels, data can be provided for previously hard-to-reach patient groups, such as children and elderly people.	
High Throughput Analysis Could soon be possible.	

Advantages and disadvantages of using an electronic tongue for formulation development.

that they become stuck in the throat, or that they have an unpleasant taste or odor. Those surveyed did not experience similar difficulties swallowing foodstuffs or liquids.

When faced with tablets or capsules to swallow, people used various techniques to ease the process. 32% tried breaking them, 17% crushed them and dissolved them in water, and 9% chewed them. This is concerning as these approaches have the potential to negatively affect release profile, bioavailability, and medical efficacy of the API. Most worrying of all is that 8% simply resorted to not taking their medication at all.

Some people described other challenges with tablets and capsules. Older people often found it hard to press them out of the blister packaging, while younger people highlighted the inconvenience of taking them "on the go." User-friendly solid oral dosage forms offer a great alternative that overcome these issues (Figure 1).

Taste has been shown to be an important factor in how people perceive medications, and a negative experience can impact patient compliance. This is true for user-friendly dosage forms that spend longer in the mouth but also for conventional tablets and capsules. Thus, in order to develop a successful product, the pharmaceutical industry must ensure it tastes good.

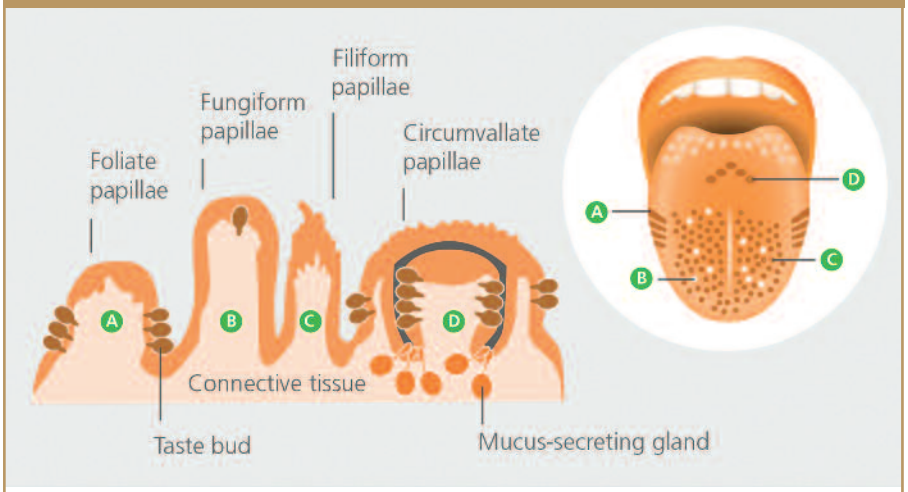
THE HUMAN SENSE OF TASTE

Humans rely on a combination of appearance, smell, taste, and texture to form a sensory impression for anything we consume. This is as true for pharmaceuticals as it is for foodstuffs. User-friendly dosage forms spend longer in the mouth than conventional tablets, making the sensory impression even more crucial.

For the pharmaceutical industry, appearance and texture are relatively easy to measure using various analytical instruments, as well as forming an assessment "by eye." All this can be achieved without unnecessary exposure to drug substances. Smell and taste, on the other hand, are harder to assess. A "sniff test" works well for some low-risk pharmaceuticals but would be unsafe for more toxic APIs. Likewise, it's possible, but far from ideal, to ask people to assess the taste of pharmaceuticals.

The human (or indeed mammalian) sense of taste is of evolutionary importance, and it's no exaggeration to say that it can be a life-saver. Toxic substances will often taste bitter while sweetness is usually associated with safe food and energy. Substances dissolved in the mouth stimulate taste receptors. These are located within taste buds, which are found around small structures called gustatory papillae on the tongue, soft palate, upper esophagus, and

FIGURE 2



The tongue comprises three types of papillae containing taste buds, plus the filiform papillae that only detects the texture of food.

epiglottis. We each have around 10,000 taste buds, although these are known to reduce in number as we age, particularly beyond the age of 50. As a result, we taste things differently later in life.

There are five basic tastes that are detected by taste receptors: saltiness, sweetness, bitterness, sourness, and umami (which corresponds to the flavor of glutamates and means "delicious" in Japanese and is often described as "savory" in English).

The complexity of how we taste creates an impression that lasts a long time (compared with smells, which are experienced for only a short time but are remembered well). This impression allows us to differentiate between initial taste and aftertaste – wine tasting notes provide a perfect example of this. Aftertastes may differ considerably from the flavor of what was consumed, and pose a particular problem for medicines.

We know that people taste differently and thus have different taste experiences of the same substance. This is not only caused by age but can also have genetic underpinnings. Based on an individual's taste bud profile, some tasters may be more sensitive to particular flavors than others. Likewise, some medicines and medical conditions themselves can alter people's perception of taste.

PALATABILITY OF PHARMACEUTICALS

To ensure both market success and patient adherence, it is important that all oral pharmaceuticals – but particularly user-friendly dosage forms – taste pleasant. When developing a new foodstuff, it's perfectly acceptable to ask a panel of people to assess the taste. For pharmaceuticals, however, this is more problematic. There are obvious ethical issues concerning giving a healthy person a medicine unnecessarily – particularly if it could have adverse pharmacological effects. Furthermore, molecules that are not FDA approved cannot be tested. A human tasting panel, therefore, can essentially be considered as a clinical trial and requires approval by an ethics committee. This makes it challenging and time-consuming to test even a few substances.

Most APIs have a particularly bitter taste, posing an additional obstacle for the pharmaceutical industry. Taste-masking must be employed – through addition of sugars, sweeteners, and flavorings, or use of coating technologies – to overcome this. At HERMES PHARMA, we know that formulation scientists experienced in taste-masking are able to make recommendations for which flavors to combine with which APIs and are also aware of which flavors are preferred in different geographies. For example, sour-tasting APIs are best taste-masked with flavors that include sour components. This means that citrus and berry flavors are suitable options but banana, caramel, and peach are not. Such expertise reduces the time spent in product development compared with a solely trial-and-error approach.

Today, the most common approach to assessing the relative success of taste-masking efforts, together with other organoleptic properties, is via a human tasting panel that records its immediate impressions on a questionnaire. However, due to inter-individual variability, sensory impressions are subjective – regardless of how well you train and calibrate your tasting panel. Most often, it is only possible to use healthy adults, which can also affect the results. Pediatric and geriatric patients are only permitted in exceptional circumstances.

ELECTRONIC TONGUE INSTRUMENTATION

A new instrument that is slowly starting to be adopted by formulation development scientists is the electronic tongue. This technology has been designed around how we know humans taste substances and can rapidly detect all the organic and inorganic compounds responsible for taste in a liquid sample. Sweet, salty, sour, bitter, and umami tastes are all tested for, together with metallic, pungent, or astringent components, and a taste profile is built accordingly.

Unlike human tasting panels, the data

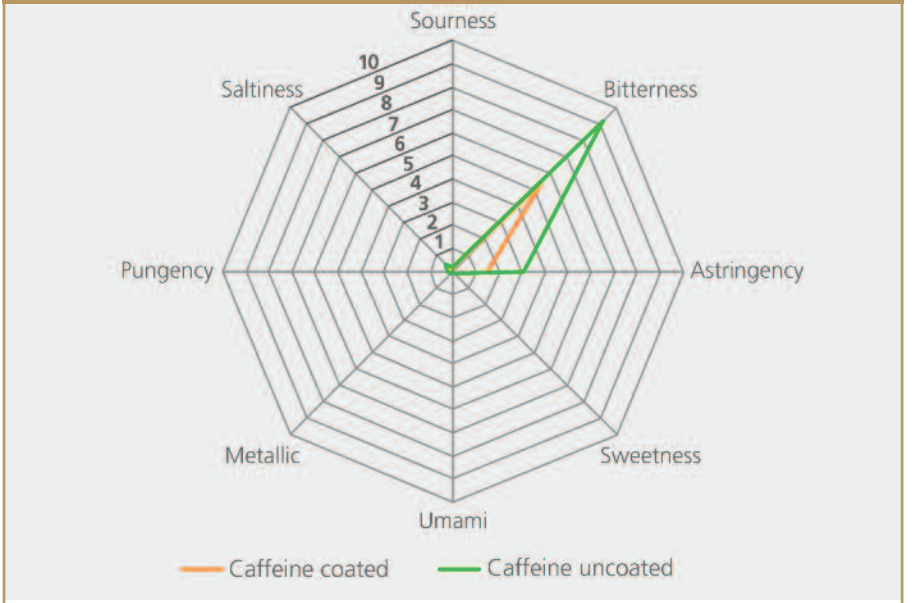
generated by the electronic tongue is not subjective, making it possible to reliably compare taste profiles between different substances. In fact, the instruments, methods, and data can all be qualified and validated, making this approach ideal for the pharmaceutical industry.

A significant advantage of the electronic tongue is that many more samples can be tested than via human tasting panels. This affords the opportunity to incorporate taste testing into stability studies and in formulation development – both of which can help reduce the time a product spends in development and minimize costs.

There are two electronic tongue instruments available on the market, although a number of academic institutions have developed their own versions for research purposes. Manufacturers are currently working on automating the electronic tongue and optimizing it for high throughput testing.[2]

Electronic tongues comprise three key components: sensory array, signal emitting/receiving equipment, and pattern recognition. The detection thresholds of the sensors are similar to, if not better than, those of human taste receptors. And the information provided by each sensor is complementary, with the combination of all the sensors providing a unique fingerprint for the substance being tested. Electronic signals, like those transmitted by nerves in humans, are generated as potentiometric variations. The electronic tongue uses statistical software as the "brain" to interpret and translate the sensor data into taste patterns. This can be done either graphically or mathematically. A graphical approach sees the signal from the various sensors added in a radar plot (Figure 3). Comparisons between different plots/substances are made visually. Alternatively, data from the different sensors can be processed mathematically via a multi-variate data analysis, such as principle component analysis (Figure 4). Either way, it is possible to compare the whole profile or just selected factors, such as sourness or bitterness, between different samples.

FIGURE 3



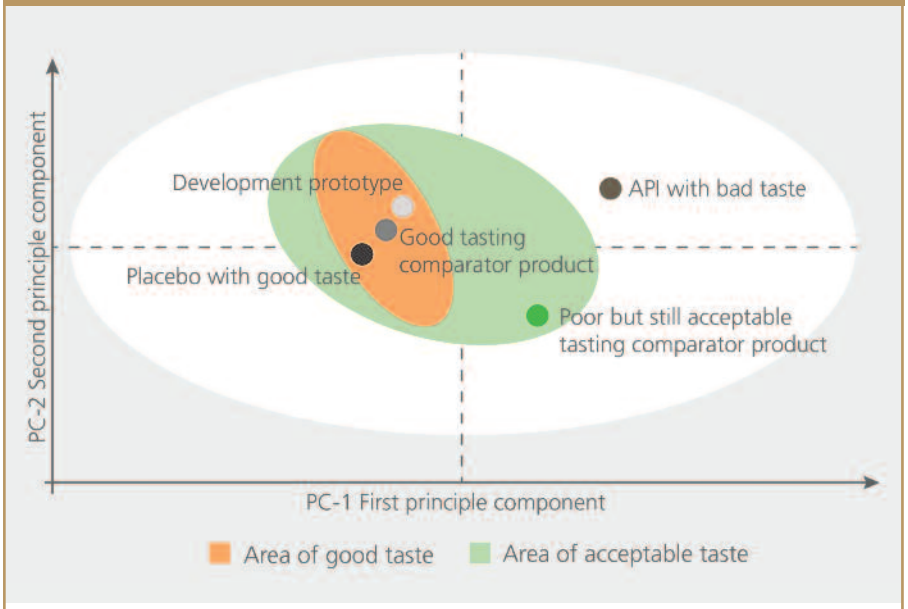
Comparison of caffeine before and after taste-masking. Taste characteristics were assessed on a scale from 0 to 10, where the stronger the characteristic, the higher the score. Hot-melt coating was used to significantly reduce the bitter and astringent taste of caffeine. While untreated caffeine cannot be formulated into an ODG, such taste-masked intermediates may easily be formulated into a pleasant tasting product.

It is important to note that only liquids can be analyzed using the electronic tongue. Solutions require no pre-treatment, except perhaps filtration. Solid formulations, however, must be at least partially dissolved before analysis. This dissolution step should replicate the physiological process as closely as possible. For example, as orally disintegrating granules (ODGs) will only partially dissolve in the mouth, analysis should be made on the fraction that dissolves before swallowing. This could be replicated in the laboratory by adding a known quantity of artificial saliva to the ODG for say 1 minute (the time needed to salivate and swallow the ODG in two to three gulps) and then filter to collect only the amount of the ODG that is dissolved in that time. Electronic tongue analysis can be performed on this sample. Aftertaste (to accommodate the few granules remaining between the teeth, for example) can be analyzed by dissolving the complete ODG and comparing it with the 1-minute sample. A similar approach can be used for tablets, which spend only seconds in the mouth before being swallowed with water. Only the film-coating is tasted with the tablet-core/API remaining undissolved.

GUIDING FORMULATION DEVELOPMENT

So, how can data generated through electronic tongue analysis be used to direct formulation development? One option is to identify a reference substance, one that is known to taste good, with the aim of re-creating the same taste (as closely as possible) with the product that is under development. When data is shown on a PCA plot, the final formulation should be

FIGURE 4



Principle component analysis (PCA) reduces large, multifactorial data sets so that differences between samples are highlighted and easier to compare. Using electronic tongue analysis, the flavor of a single product may comprise eight individual tastes. PCA is used to condense this data to just two principle components, which could be an individual taste (eg, sourness) or an abstract mathematical term (eg, bitterness² x astringency).

as close as possible to the reference product and/or placebo and distant from the original API. This top-down approach is ideally suited to the development of generic formulations in which there is an existing product that can be used as a reference substance. Ideally, there would also be supporting data available that demonstrates the market acceptance of the original product. Such data would be particularly advantageous if the product was targeted at a difficult to access market segment, such as pediatric medicines.

Alternatively, if there is no reference substance available, a pleasant-tasting placebo is created, which can be tested both by the electronic tongue and by a human tasting panel. Afterward, formulation scientists will attempt to re-create the same flavor in the drug product by adding flavorings and sweeteners to the API or coating it. Success is measured via comparing electronic tongue data with that of the placebo. This bottom-up approach carries the additional advantage that both the placebo and the drug product taste alike and so do not bias the results of later clinical trials.

SUMMARY

Regardless of whether a top-down or bottom-up approach is used, the goal is the same – to make the taste profile of a drug in development match that of a chosen, pleasant-tasting drug/placebo and to provide evidence of this via electronic tongue analysis. This analysis is more reliable and more consistent than the data generated using a human tasting panel. Human perception of taste varies considerably from person to person and often from day to day for an individual. It also allows pharmaceutical companies to employ a more ethical approach to assessing taste, by removing the need to administer medicines (that are still in development) to healthy volunteers. In addition, electronic tongue analysis helps to provide data for medicines targeted at hard-to-reach patient populations, such as infants and elderly people.[3] Having overcome the ethical problems of taste tests, the electronic tongue approach enables formulation scientists to perform more taste tests, and earlier in the formulation development process – with the dual benefits of shortening development times and reducing costs.[3] For these reasons, it is likely that we will see increased uptake of electronic tongue technology throughout the next few years. ◆

REFERENCES

1. www.swallowingtablets.com
2. Cioseka P, et al. Towards flow-through/flow injection electronic tongue for the analysis of pharmaceuticals. Sensors & Actuators B: Chemical. 2015;207(Part B):1087-1094.
3. Campbell GA, et al Evaluating the taste masking effectiveness of various flavors in a stable formulated pediatric suspension and solution using the AstreeTM electronic tongue. Powder Technology. 2012;224: 109-123.

BIOGRAPHY

Dr. Detlev Haack is the Director Research & Development at HERMES PHARMA. He earned his PhD at the University of Hamburg on the subject of Chemical and Physical Stability of Piroxicam in solid dispersion with PEG and PVP. In 1997, he received approbation as a pharmacist. From 2003-2007, Dr. Haack was Manager Sales & Business Development at Hermes Arzneimittel GmbH. He held the position of Associate Director R&D there from 2007-2012 before becoming Director R&D in 2013. His career includes a previous position as Head of Production at Altana Pharma Oranienburg GmbH.

ANTIMICROBIAL RESISTANCE

MGB: The Minor Groove Binder

By: Dawn A. Firmin, MSc, PhD

INTRODUCTION

An increase in resistant strains of bacteria - coupled with a lack of commercial interest in developing new antibiotics - means that useful antibiotics are in short supply, and becoming less effective, with no new classes of antibiotics having been developed for 25 years.

The majority of severe *Clostridium difficile* infection (CDI) cases occur in a healthcare environment, such as hospitals or care homes. Older people are most at risk from infection. Those aged over 65 account for three quarters of all cases. The UK Office of National statistics reported that in England and Wales, the number of CDI cases increased from 44,107 to 51,690 between 2004 and 2005, with 2,700 deaths recorded in 2011.

Recently, the US Centers for Disease Control (CDC) reported that hospital-based CDI incidence was 250,000, with 14,000 deaths. The most pathogenic strain of C. *diff,* NAP1/027, which has emerged in recent years, tends to cause more severe infections and is becoming globally more prevalent. In the US, it causes around 50% of all CDI infections, in Canada, near 80%, and in in England 36%. The current therapies for CDI, metronidazole, vancomycin, and recently fidaxomicin, have very limited activity against this strain as they have predominantly bacteriostatic activity. By contrast, MGB-BP-3 has a strong bactericidal effect against the majority of C. *diff* strains, including the most virulent NAP1/027 strain.

The current therapeutics for CDI are associated with high recurrence rates due to their predominantly bacteriostatic activity, and have a weak effect on C. *diff* sporulation. MGB-BP-3 has shown to be more potent in reducing C. *diff* sporulation than vancomycin. In contrast to the existing CDI therapy, MGB-BP-3 is active against vancomycin-resistant enterococci (VRE), which are found in up to 50% of CDI patients, coinfection with which is often responsible for a patient's poor prognosis.

Additionally, MGB-BP-3 has been shown to act against C. *diff* within the first hour of administration, whilst vancomycin requires up to 24 hours to achieve an optimal effect. The economic burden of CDI is estimated to be $7 billion, or $6,000 per patient, for the cost of hospitalization and standard treatment. All these factors indicate that MGB-BP-3 is more active in CDI treatment and has the potential of substantially benefitting CDI patients and reducing hospital days and overall CDI treatment costs.

The World Health Organization considers drug-resistant infection to be the greatest challenge in infectious disease. Director of the Wellcome Trust, Jeremy Farrar, claims that drug-resistant infections are "on the scale of climate change."

Governments have only recently begun to grasp the scale of the problem, with health authorities in the US and Europe introducing the GAIN Act (Generating Antibiotic Incentives Now) in 2012, which aims to facilitate a faster and less-expensive process to bring novel antibacterial agents to the market.

In the UK, Lord Jim O'Neill was appointed in May 2015 by Prime Minister David Cameron to chair a review into the crisis of antimicrobial resistance (AMR).

The AMR Review, which concludes this summer, has so far published four of the six planned papers, analyzing key topics affecting the global issue of antimicrobial resistance and the use of antibiotics in agriculture; antibiotic misuse and over-prescription, and the importance of better diagnostics.

In his review, Lord O'Neill estimates that by 2050, infections

untreatable with antibiotics could cost the global economy $100 trillion, and kill 10 million people a year. However, the report also shines a light on the industry as a whole, suggesting in part that lack of research in this critical area is down to antibiotics previously being expensive to develop, providing only small returns to drug companies.

In January this year, at the World Economic Forum in Davos, 85 pharmaceutical companies joined together to call on governments around the world to develop new ways of remunerating them in order to develop antibiotics. In a joint statement, they said that the reward for developing antibiotics historically "did not reflect the benefits they bring to society."

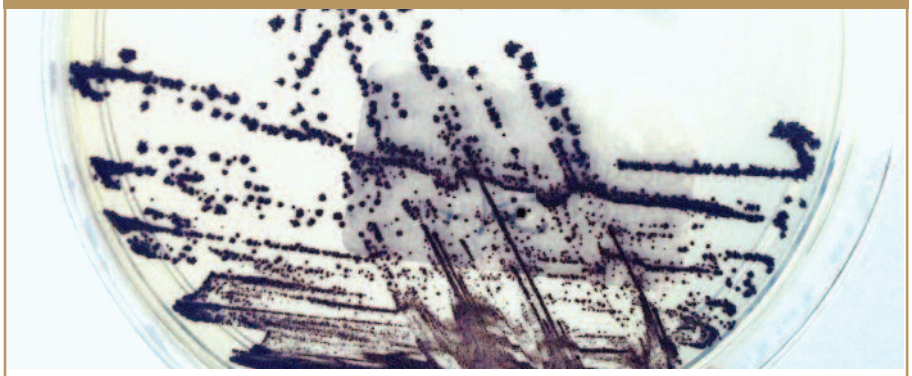
The declaration from drug and diagnostics companies, including Johnson & Johnson, Roche, Novartis, and Pfizer, called for governments to "commit funding and support the development and implementation of transformational commercial models that enhance conservation of new and existing antibiotics."

After years of scaling back research into new antibiotics owing to these low returns, spurred on by this growing awareness of the antibiotic crisis, the biopharmaceutical industry has made some moves toward re-entering the field. In particular, recent development has focused on Gram-positive infections, responsible for a large proportion of serious infections worldwide.

GRAM-POSITIVE PATHOGENS & THE RISE OF *CLOSTRIDIUM DIFFICILE*

Gram-positive pathogens include bacteria, such as Methicillin-resistant and susceptible *Staphylococcus* species, pathogenic *Streptococcus* species, and Vancomycin-resistant and susceptible *Enterococcus*, as well as *Clostridium difficile* (*C. diff*).

FIGURE 1



***Clostridium difficile*: A spore forming Gram-positive bacteria, located in the intestine, associated with antibiotic use.**

Clostridium difficile infections are on the rise, for example, with recent estimates suggesting that up to a half a million cases a year currently occur in the US alone.

The UK Office of National statistics reported that in England and Wales, the number of CDI cases increased from 44,107 to 51,690 between 2004 and 2005 in the over 65s, with 2,700 deaths recorded in 2011. Similarly in the US, 95% of 14,000 deaths attributed to CDI were in those aged 65 and over. The direct economic burden of managing CDI in developed countries is estimated to be approximately $7 billion.

Data also shows cases of CDI more than double the risk of death within 30 days of diagnosis, and causes or contributes to 40% of deaths that occur within 3 months of diagnosis. Furthermore, recently evolved hyper-virulent strains of *C. diff*. produce robust amounts of the disease-causing toxins, more spores and additional surface proteins that help it to persist in the gut environment. Up to 25% of treated patients have a CDI recurrence within a month after initially successful therapy; the total cost of CDI in the US or Europe is estimated to be up to $6 billion a year.

A NEW CLASS OF ANTI-INFECTIVE MEDICINE

Glasgow's MGB Biopharma began operations in April 2010, funded by an Angel syndicate and the Scottish Co-Investment Fund. The company has since been working on a new agent for Gram-positive infections based on Minor Groove Binder (MGB) technology evolving from the University of Strathclyde in Scotland.

MGB's experienced management team has dedicated its focus to the development of a new class of small molecules, with specific antibacterial activity against susceptible and resistant bacteria – making rapid progress against Gram-positive pathogens such as *C. difficile*.

The company is currently advancing lead product MGB-BP-3, which is being developed for the oral treatment of CDI.

MGB-BP-3 is a synthetic polyamide directed against Gram-positive bacteria, developed by Professor Colin Suckling at the University of Strathclyde. It binds to the

"After years of scaling back research into new antibiotics owing to these low returns, spurred on by this growing awareness of the antibiotic crisis, the biopharmaceutical industry has made some moves toward re-entering the field. In particular, recent development has focused on Gram-positive infections, responsible for a large proportion of serious infections worldwide."

minor groove of bacterial DNA; these are the grooves created from the close proximity of DNA strand backbones.

Research into minor groove binders, an entirely novel drug class, including its failures, has proved to be an important event in advancing the development of new antibiotics that could be resistant to potentially increasingly fatal pathogens. Consequently, this is the first time that minor groove binders are being investigated as an antibacterial agent, creating an entirely new class of antibacterials with a new mechanism of action. Minor groove binders as a class are chemically very heterogeneous, with their respective antibacterial, antifungal, antiviral, anti-parasitic, and anticancer activity.

The common feature of these compounds, including MGB-BP-3, is that they recognize specific regions of DNA and appear to be able to achieve high selectivity and efficacy by interrupting the biochemistry of a cell at a fundamental level. The activity of minor groove binders are determined by their ability to bind to sequences that are rich in the amino acid base pairs A and T within the minor groove of DNA, in a sequence and conformation-specific fashion.

As a result, this process interferes with transcription factors and alters genetic regulation. Some compounds belonging to this group are already under clinical development or are even commercially available, such as pentamiden and furamidine against a range of human parasitic diseases, and brostacillin as an anticancer agent.

MGB-BP-3 has the potential to provide substantial benefit to patients, particularly the elderly and the immuno-compromised, in an area of increasingly unmet medical need, as the problem of bacterial resistance to current therapies is becoming acute. In combatting CDI and reducing its recurrence, MGB-BP-3 has the potential to alleviate the ever-increasing financial strain placed upon healthcare systems. The current gold standard for CDI treatment is vancomycin, and resistance to this drug is increasing, with recurrence rates now estimated to be approximately 30%. MGB-BP-3 is able to offer a potential cure to CDI by providing superior treatment. In contrast to vancomycin, which is mainly bacteriostatic, MGB-BP-3 is, with its novel mode of action, strongly bactericidal against the majority of *C. diff* strains, including the most virulent strain NAP1/027. As such, it reduces the sporulation process responsible for the survival of *C. diff* and its regrowth, which causes disease recurrence.

A BRIGHT FUTURE

In December 2015, MGB Biopharma successfully completed a Phase I clinical trial of an oral formulation of MGB-BP-3. The double-blinded, placebo-controlled Phase I clinical trial assessed the safety, tolerability, and pharmacokinetics of single

and multiple ascending doses of oral MGB-BP-3.

In the single ascending dose element of the study, dose levels of MGB-BP-3 were increased from 250 mg to 2000 mg. In the multiple dose part of the study, 250 mg, 500 mg, and 1000 mg doses of MGB-BP-3 were given twice daily for 10 days. The Phase I study showed that MGB-BP-3 was well tolerated with no serious side effects being observed.

MGB Biopharma has undertaken extensive formulation work aimed at developing a freeze-dried product that can be administered intravenously. This formulation of MGB-BP-3 will address systemic Gram-positive infections, such as MRSA, VRE, and *Streptococcus*. Pivotal proof-of-concept and ADME studies assessing IV MGB-BP-3 against *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, and *S. pneumoniae* have been completed. Metabolism studies using radiolabelled MGB-BP-3 to determine metabolite profile and identification, and in parallel, an *in vivo* study to determine mass balance and tissue distribution of MGB-BP-3 are ongoing. Preliminary non-clinical safety and tolerability studies are ongoing, and we expect formal GLP safety pharmacology and toxicology studies to follow.

MGB successfully completed a topical formulation feasibility study with its lead antibacterial MGB-BP-3 in November last year. The pre-clinical study assessed two preliminary topical formulations of MGB-BP-3 in a skin infection model against a methicillin resistant *Staphylococcus aureus* (MRSA). The study showed that both formulations of MGB-BP-3 were successful in killing approximately 60% of the MRSA present. These very promising findings pave the way for MGB Biopharma to begin a full topical formulation development programme for MGB-BP-3 with the goal of commercializing this novel antibacterial for a range of important skin infections.

The successful completion of Phase I study with oral MGB-BP-3 was a major milestone for MGB Biopharma and means the company is well-placed to commence a Phase II study with oral MGB-BP-3, a further important step as it works to bring this truly novel antibiotic to market as quickly as possible.

It is encouraging to see that drug development companies are realizing that, while innovation needs to be rewarded, public health also has to be safeguarded at all costs. MGB Biopharma now intends to work with partners to fully capitalize on the multiple value-creating opportunities offered by its broad and innovative anti-infectives platform.

With political pressure on drug companies around the world, one thing is clear. The AMR Review and GAIN Act show how far and how quickly the debate into tackling antimicrobial resistance is moving. The political support now exists, and this needs to be matched with commitment from the broader industry – as well as companies like MGB Biopharma. ◆

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

BIOGRAPHY

Dr. Dawn Firmin is responsible for planning, managing, and executing the pharmaceutical development of the MGB Pharma's programs and providing leadership to the project teams. She is a scientific professional with 10 years of combined experience in immunology and infection, toxicology management, and the management of drug development of NCEs. Her expertise lies in her knowledge and experience of managing all preclinical and Phase I activities of the drug development process, including pre-IND meetings. Dr. Firmin was a Post-Doctoral Immunology Research Scientist at the University of Glasgow, specializing in a mechanistic in vivo model of Ankylosing Spondylitis. Prior to this, she worked for Charles River Laboratories, where she was a Senior Assistant Scientist and Project Manager of toxicology studies. Before joining CRL, she earned her PhD in Immunology and Infection at the University of Aberdeen and her MSc in Medical Diagnostics at Cranfield University. She has authored and co-authored academic papers and is a member of the Scottish Life Science Association.

Special Feature

Formulation Development & Manufacturing—CDMOs Offer Speed, Advanced Technologies, & the Ability to Handle More Potent APIs

By: Cindy H. Dubin, Contributor

The business model for a contract development and manufacturing organization (CDMO) continues to evolve, becoming a one-stop-shop of value-added services with an increased focus on pre-clinical development services through commercial manufacturing.[1] It is these services that help differentiate one CDMO from the other.

Some CDMOs are expanding services into biologics and biosimilars manufacturing as well as high-potency active pharmaceutical ingredient (HPAPIs). Last year, CordenPharma completed its expanded development capabilities for mid-scale (up to 20 kg) contained capacity of highly potent and oncology oral dosage forms in its German manufacturing facility. The new and expanded capability provides customers a complete offering in the contained manufacturing of oral dosage from grams to 150 Kg. And Catalent, through its wholly-owned subsidiary, Redwood Bioscience, formed a research collaboration with Roche to develop molecules coupling different therapeutic modalities using Catalent's proprietary SMARTag technology, an antibody drug conjugate (ADC) platform.

Pharma is also looking to CDMOs to increase R&D efficiency by relying on specialized assistance from CDMOs that have a deep understanding of the therapy area, route of administration, and of applicable delivery technologies, says Julien Meissonnier, Catalent's Vice President of Science & Technology. "Pharma customers are becoming increasingly interested in applying advanced technologies to help resolve challenges, such as spray drying, hot-melt extrusion, and advanced lipid-based formulations. In the biologics field, technologies such as protein-conjugation are experiencing a new wave of innovation to improve the accuracy and reliability of drug conjugation."

Of course, no matter how successful the development, commercial manufacturing and speed to market are crucial. Mr. Meissonnier says that 75% of R&D pipelines are driven by venture capital or small capital investment companies, which look for accelerated development programs. In addition, to reduce fixed expenses, big pharma requires CDMO partners that are highly skilled formulators, with a deep and broad understanding of how a product can be efficiently manufactured for launch and throughout its life.

In this exclusive *Drug Development & Delivery* report, some of the industry's leading CDMOs highlight their capabilities in the areas of speed, quality, technology, and handling of complex APIs.

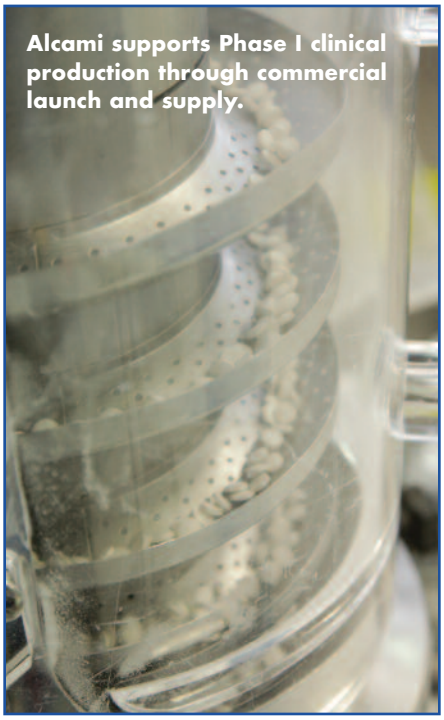
Catalent's acquisition of Pharmatek, a U.S.-based specialist in drug development and clinical manufacturing, added extensive early-phase drug development experience and spray drying to the company's toolkit of bioavailability solutions.

Alcami: Integrating API & Formulation Development

Alcami offers fully integrated services that can take a client from API synthesis and characterization through formulation development and manufacturing for oral and parenteral drug products. The company can work with highly potent, hazardous compounds as well as controlled drugs. "Alcami has received an increase in the number of requests for development and manufacture of highly potent or hazardous compounds. These present some unique challenges in safety, formulation, and manufacturing of very low dose products," said Elsie Melsopp, PhD, Principal Scientist-Formulation Development, Alcami. "Alcami is experienced with formulation of poorly soluble compounds, and we are looking to expand our capabilities in this area in the future."

"We have seen more interest in the development of poorly soluble compounds, BCS Class II and IV," says Matthew Schineller, Principal Scientist-Formulation Development, Alcami. "Some sources estimate that nearly 40% of new drug candidate compounds are poorly water soluble. Companies are also applying new technologies to the development of compounds that were abandoned due to poor oral bioavailability,"

Alcami has several offerings that set it apart from its competitors, explains Walter Holberg, Scientific Advisor-Operations Lab Support, Alcami. For instance, its ProForm Select™ program is a service that integrates the API development and formulation development processes in parallel. "Our scientists help customers develop a scalable synthesis route and molecular characterization, including solid-state chemistry," he says. "We perform an in-depth assessment of the target product profile for the drug molecule and potential drug product, and a GAP analysis of client needs to support regulatory filing. This results in faster time to the clinic, improved process stability, and mitigated risk, enabling us to streamline the drug development and manufacturing process."



Alcami supports Phase I clinical production through commercial launch and supply.

As an example, one client was experiencing a six-month manufacturing delay that threatened to derail an impending clinical trial due to inconsistent dissolution and lot-to-lot variability in the API. As part of the ProForm Select process, Alcami identified the source of the API issues as variable crystal habits in a single polymorph. "A selective and robust crystallization process was developed that eliminated the variability in the API and therefore the drug product," says Mr. Holberg.

Almac: Expanding GMP & Service Footprints

To address capacity constraints, Almac has expanded its operational footprint significantly, including the expansion of chemical and microbiological testing laboratories, with the addition of a further facility that offers a threefold increase in its development GMP footprint. Within this facility, multiple Xcelodose® units will enable Almac to fill both API and simple blends into capsules for Phase 1 and 2 trials. Additionally, the facility comes purpose-built with multiple Highly Potent Processing Suites. Almac also added mini-tablet/granule/powder in stickpack and mini-tablet in capsule capabilities to its technology list to deliver novel pediatric dosage forms.

"We purposely couple our commercial and development manufacturing assets to facilitate a commercial solution to late-phase/registration development, providing our clients with an integrated solution through development and into commercialization," says David Downey, Vice President Commercial Operations, Almac.

As Almac improved its GMP footprint so too is the company assessing further

Due to the increase in demand for the development of pediatric dosage forms, such as mini-tablets, Almac acquired a Merz stickpack machine.

specialist services for clients' drug substance, drug product, and clinical packaging needs from one site. "Reduced risk, compressed timelines, and reduced vendor management are key considerations for our clients when offered this 'one-stop' solution, particularly for our biotech clients seeking the simplest, fastest route to clinic and market," says Mr. Downey.

As an example of how one provider can offer a multi-disciplinary solution, Tom Moody, Vice President Technology Development and Commercialization, Almac, explains how Almac completed several projects involving carbon-14 labelling of ADCs for a US and European client. The strategy for isotopic labelling of the ADC is to prepare a product with the label in either the linker, in the payload, or in both units.

Prof. Moody explains that the cytotoxic drug was attached to the linker via the conjugate addition of a thiol-SH on the drug with a maleimide moiety on the linker. This resulted in a [14C]-labelled linker-drug complex bonded together by a non-cleavable thioether linkage. This then underwent purification using ultrafiltration/diafiltration (UF/DF) to remove unbound [14C]-linker from the reaction mixture.

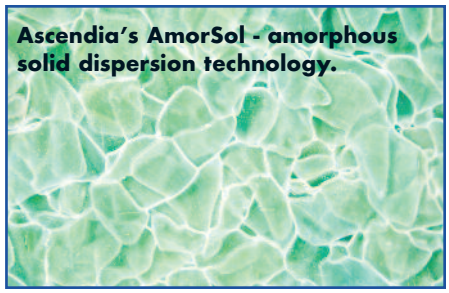
The [14C]-Drug linker conjugate was attached to the mAb via amide bond formation between a random surface epsilon-amino group of lysine and an activated ester moiety on the [14C]-linker-drug complex. The [14C]-labelled ADC was then purified by HIC chromatography, concentrated using UF/DF, filtered through a 0.22micron filter, and formulated in a pharmaceutical buffer. Stringent biological handling techniques were maintained throughout the manufacture to minimize endotoxin and bioburden levels. The manufacture resulted in a formulated [14C]-labelled ADC with a specific activity of 110mCi/mmol.

AMRI: Involved Throughout a Product's Life Cycle

During the past few years, AMRI has expanded its portfolio of services and products through acquisitions and organic growth initiatives to address the increasing trend toward pharmaceutical outsourcing. AMRI now provides end-to-end sterile drug dosage form development and manufacturing with four facilities that handle pre-formulation and formulation in Glasgow, UK; process engineering in Burlington, MA; full-scale commercial manufacturing in Albuquerque, NM; and ophthalmic, cytotoxic, and complete commercial manufacture in Leon, Spain.

Although still viewed as a core competency by some of the largest pharmaceutical firms, formulation development will increasingly be outsourced as CDMO involvement continues through a product's life cycle. AMRI's Glasgow, Scotland, facility has experienced that shift, seeing direct interest in its core expertise of development and formulation, in addition to lyophilization process development, explains David Stevens, Vice President, Sales and Marketing, Drug Product, AMRI. "In some cases, projects involve addressing challenges created by a silo approach at the interface between formulation development, process development, and full-scale final product manufacture."

AMRI also specializes in handling products that have high barrier-to-entry challenges, such as sterile products, controlled substances, steroids, high potency compounds, monobactams, and hormones.


Ascendia's AmorSol - amorphous solid dispersion technology.

Ascendia Pharmaceuticals: Broad Range of Formulation Development Services

One trend that has become apparent over the past couple years is the growing diversity in types of projects that are requested. "In the past, it was common for the majority of projects to be orally administered, small-molecule products, often controlled release in some fashion," says Jingjun "Jim" Huang Huang, CEO, Ascendia Pharmaceuticals. "Lately, we have worked on projects that have included long-acting injectable depots, ophthalmic dosage forms (both drops, and vitreal injections), and injectable nano-emulsions for immediate release."

Ascendia Pharmaceuticals is a specialty contract development and manufacturing (CDMO) company that provides outsourced services to partners for developing new formulations, especially for poorly-water soluble molecules. Ascendia also provides small-scale cGMP manufacture for clinical trial materials, including injectable dosage forms.

To illustrate the type of specialized and broad formulation development services the company offers, Ascendia has expertise in developing nano-emulsions (using homogenizers and/or microfluidizers), solid-lipid nano-particles (both IR and long-acting), hot-melt extrusions, solvent-based

"The industry is moving away from the "blockbusters" and is instead focusing on narrow indications or diseases, currently without therapeutics, as it boosts the chances of getting regulatory approval and can help the drug get to market as fast as possible," says Julien Meissonnier, Catalent's Vice President of Science & Technology.

spray-dried products, lyophilized dosage forms, and autoclaved injectables. "We often combine processes to develop a unique product that addresses the physical attributes of the drug substance, the delivery route, the pharmacodynamic aspects of the drug product, and whether the final dosage form requires terminal sterilization or aseptic processing," says Dr. Huang.

Ascendia does not focus on a single drug delivery platform, but instead provides contract formulation development for nearly all routes of administration. In addition, Ascendia has an analytical sciences group to handle that aspect of drug development, and recently added small-scale cGMP manufacturing so that an optimized formulation can be quickly taken into an animal toxicology study or a first-in-man study.

The majority of Ascendia's work is in repurposing an old drug in a new delivery format or indication and enhancing solubility dosage forms for NCEs, which need to be cost efficient. "Many of these projects are intended for proof-of-concept and the work needs to be done rapidly and within a set budget," explains Dr. Huang. "Our clients can go from pre-formulation to *in vivo* proof-of-concept relatively quickly and with a known expense, which can be beneficial for making efficient decisions on the viability of an early-stage drug program."

As an example, using its AmorSol technology, Ascendia developed a spray-dried amorphous solid dispersion of a client's compound that was known to be poorly water soluble, and its intrinsic solubility was not high enough to be adequately dosed for human clinical studies. The spray-dried formulation was utilized to develop an immediate-release tablet for a Phase 1 clinical study. Dr. Huang explains that the tablet formulation was prepared by dry granulation of the amorphous dispersion using milling and roller compaction. "The project went from initiation of formulation development to preparation of clinical materials in just five months," he says. "The amorphous dispersion formulation of the compound resulted in improved physical and chemical stability, and the resultant tablet formulation had higher bioavailability compared to the original tablet formulation."

Catalent: Addressing the Need for Speed

"The industry is moving away from the "blockbusters" and is instead focusing on narrow indications or diseases, currently without therapeutics, as it boosts the chances of getting regulatory approval and can help the drug get to market as fast as possible," says Julien Meissonnier, Catalent's Vice President of Science & Technology. "The effect of this trend creates the need for revised formulation development and manufacturing and scale-up strategies."

Mr. Meissonnier says that more complex molecules are appearing in development pipelines and that these require more sophisticated delivery technologies. Thus, complexity must be addressed earlier, ideally starting at candidate selection, in pre-formulation and before pre-clinical formulation. All these efforts are made to provide faster outcomes for customers at the early (preclinical and Phase 1 and later stages of development).

In the case of Trio Medicines Ltd (Trio), a London-based pharmaceutical company, its lead compound, TML-2, is the acetyl prodrug of TML-1, a novel, well tolerated G-protein coupled receptor antagonist, which shows clinical promise but has limited bioavailability, owing to low solubility, explains Brian N. Woodrow, PhD, Director, Sterile and Biologics Analytical Development, Catalent.

Catalent's Science & Technology advisors employed the OptiForm® Solution Suite, an integrated platform with a structured three-step approach, to assess, enhance, and recommend delivery options for the compound. During the assessment

phase, Catalent conducted a series of tests to determine the molecule's physicochemical properties and its chemical compatibility with different excipients, the molecule's solubility and its developability classification system (DCS), solid-state characterization, and stability. At the enhance phase, Catalent evaluated three enabling technologies in parallel, based on the data from the "assess" phase. These included lipid-based formulation, amorphous solid dispersion, and particle size engineering. In 12 weeks, Catalent provided prototypes employing all three technologies for use in an animal PK study, and delivered a full report with recommendations and all data, which included two weeks' stability testing data.

Trio tested all the prototypes in the animal study, and the data showed the bioavailability of all prototypes for TML-2 was greatly increased, says Dr. Woodrow. Among these prototypes, micronization (particle size engineering) showed the most substantial bioavailability enhancement (4 times).

At the early stages of the development process, which spans from drug candidate selection to Phase 1 clinical studies, Catalent offers a continuum of solutions, including druggability, preformulation, toxicity enabling formulation, formulation screening, and fast clinical supplies to Phase 1. When incorporated, these solutions accompany a molecule to proof-of-concept in-man studies. "This continuum leverages differentiated enabling technologies, often targeted at addressing complex bioavailability challenges that go way beyond simple exposure issues, and ensure successful dose escalation in single ascending dose studies," says Mr. Meissonnier.

At later stages of product development, Catalent leverages a toolkit of differentiated technologies to ensure appropriate matching to complex release profiles. This toolkit of technologies addresses complex extended-release profiles, as well as the growing demand in targeted release delivery.

Savings in development time are important. But with regulators making ever-more stringent demands for broader, increasingly global clinical trials, working with a company that can offer strategies and methods to accelerate a product's journey through the trial process to marketing authorization and commercial manufacture, is critical, says Mr. Meissonnier. "This holistic view of development to commercialization can maximize the time a product enjoys patent protection, and reduce how long it takes for it to recoup its development costs."

CordenPharma: Focusing on Small-Molecule Oncolytics

Cancer remains the second leading cause of death and represents the largest category of new medicines. A range of new mechanisms is expected to drive innovation and growth for the CDMOs that have the right expertise and capabilities in this area, says Jason Bertola, Director, Global Highly Potent & Oncology Platform, CordenPharma International. "Greater understanding of cancer progression has led to the development of increasingly targeted approaches, which mean not only increased safety and efficacy for the patients but also increased manufacturing requirements and need for containment and engineering controls," he says. "For example, antibody drug conjugates (ADCs) offer better safety profiles for patients, but manufacturers must be able to produce and handle cytotoxic drugs that are significantly more potent than their chemotherapeutic predecessors."

Manufacturing at CordenPharma Plankstadt (Germany).

Despite significant focus on biologics, small molecules still represent more than half of the total market. For instance, tyrosine kinase inhibitors and poly ADP-ribose polymerase inhibitors are among the small-molecule targeted therapies. These products are also driving the need for oral solid dose highly potent manufacturing. Some estimates predict oral oncolytics to be 25%-30%[2] of the market, double the figures from 10 years ago.

CordenPharma's service offering targets the oral formulation development and manufacturing of oncolytics. "Recent investments have expanded our capabilities to develop and supply clinical trial materials and small-scale manufacturing. Engineering controls are in place to allow the safe handling of compounds in development and manufacturing," he says.

HERMES PHARMA: Ensuring Quality Right From the Start

Quality has always been a key priority for the pharmaceutical industry, however, over the last year CDMOs like HERMES PHARMA have observed an increased em-

Dissolution apparatus and spectral photometer (HERMES).

phasis on tackling quality upfront in the pharmaceutical manufacturing process. "Using approaches such as Quality by Design (QbD), quality is more often being considered during formulation development rather than waiting until the product is designed and then deciding how quality will be assured," says Dr. Martin Koeberle, Head of Analytical Development & Stability Testing at HERMES. "This approach makes sense – after all, quality can't be tested into a product, it needs to be there by design."

HERMES PHARMA specializes in the development and manufacture of user-friendly oral dosage forms such as effervescent tablets, orally disintegrating granules (ODG), lozenges, chewable tablets, and hot and cold instant drinks. "By developing such dosage forms, healthcare companies can increase revenue, prolong product lifecycles, and differentiate themselves from the competition," he says. "More importantly, improved patient experience can increase compliance and boost the effectiveness of treatment."

To improve patient compliance, HERMES offers expertise in flavorings and taste-masking technologies. Dr. Koeberle explains that HERMES was recently asked to apply these technologies to a pharma client looking to develop a sour and metallic tasting API into a pleasant tasting expectorant in the dosage form of an ODG. This dosage form consists of small granules that are applied directly into the mouth, are easy to swallow, and don't require water.

"We achieved a pleasant tasting ODG using hot melt coating (HMC), a solvent-free coating technology that offers short processing times and low costs," he says. "Applying QbD principles, it was possible to define a design space for this HMC process such that different API qualities can be used while constant product quality and performance are ensured. The bioequivalence study in which the ODG was compared to film-coated tablets was successful. This approach, which is now approved by the authorities, permits flexibility in manufacture (through the option to use different API qualities) thereby reducing costs. Not only were we able to rise to the challenge of developing a pleasant ODG, we made it more cost-effective to do so."

In an effort to control quality, there is also an increased customer preference for outsourcing both formulation development and clinical trial sponsorship to the same CDMO. This approach offers a number of efficiency gains, particularly that the customer (and the CDMO) has one fewer business partner to deal with, so coordination and project management is reduced. This also means better communication and clearer responsibilities.

"With customers keen to work with a single CDMO, a key development for HERMES PHARMA has been to establish a quality system for Good Clinical Practices (GCP) so that we can now act as a sponsor of clinical trials, as well as provide formulation development expertise," says Dr. Koeberle. "This has involved setting up the necessary documents and contractual agreements between HERMES PHARMA and subcontractors, in addition to auditing the relevant subcontractors."

Lonza: A Holistic Approach to Product Development

Lonza's Drug Product Services (DPS) group is focused is on the target product profile—the intended product design to enable competitive, quality, efficacy, and safety for patient treatment. "We support our customers by answering critical product design questions, providing patient treatment options, and developing and commercial-

Lonza's Drug Product Services team offers comprehensive, integrated services for drug product development.

izing parenteral products," says Dr. Hanns-Christian Mahler, Head of Drug Product Services for Lonza.

An integrated drug product design is integral to a successful product, he adds. "DPS combines expertise in formulation development, process design, primary packaging, patient usability, and administration. Our Drug Product Services include rapid early-stage development, robust late-stage development, and comprehensive product lifecycle development services."

Additionally, Lonza's Forensic, Particle and Container Closure Integrity (CCI) labs provide expertise and support for specialized hot topics. One new technology used in the CCI lab is a custom-designed, highest-sensitivity, helium-based leak test that evaluates products at a variety of temperatures. "We are the only company that currently offers this method for frozen products down to -80°C," says Dr. Mahler.

Lonza DPS also assesses root causes of fogging or haze from lyophilisates, and defines mitigating strategies related to formulation, primary packaging, and process design.

"Formulation development and drug product manufacturing of biologics are finally being recognized as more than a commodity," he says. "In product development, direction is equally as important as speed. An intimate knowledge of how biotechnology, pharmaceutical sciences, regulatory requirements, health authority requirements, and medical sciences relate to each other is required to deliver a holistic approach to formulation development and manufacturing."

Dr. Mahler notes that it is also critical to explore the potential impact of excipients and their behavior and stability in a formulation on product compliance to regulatory requirements, and the volume that can be injected subcutaneously or intraocularly.

Particle Sciences, a Lubrizol Company: Offering an End-to-End Solution

Pharma clients seem to be demanding a CDMO model that provides an end-to-end solution. Since becoming part of Lubrizol LifeSciences, Particle Sciences (PSI) offers exactly this – starting from polymers, through formulation development and into commercial manufacturing on a global scale. "This model minimizes cost and risk of tech transfers in addition to shortening development timelines," says Mark Mitchnick, CEO of Particle Sciences/CMO-Lubrizol LifeSciences.

PSI has a repertoire of formulation technologies focusing on BCS II and IV molecules as well as biopharmaceutical products, including peptides, nucleotides, vaccine antigens, and adjuvants. "We believe there are a limited number of viable drug delivery and formulation approaches: particle size reduction, amorphous forms, permeation enhancers, lipidic and polymeric systems, and non-covalently binding products to nanoparticles/excipients," says Robert W. Lee, PhD, Vice President Pharmaceutical Development Services, PSI. "We also believe that one size does not fit all as each approach can easily yield a different biological response."

Key to Lubrizol's clients' successes is the ability to work with a range of small and large molecules, including highly potent or DEA-controlled substances. "It is of utmost importance to quickly progress the molecules from the bench-top into the clinic with our cGMP production of both sterile and non-sterile products," says Joey Glasco, Global Market Manager Drug-Eluting Devices & Pharmaceutical Services, Lubrizol LifeSciences-Particle Sciences. "In many cases, these programs are nascent and require 'industrialization' to scale up for GMP production."

PSI claims to be the first fee-for-service organization to commercially manufacture nanoparticles and nanoparticulate suspension formulations under aseptic conditions. In fact, the company has designed a soon-to-be-commercial-ready facility (Q3 2017) based on the ability to manufacture nanoparticulate and other complex formulations such as PLGA microparticle depots and drug eluting devices.

PSI has acquired LyoCell® technology, a patented drug delivery technology based on the use of reverse cubic and hexagonal phase lyotropic liquid crystalline nanoparticles. This technology is used for solubilizing drugs and improving their absorption and duration of action. Originally developed to deliver anesthetics via an intravenous route of administration, its utility has been expanded to include a variety of APIs, non-API containing formulations, and other routes of administration, including oral, topical, ophthalmic, and mucosal. "By understanding the thermodynamics and phase diagrams of lipidic systems that govern emulsions, liposomes, micellar solutions, and Cubosomes®, LyoCells allows the formulator to take advantage of the potential that is inherent in lipid/co-solubilizer/water systems," says Dr. Lee.

The formulation of biologics is another growth area for PSI, which has developed proprietary approaches, including SATx® (Surface Arrayed Therapeutics). "SATx is our approach to targeted pharmaceuticals that can be used for therapeutics as well as the formulation of potent prophylactic vaccines for mucosal and parenteral administration," explains Robert Becker, Vice

Highly efficient state-of-the-art filling line in Siegfried's award-winning sterile facility in Hameln Germany.

President Biopharmaceutical Sales and Business Development, PSI. "Targeted drug products are a key objective of pharmaceutical development."

Siegfried: Packaging Plays a Critical Role in Production

Based on the trends in demographical change, growth of chronic diseases, and the increasing price pressures in healthcare provision, there are visible developments in the primary and secondary packaging of finished drug products, their production processes, and production equipment, says Dr. Olaf Schrake Head Key Account Management Drug Product Sterile EU/ROW, Siegfried.

"Primary and secondary packaging is coming ever closer to patients, as many drugs are increasingly being administered at home," he says. "This is one reason why the number of new products filled in cartridges and prefilled syringes has been increasing significantly within the last years."

Medication errors can be reduced by the right choice of primary packaging material and smart secondary packaging material, he continues. While ampoules are manufactured in high numbers, certain safety aspects make other containers, such as vials, more attractive.

"In our plants for sterile liquids, we offer a variety of presentations for the finished products," says Dr. Schrake. "The customer can choose an ampoule, but for markets not supporting ampoules, and for more innovative products, we offer production with state-of-the-art, highly efficient vial lines that cater to both small and large batch sizes. Additionally, we have dedicated fill/finish capacity for both cartridges and prefilled syringes."

In 2016, Siegfried implemented a new GMP vial line that fills small-scale batches economically and enhances capacity. Low-volume dispensing technology and disposable product paths for high-value products speed up validation and development for many of the processes used for filling of biologics. The Hameln site is an accredited sterile facility offering 9 filling suites and with a large multi-purpose inspection and packaging hall.

Dr. Schrake also notes the trend to large molecules as having a strong impact on production equipment and processes. He says: "As we see the growth in biologics for orphan and niche diseases, more formulations are turning to lyophilization to further stabilize and extend shelf-life of the product. Siegfried has invested in increased water for injection (WFi) capacity and offers dossiers for a number of formats. The end result allows parallel development and manufacture, decreasing time-to-market, and focuses on project management and joint project planning."

As an example of how Siegfried works with clients, one customer with an innovative product searched for a CDMO to market the product in the US. The product was partly developed and already produced by another CMO that had issues complying with FDA requirements. "Key to the switch was a focused hands-on, project partnership, whereby both companies committed to a fast-track program," says Dr. Schrake. "The tech transfer was completed within record time; equally, the filling lines were adapted to the customer's specific needs and validation batches were successfully produced, also in record-time." ◆

References

1. High-Potency APIs and Biologic Manufacturing Present Strong Growth Opportunities for Contract Manufacturing Organizations, Frost & Sullivan, Sept. 28, 2016, https://ww2.frost.com/news/press-releases/high-potency-apis-and-biologic-manufacturing-present-strong-growth-opportunities-contract-manufacturing-organizations/.

2. Mosely WG, Nystrom JS. Dispensing oral medications: why now and how, Community Oncology. 2009; 6:358-61.

CLINICAL TRIALS

It's Time to Revamp the Unsexy Plumbing of Clinical Trials

By: Craig Morgan

INTRODUCTION

There is no doubt that clinical research is critical to the advancement of medicine and public health. But conducting such research is a complex, resource-intensive endeavor that relies on a multitude of stakeholders, workflows, processes, and information systems. Clinical trials play an essential role in the drug development process by effectively demonstrating the efficacy and safety of a pharmaceutical compound – but they are not for the faint of heart, conducting even one is a monumental task with complex processes and issues that can surface and derail a study's timeline. As a result, delays in regulatory filing, market entry, and ultimately, the delivery of new therapies to patients are all too common.

With a large number of drugs coming off patent, known as the patent cliff, there is intense pressure to speed clinical trials and restrain costs, but inefficiencies tied to complicated protocols, globalization, and paper-based methods have stalled these efforts.

Pharmaceutical companies also need an efficient process for eliminating unsuccessful trials earlier or intervening before a "rescue" is required, which enables resources to be deployed more effectively. Because clinical trials are a major overhead, improved cost control and effective management of resources are key corporate objectives.[1] According to the Clinical Trials Transformation Initiative (CTTI), most of the costs incurred in clinical trials are associated with human time and effort, so unnecessary complexity can be both burdensome and expensive.[2]

These issues notwithstanding, the sheer number of potential therapies that are coming into the clinic is exasperating patient enrollment challenges. Unfortunately, such enrollment barriers mean treatment options often don't make it to patients in a timely matter, if at all. According to a report from a major National Cancer Institute (NCI) and the American Society of Clinical Oncology (ASCO) sponsored conference, "Poor enrollment onto trials threatens to slow progress in cancer care at a time when advances in science are enabling new opportunities for prevention and treatment."[3]

TECHNOLOGY BRINGS OPPORTUNITIES & CHALLENGES

Growth in regulatory complexity and global outsourcing has created unique challenges and a multitude of technological solutions aimed at automating clinical operations. Technology solutions in the eClinical stack, such as clinical trial management system (CTMS), electronic data capture (EDC), electronic trial master file (eTMF), and study startup (SSU), represent quantum leaps forward for the industry, but also have their share of challenges. The reality is that often these systems are not integrated, resulting in an array of technologies that offer invaluable, yet different, views of the clinical research environment. Frequently, lack

of or poor integration between such critical systems leads to manual reconciliation of data that is linked but resides in two or more different systems, representing a time sink for study teams that not only reduces their productivity but can lead to delayed or poor decision-making. It also does little to promote collaboration; disparate systems inevitably lead to a proliferation of Excel spreadsheets across the organization used by individuals to track key data for which there is no single source of the truth. The problem goes far beyond a technology integration challenge. At its core, clinical research paradigms are shifting, driven by new technologies that move the focus from back-office data capture and aggregation tools that are loosely integrated to cloud-based apps and modern application development architectures that enable teams to collaborate in real-time.

It's long overdue. Cloud-based technology has been transforming many sectors of the economy and now it is finally poised to address clinical trials - one of the most manual, error prone, complex, bureaucratic, and, above all else, expensive bottlenecks in the pursuit of new disease treatments.

According to research by leading analyst firms IDC and Forrester, the cloud has become a core element of an enterprise's technology strategy.[4] Over the past few years, the conversation around cloud adoption has moved from "if" to "when" and "how." The cloud remains one of the most disruptive changes in computing in years with a compelling value proposition that continues to propel adoption. It now drives transformative innovation, enabling organizations to compete more effectively by instantiating processes that deliver reduced cycle times and increased productivity. The emergence of a global

computing cloud heralds the arrival of entirely new classes of innovation across applications and markets, including healthcare.

Technology adoption is most obvious at the front end of healthcare, where health payment solutions, data analytics tools, telehealth, wearable devices, and other products and services are addressing the needs of both businesses and consumers. But just as important is what's happening behind the scenes, in the healthcare system's back-end infrastructure.[5]

While many individual aspects of the clinical trial process could be enhanced, Janet Woodcock, MD, Director, Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA), calls for a focus on "transformational change in the way clinical research is conducted."[6] She describes a vision of clinical research in the United States akin to the national highway system or the national energy grid – in other words, infrastructure, which could link research and community practice, and facilitate universal participation in the generation of new clinical evidence and its subsequent adoption by physicians.

But what exactly does clinical trial infrastructure mean? In 2010, the National Academy of Sciences took a look at the key elements a clinical trial infrastructure.[7] They published the results of a workshop conducted by the Institute of Medicine (IOM) on transforming clinical research in the United States. A number of workshop participants lamented that most clinical trials are conducted in a "one-off" manner. The term "one-off" alludes to the current situation in which the necessary components of a trial (usually a single coordinating center and multiple research sites) are brought together for a discrete period of time and disbanded once the trial is completed. Significant time, energy, and money are spent on bringing the disparate resources for each trial together. Some workshop attendees suggested that efficiencies could be gained by streamlining the clinical trials infrastructure so that those investigating new research questions could quickly draw on resources already in place instead of reinventing the wheel for each trial. Sadly, the clinical trial infrastructure is much the same today as it was in 2010, but growing discontent, dismal performance metrics, financial pressures, and new technologies are finally moving the needle. And while automation has been strongly focused on study conduct, stakeholders are becoming increasingly aware that better study startup (SSU) processes are linked to shorter clinical timelines renewing an emphasis on better infrastruc-

ture, resulting in better study quality, faster start-up times, and fewer costly one-offs.

Study start-up, a perpetual bottleneck in clinical trials, includes activities, such as country selection, pre-study visits, site selection and initiation, regulatory document submission, contract and budget execution, and enrolling the first patient.

Jeff Kasher, President of Patients Can't Wait, and formerly VP Clinical Innovation and Implementation at Eli Lilly and Company, comments "With globalization expanding its footprint, improved study start-up is essential for building speed into the clinical development process. Conducting clinical trials in places with unfamiliar regulatory pathways and limited infrastructure is highlighting the value of study start-up technology that allows for better SOP and regulatory compliance."

HOW THE CLOUD IS TRANSFORMING STUDY START-UP: THE "CONNECTED EXPERIENCE"

Agile companies are seizing opportunities around the cloud to drive innovation by creating operational efficiencies and engaging study teams in new ways. Whether an enterprise wants to consume or offer cloud services - they can leverage the cloud to achieve new levels of the "Connected Experience" across the clinical research value chain, from the study team to investigators and contract research organizations (CROs).

So what does the "Connected Experience" look like in the context of study start-up? Timeline reductions are achieved using: alerts (which are automatically triggered as the clinical trial unfolds), document collection, and version control and status reporting, which reduce the number of hand-offs, errors, and downtime events that can occur during the start-up phase of clinical trials. The use of a purpose-built study start-up tool allows for the seamless sharing and visibility of documents and associated information in real-time (globally) facilitating hand-offs. Delays due to documents sitting in siloed email boxes are eliminated as role management ensures continuity in the absence of a team member and real-time reporting negates the need for status meetings, where dated, manually prepared reports are reviewed for budget and timeline compliance.

The SSU infrastructure allows milestones to be tracked, improves communications among partners, acts as a central repository for study documents, and integrates the flow of information from various data sources in a compliant manner.

With the advent of intelligent document routing technology, stakeholders have the ability to support country-specific document regulatory workflows. This functionality automates compliance with SOPs, which, in conjunction with regulatory guidelines, help improve the operational efficiency of clinical trials. Historically, regulations have not provided specific guidance on the format or content of SOPs, allowing companies to design SOPs that best conform to their unique practices.[8] But the long history of their being confusing, overly complex, or existing in paper format has led to their less than consistent use, even avoidance.

These infrastructural changes represent a transformational change envisioned by Woodcock, combing data integration with innovative cloud-based solutions and advanced APIs for seamless integration.

Using this approach, bottlenecks that typically occur throughout the start-up phase of clinical trials are reduced, bringing greater efficiency to the critical path and tighter adherence to timeline and budget. With these and other innovations dependent on integrated data, the unsexy plumbing at the backend of the healthcare system has never been more important and represents a plethora of opportunities to reduce costs, streamline processes, and shape the future of an industry that services all.

THE CLOUD IS THE KEY TO CONNECTING THE CLINICAL RESEARCH VALUE CHAIN

As clinical trials continue to evolve, drug companies will no longer be able to rely on existing, tried-and-tested manual methods or point solutions for success. Technology integration in the eClinical stack, though a necessary component of the solution, is not sufficient to bring about the step change in productivity that has to happen. Why? Collaboration and the "Connected Experience" means more than just being able to access the same data. It requires the translation of that data into targeted information based on user roles. It also requires the ability to distribute work throughout the team, with appropriate approvals and audit trails along the way, through configurable workflows. It's a new paradigm driven by service-oriented, cloud-based solutions that leave the unsexy plumbing of traditional clinical trial systems behind. The result? An end-to-end clinical trials infrastructure utilizing "best-of-breed" technologies to meet the formidable challenges that lie ahead.

REFERENCES

1. Pharmaceutical Clinical Development: Electronic Data Capture (EDC) as a means for e-clinical trial success https://www-07.ibm.com/services/pdf/IBM_Consulting_Pharmaceutical_clinical_development.pdf.
2. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. http://www.ncbi.nlm.nih.gov/books/NBK50882/.
3. The National Cancer Institute–American Society of Clinical Oncology Cancer Trial Accrual Symposium: Summary and Recommendations. October 15, 2013, doi: 10.1200/JOP.2013.001119. http://jop.ascopubs.org/content/9/6/267.long.
4. 5 IT industry predictions for 2016 from Forrester and IDC. Available at: http://www.cio.com/article/3006976/it-industry/5-it-industry-predictions-for-2016-from-forrester-and-idc.html.
5. Techcrunch "Unsexy Plumbing," Integrated Data And The Future Of the Healthcare System http://techcrunch.com/2015/12/06/unsexy-plumbing-integrated-data-and-the-future-of-the-healthcare-system/.
6. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. http://www.ncbi.nlm.nih.gov/books/NBK50882/.
7. Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. Washington (DC): National Academies Press (US); 2010. 1, Introduction. Available from: http://www.ncbi.nlm.nih.gov/books/NBK50879/.
8. Kumar M. SOPs: Least understood, most important tool to ensure regulatory compliance. Regulatory Focus. October 2011. Available at: https://www.amarexcro.com/articles/docs/RAPS_Focus_SOPs_Oct2011.pdf. Accessed February 15, 2016.

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

BIOGRAPHY

Craig Morgan is a technology and life sciences management professional with more than 15 years of experience in the application of informatics and bioinformatics to drug discovery. He currently heads up the Marketing and Brand Development functions at goBalto, working with sponsors, CROs, and sites to reduce cycle times and improve collaboration and oversight in clinical trials.

Drug Development
EXECUTIVE

Vetter: Establishing a Successful Clinical Fill & Finish Manufacturing Site for Biologics

Susanne Resatz, PhD
President

Vetter Development Services USA, Inc.

Small biotech companies are faced with a series of issues when it comes to early drug development. One such issue is the critical lack of experience in key areas, which leads to employees' multi-tasking, having less internal expertise for manufacturing and sourcing, and an increased reliance on outside expertise. They also face a lack of financial resources and limited access to capital. With less patience expressed by the investor due to their inability to find the time to communicate their progress, securing additional funding is difficult. Finally, their high-value compounds often have limited availability and generating enough of the compound for the development phase is a challenge, with long lead times for their API being common. The right partner can support the small biotech by offering an additional level of resources and expertise, help enable right-first-time, result-saving costs and provide support through flexibility and problem-solving to handle investor communications for the next funding milestone. They can also help to optimize yield through equipment and process strategies (eg, filling machine design, multipurpose sampling, etc). Having the right site is crucial in serving the customers' needs. It is now 5 years since Vetter opened its clinical fill & finish facility in Chicago, successfully serving its customer base with their needs in mind. What are the specific needs of the small biotech and how is Vetter helping them to meet them? *Drug Development & Delivery* recently interviewed Dr. Susanne Resatz, President of Vetter Development Services USA, Inc., to discuss the many benefits to small biotech companies in utilizing the services of a full-service CDMO, and what advanced services the Chicago-based facility offers its growing customer base.

Q: For our readers who are not yet familiar with your company, can you briefly discuss Vetter and what service portfolio it offers?

A: Vetter is an independent contractor development and manufacturing organization (CDMO) specializing in the aseptic filling of syringes, cartridges, and vials. Our state-of-the-art facilities located in the US and Europe provide support for early stage drug products, with seamless transfer to Vetter Commercial Manufacturing for large-scale production. In addition to these locations, in November 2014, taking advantage of a rapidly growing Asian healthcare market and to better support our customers and develop new business, we announced the opening of our first Asian office in Singapore, and in October 2015, we announced the opening of new business office in Tokyo.

As a world-leading CDMO, we have extensive experience in working with biologics and other complex compounds, including monoclonal antibodies, peptides, interferons, and vaccines. And, because we are a full-service provider we can support our customers' products throughout their lifecycles, from preclinical development through global market supply. We are the originator of dual-chamber technology, which enables easier, safer lyophilized drug administration, and we are a leader in the use of RABS technology in cleanrooms, which mitigates risk of product contamination throughout the manufacturing process. Finally, it is important to note that as a family owned independent company, we do not manufacture our own drugs but focus solely on our customers' product success.

Q: A small biotech needs additional experience, so how did Vetter build up skills and the right structure?

A: Our intent was to create a new facility with a knowledge base anchored in Vetter systems. We began by first focusing on the skills that would be necessary for the customers we wanted to serve. Once determined, we constructed a team of Vetter Ravensburg employees who had the essential knowledge base in the different areas and systems. They were further trained at Ravensburg prior to relocating to Chicago. We also hired from the local Chicago pharmaceutical/biotech talent pool, which is quite substantial given the nature of the surrounding area with its many universities and varied pharmaceutical industry. Every employee had to have the technical and industrial knowledge as well as the customer experience that would match the needs of our customers. Next, we focused on the structure of the team itself, aiming for a balance of site and corporate resources that had all key functions on site. As critical mass was achieved, we added support functions as necessary. Our project teams were created using the existing Vetter project team structure and project management tools. Our customers were assured there would always be easy access to our support staff of specialists, and we allowed for a direct relationship between the customer and Vetter's subject matter experts (SMEs). Finally, we encouraged strong ties to our commercial production teams through ongoing visits to our Ravensburg site for regular meetings with their commercial counterparts.

Q: How can the right capabilities (building & facility) serve the needs of small biotechs, how did Vetter approach it?

A: The key to serving the needs of our smaller biotech customers is in our overall approach to layout and material flow. We see this as a three-step process. In the first step, we need to allow for close proximity of manufacturing and testing spaces. To achieve this, we designed the facility to allow for compounding adjacent to the filling area with the visual inspection area adjacent to the cold storage area. Chemical and micro labs are next door to manufacturing. Second, in order to limit the time materials are at room temperature, we installed the freezers and refrigerators adjacent to manufacturing. Third, to maximize usage of limited storage space, we only expand the space as needed and make use of qualified portable units for cold and frozen storage.

As for how we approach serving the needs of small biotechs, we aim to do it - "right the first time." In order to achieve this goal, we incorporate multiple formats of equipment that result in minimum line losses and maximum yield. Our machines allow for a

"We are thrilled with our performance at our Skokie facility and our overall success to date. Many of our customers have returned for development work for a second, third, or even fourth molecule. Furthermore, our outlook for future performance is very positive as demonstrated by a solid pipeline filled with high quality customer projects for biologics."

high level of environmental control but also easy changeovers. Our systems are scalable and have the ability to transfer to commercial lines. For example, we use RABS technology on all Vetter lines. Our yields are 100% in-line check weigh for vials, and we also have handling units for vial filling. Our approach is to establish platform processes that minimize risk through technical batches and machine runs. We minimize line losses and maximize yield by optimizing our tubing and break tank. Our operators are focused on yield, which is tracked as KPI. We are always focused on ways to improve. Wherever feasible, our clinical processes are a scaled-down version of established commercial processes. Finally, our documentation is consistent, which allows for easier identification of gaps during transfer.

Q: Due to the lack of financial resources, are timelines and scheduling important topics?

A: Project timelines and batch scheduling are an important consideration in manufacturing processes. The quick implementation of new products means we use platform processes and materials and project schedules that focus on GMP batch manufacturing dates. We are well aware of our timeline commitments and set and track project milestones as KPIs. We also maintain open communication with our customers so that the risks involved in the project are transparent. We allow for flexibility in our scheduling to support capacity reserve each month, and we schedule meetings with project managers and SMEs to quickly address any risks or changes.

Q: So how did the Chicago site perform within the past 5 years?

A: We are extremely pleased with our past years' performance at this facility, and our overall success to date. Many of our customers have returned for development work for a second, third, or even fourth molecule. Furthermore, our outlook for future performance is very positive as demonstrated by a solid pipeline filled with high-quality customer projects for biologics. We have solid experience with more than 60 compounds, and have already made more than 5 transfers to our European facilities for development and commercialization with more to follow in the near future. And, it is heartening to know that the drugs that we are developing at this facility for our customers are then used to help people around the world. Drugs we have under development for our customers include treatments for blood cancer, muscular dystrophy, wound healing, and dwarfism. ◆

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

Get Educated. Stay Innovative.

New in 2017: The Connect Conference Program

CPhI CONNECT

May 16-18, 2017
Pennsylvania Convention Center
Philadelphia, PA, USA

Powered By

ACS Chemistry for Life®

USP U.S. Pharmacopeial Convention

To strategically address the industry-driving changes within the fine & specialty chemical and pharmaceutical industries, CPhI North America has partnered with the American Chemical Society (ACS), the largest scientific association in the world, and the U.S. Pharmacopeial Convention to bring you a market-leading conference program.

The CPhI Connect Conference Program will have four tracks featuring sessions such as:

- **Innovative Breakthrough Technologies for Drug Targets and Emerging Pathways**
- **Formulation Trends for Topical Dosage Forms** Sponsored By: BASF
- **Navigating GDUFA — Reduce Cost and Accelerate Delivery**
- **Packaging Innovation**
- **Pharmaceutical Impurities**
- **Legal and Policy Strategies for Drug Companies in Today's Global Market**
- **Accelerating Your Product's Development: Practical Considerations from Pre-Clinical through Commercial** Sponsored By: Catalent
- **Determining the Value of Re-Shoring Drug Ingredient Manufacturing** Sponsored By: BIOSPECTRA
- **...and more!**

Go to schedule.cphinorthamerica.com to see the full lineup.

Save up to $200 when you register today!

To register, go to: cphinorthamerica.com/register and use PROMO Code DDD20 to receive an additional 20% off your conference pass when you register before May 15, 2017.

Schedule is subject to change. Discount applicable to non-exhibiting badges only.

CPhI north america

In Partnership With

icse FDF InnoPack informEx

UBM

ANTIMICROBIAL LIPIDS

Attenuating the Use of Medically Important Antimicrobial Drugs in Food-Producing Animals: What Role Can cGMP Lipids Play?

By: Ryan Littich, PhD

ABSTRACT

The US Food and Drug Administration (FDA) recently issued guidance intended to curtail the use of medically important antibiotics in agricultural applications. In the wake of these recommendations, the veterinary medicine community has mobilized to define and commercialize effective alternative pathogen controls. In this article, we draw attention to the scope of the challenge by highlighting some of the most significant, pathogen-borne diseases relevant to food-producing animals. We also review the antimicrobial properties intrinsic to midchain triglyceride lipolysis products, and present the question: What is the untapped potential of these safe-for-consumption, environmentally benign, and mechanistically privileged antimicrobial natural products?

INTRODUCTION

"A definitive link (exists) between the routine, nontherapeutic use of antibiotics in food animal production and the crisis of antibiotic resistance in humans."[1] In 2012, as part of a campaign to reduce the selection pressure that drives the advancement of antibiotic-resistant bacteria strains, the FDA issued Guidance for Industry (GFI) #209, which aims to limit the agricultural use of antibiotics that have important human therapeutic applications,[2] and defines two principles for judicious drug use in food-producing animals. Administration should be (1) limited to those uses that are considered necessary for ensuring animal health, and (2) limited to those uses that include veterinary oversight or consultation. As a corollary, in 2013, the FDA published means for voluntarily phasing out growth promotion indications for medically important antibiotics in accordance with GFI #209.[3] In line with these recommendations, the veterinary health community is striving to bring alternative approaches for mitigating pathogen-borne diseases to bear while maintaining the industry's ability to meet the nutritional demands of a growing global community.

Of course, finding alternative means for preventing, treating, or controlling pathogen-borne diseases in food-producing animals is no easy feat. Pathogenicity ties to a wide array of bacteria (e.g., Gram-negative, Gram-positive, both), can manifest in myriad disorders, and can impact every food-producing animal species. The permutations are daunting and, as a result, comprehensive solutions will continue to be difficult, if not impossible, to identify. The challenge is exacerbated by the fact that antibiotic drug innovation has significantly lagged behind the pace of resistance development.[4,5] The following underscores some of the most pressing indications relevant to different agricultural livestock. Midchain triglycerides, in view of the antimicrobial properties of their lipolysis products, are also discussed as a potentially untapped resource for protecting the food supply and reducing the selection pressure that breeds microbe antibiotic resistance.

UNDERSTANDING THE BREADTH OF THE CHALLENGE

Perhaps the best way to communicate the scope of the selection pressure reduction/animal health protection conundrum is to call attention to some of the challenges recently presented in the open innovation forum. Stakeholders from the animal pharmaceutical industry (e.g., Elanco) have recently issued requests for proposals relevant to swine, poultry, and cattle health. The following case studies are by no means comprehensive, but they do serve to illustrate the breadth of the challenge.

Case Study 1: Ruminant Mastitis

Ruminant mastitis is an inflammatory reaction of udder tissue that is often attributable to bacterial infection. It is the most prevalent disease in dairy cattle in the United States, and is the costliest affliction for the dairy industry. Mastitis accounts for losses of approximately $200 per year, per cow.[6] If the underlying infection persists unchecked, it can be fatal for the animal. Single pathogens or combinations thereof can spur mastitis. The Gram-positive bacteria staphylococci and streptococci are the most commonly observed causative pathogens, but Gram-negative bacteria, such as *E. coli*, have also been observed to cause the disease. *Mycoplasma bovis* is yet another pathogen of increasing relevance as a cause of mastitis. Absent the ability to broadly administer antibiotic mitigations for mastitis going forward – and in view of the 20% infection rate (despite antibiotic regime implementation) – alternative approaches are urgently needed for preventing, treating, or controlling mastitis in dairy cattle and other ruminants.[7,8]

Case Study 2: Porcine Ileitis

Proliferative enteropathy (PE, also known as ileitis) is one of the most prevalent and economically detrimental diseases affecting the global swine industry.[9] Ileitis is caused by the bacterial pathogen, *Lawsonia intracellularis*. The Gram-negative bacterium infects the enteral epithelial cells of the animal, triggering hyperplasia and inflammation in the small and large intestines. To illustrate its economic impact, a recent study of a 735 sample population found an infection rate of 16.87%,[10] and the cost to treat PE is estimated at $2 to $3 per pig ($15 in severe cases).[11] Vaccination, antibiotic treatments, or combinations thereof are effective in the mitigation and treatment of natural and clinically mediated outbreaks of ileitis in pigs.[10] GFI #209 and GFI #213 may limit, however, the continued use of streptogramin (eg, Virginiamycin), macrolide (eg, Tylosin), tetracycline (eg, chlortetracycline) and fluoroquinoline (eg, Enrofloxacin) class treatment options.[11,12] Animal health stakeholders are therefore seeking to bolster the available solution set, which presently includes Enterisol® Ileitis vaccine and veterinary use-approved pleuromutilin class antibiotics (eg, Tiamulin).[13,14]

Case Study 3: Necrotic Enteritis in Poultry

Gram-positive *Clostridium perfringens* have been cited as one of the most common causes of food poisoning in humans, often resulting from insufficient poultry and meat cooking times and temperatures.[15] In living food-producing fowl, necrotic enteritis is one of the most prominent manifestations of *C. perfringens'* enterotoxins. The food safety implications, higher rates of mortality, and stunted animal growth associated with necrotic enteritis are estimated to cost the global poultry industry more than $2 billion annually.[16,17] Until recently, food- and water-borne dispensation of antibiotics was adequate in keeping C. perfringens' pathogenicity at bay. Because some of the administered classes of antibiotics saw shared use in human therapeutics, and because some were used principally for growth promotion, this preventive measure was discontinued. To meet the aspirations of GFI #209 and GFI #213 and protect the health of this integral food-producing animal category, new options are required to control the disease.

ANTIMICROBIAL LIPIDS' RELEVANCE IN THE "POST-ANTIBIOTIC ERA"

The *in vitro* antimicrobial and antiviral potential of fatty acids and monoglycerides has been extensively documented in the primary and secondary scientific literature,[18-20] with the phenomenon first having been documented (in the modern scientific era) in the late 19th century.[21,22] Studies of the biological ramifications of ingesting triglycerides comprising these fatty acids and monoglycerides, however, are perhaps lesser known. For example, a series of inquiries correlating certain dietary lipids and a reduced incidence of pathogen-borne infectious diseases was the subject of unrelated research, which nevertheless seeds a potential approach to mitigating antibiotic resistance.

STUDIES REVEALING LIPIDS' ANTIMICROBIAL PROPERTIES SPUR IMPORTANT QUESTIONS

The antibacterial contribution of fatty acid triglycerides in human colostrum and

milk, and the mechanism by which these lipids realize their antibiotic potential, was defined as part of a broader initiative to rationalize higher infection resistance observed in breast-fed, versus bottle-fed, infants.[23-26] In their seminal 1978 publication, Welsh and May observed that the lipolysis products of colostral lipids – in particular, monoglyceride and fatty acid fractions – were implicit resistance factors in human milk.[27-29] Isaacs and coworkers further substantiated this finding, defining the role of endogenous lipases (lingual and gastric) in unmasking milk triglycerides' antimicrobial activity in the gastric environment.[30-32] Important contemporary research conducted by Kabara et al significantly expanded the understanding of fatty acid/monoglyceride structure-antimicrobial function relationships;[33-37] the superior antibacterial potency of midchain acids and MAGs became clear. In view of this work, Isaacs et al went on to compare the lipase-mediated antiviral potential of infant formulas containing midchain triglycerides against those exclusively containing long chain triglycerides. MCT-containing formulas exhibited much more potent antimicrobial activity than those containing conventional dietary lipids.[38-40] These studies raise important questions as to whether masked antimicrobial triglycerides (ie, midchain and particular structured triglycerides) can meaningfully reduce the incidence of pathogen-borne enteric diseases in agricultural animals.[41]

Is there an analogy to be established with observations of reduced infection occurrence in human infants? If the *in vivo* mechanism of coaxing certain lipid triglycerides' antimicrobial activity holds, the answer is likely "Yes."

TABLE 1

Gram-Positive Bacteria	Antimicrobial Monoglyceride(s)	Antimicrobial Fatty Acid(s)
Streptococci (group A)	C10:0,[33] C12:0,[33,42] C16:1[42]	C10:0,[33] C12:0,[33,42] C16:1,[42] C18:1[42]
Streptococci (group D)	C10:0,[33] C12:0,[33] C11:1,[34] C13:1[34]	C10:0,[33] C12:0[33,34]
Streptococci pyogenes	C11:1, C12:0, C12:1, C13:0, C13:1[34]	C11:0, C11:1, C12:0, C12:1, C13:1[34]
Staphylococcus aureus	C10:0,[33,42] C11:1,[34] C12:0,[33,43-46] C18:2[42]	C10:0,[33,41,42] C11:0,[34] C11:1[34] C12:0,[33,34,42,43] C16:1,[42] C18:1[42]
Corynebacterium sp.	C10:0,[33] C11:1,[34] C12:0[33,34]	C10:0,[33] C11:1,[34] C12:0[33,34], C12:1,[34] C13:1[34]
Candida albicans	C10:0,[33] C11:1,[34] C12:0[33]	C10:0,[33] C11:1,[34] C12:0,[33,34] C12:1,[34] C13:1[34]
Nocardia asteroides	C10:0,[33] C11:1,[34] C12:0[33]	n/a
Bacillus cereus	C10:0,[44] C11:0,[44] C12:0[44]	n/a
Bacillus subtilis	C12:0[44,46-48]	n/a
Enterococcus faecalis	C12:0[44]	n/a
Micrococcus luteus	C11:0,[44] C12:0[44]	n/a
Gram-Negative Bacteria	**Antimicrobial Monoglyceride(s)**	**Antimicrobial Fatty Acid(s)**
Helicobacter pylori	C10:0, C12:0, C14:0, C16:1[49,50]	C8:0, C10:0, C12:0, C14:0, C16:1[49,50]
Campylobacter jejuni	C10:0[49]	C10:0[49]
Campylobacter lari	C10:0[49]	C10:0[49]
Campylobacter coli	C10:0[49]	C10:0[49]
Escherichia coli	C10:0, [44,49] C12:0[44]	C10:0[49]
Citrobacter freundii	C10:0,[44] C12:0,[44] C14:0[44]	n/a
Pseudomon. aeruginosa	C10:0,[44] C12:0,[44] C14:0[44]	n/a
Salmonella entérica	C10:0,[44,49] C12:0,[45] C14:0[44]	n/a
Serratia marcescens	C10:0,[44] C12:0,[44] C14:0[44]	n/a

Gram-negative and Gram-positive bacteria susceptible to the antimicrobial activity of fatty acids and monoglycerides are listed with the carbon chain lengths demonstrating the greatest antimicrobial potency.

ANTIMICROBIAL LIPIDS DEMONSTRATE THE SCOPE TO ADDRESS GRAM-POSITIVE & GRAM-NEGATIVE PATHOGENS

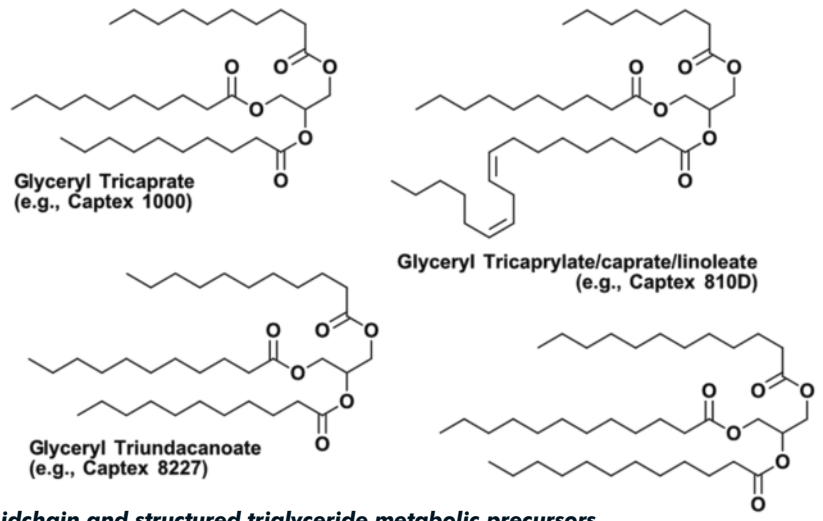
For a dietary or other adjunctive therapeutic strategy to have true utility preventing, treating, or controlling infections in animals, the antimicrobial lipids revealed during lipolysis would need to demonstrate broad antimicrobial efficacy. Indeed, Gram-positive and Gram-negative bacteria have both been shown to be susceptible to the membrane disruptive characteristics of monoglycerides and free fatty acids. Incidentally, midchain variants are the most frequently cited antimicrobial agents. Table 1 highlights specific species of bacteria and the fatty acid and/or monoglycerides that have been observed to inhibit their growth, *in vitro*. Studies conducted by Kabara,[33-37] Bergsson,[42] and McGuire[43] demonstrate that Gram-positive staphylococci and streptococci, the most commonly implicated pathogens in bovine mastitis, succumb to the action of monoglycerides

and fatty acids. Petra,[44] Thormar,[49] and Bergsson[50] have collectively shown that Gram-negative bacteria including *E. coli, H. pylori, various Campylobacter species,* and *P. aeruginosa* are vulnerable to monocaprin. These examples of Gram-negative bactericidal activity bode well for enterally released MAGs' and FFAs' potential to control pathogens responsible for ileitis and necrotic enteritis. As can be gleaned from Table 1, triglyceride lipolysis products show a much broader range of antimicrobial activity than is presently discussed.

NASCENT ANTIMICROBIAL MCT & STRUCTURED LIPIDS ARE PRACTICAL IN USE

Examining the therapeutic effectiveness of masked antimicrobial lipids represents, perhaps, a simpler task than taking on other antibiotic attenuation strategies. Certainly, the scope pales in comparison to that of developing new classes of antibiotics for animal health applications and bringing them to market. To this point, MCTs (eg, C7-C13 fatty acid triglycerides) and structured triglycerides (eg, glyceryl tricaprylate/caprate/linoleate) have a well-established record of safe use in human and animal nutrition applications (Figure 1). Additionally, there is global precedence for the use of lipid-based excipients for enhanced drug delivery in human and veterinary medicine. Implementation approaches for liquid, semi-solid, and solid lipids have also been established, lending credence to the feasibility of this unique application. Lipids can be administered in solid feed formulations, in liquid feed formulations (eg, as dilute emulsions for enteral use), and in formulations designed for modified, targeted and/or controlled release. In the latter case, liposomal, solid lipid nanoparticle and parenteral systems would come in to play. Antimicrobial lipid delivery mechanisms, and the scope of antimicrobial activity of monoglycerides and fatty acids themselves, have been very well reviewed in recent years.[18-20]

FIGURE 1



Midchain and structured triglyceride metabolic precursors for in vivo, enterally released antimicrobial monoglycerides and fatty acids. Non-limiting ABITEC portfolio examples.

AGRICULTURAL APPLICATIONS OF ANTIMICROBIAL LIPIDS ARE ALREADY UNDERWAY

Understanding the antimicrobial potential of monoglycerides and fatty acids – and triglycerides in conjunction with lipolytic enzymes – has, of course, spurred real-world application pursuits. For example, Hilmarsson et al evaluated the effect of glycerol monocaprate on broiler chickens that were deliberately, and naturally, exposed to the Gram-negative bacterium *C. jejuni*.[51] The viable bacteria count in artificially contaminated water (initially, 6 $\log_{10}$ cfu) was observed to be reduced to undetectable levels upon treatment with glycerol monocaprate emulsions (0.6% monocaprin). No infection was observed in chickens provided treated water, and healthy growth was observed in the experimental group. In a nod to the utility of MCTs as masked antimicrobials, Aurousseau et al in 1984 reported an observed 40% growth rate increase in preruminant calves that were fed a glyceryl tricaproate- or tricaprylate-containing milk substitute formulation, as compared with a formula containing tallow lipids alone.[52] The antimicrobial activity of the C6/C8 fatty acids released by gastric lipases in the gut rumen was cited as the principal rationale for the favorable growth outcomes. Perhaps most importantly, Diereck and Decuypere in 2002 methodically demonstrated the use of structured and midchain triglycerides in tandem with lipolytic enzymes to favorably impact the gut flora of piglets.[53,54] These studies reinforce the notion that enterally released fatty acids and monoglycerides constitute a legitimate and effective approach to controlling myriad enteric infections in food-producing animals.

ANTIMICROBIAL LIPIDS' ALIGNMENT WITH THE PRINCIPAL OF DOING NO HARM

Safe for Animal & Human Consumption

As previously mentioned, midchain and structured triglycerides have a well-established record of safe use in food, nutrition, and pharmaceutical applications – human and animal. It should also be underscored that antimicrobial monoglycerides and fatty acids (ie, triglyceride lipolysis products) are Generally Recognized as Safe (GRAS) by the FDA per CFR § 184.1505 and CFR § 172.860, respectively.

Environmentally Friendly

Categorically, midchain and structured triglycerides demonstrate ready biodegradability. This is a function of the fact that they comprise hydrolytically unstable ester bonds, and are composed of natural product fatty acids commonly encountered in the environment and in a wide variety of biological systems.

No Exertion of Selection Pressure

The membrane disruption mechanism underlying FFA and MAG antimicrobial properties[42,50,55,56] does not contribute to the prevalence of antibiotic-resistant bacteria. These species are not understood to invoke the reproductive or metabolic interference mechanisms common to conventional antibiotic classes.

Scalability, Relevance

Midchain and structured triglycerides can be manufactured in a cGMP environment, on scales suitable for the agricultural animal health applications proposed herein.

SUMMARY

Organizations across the food-producing animal industry are proactively doing their part to address the specter of antibiotic resistance. Among them, the animal pharmaceutical industry continues to grapple with how they will continue to enable farmers' delivery against the nutritional demands of a growing global community, while also winding down the use of antibiotics of mutual importance in human therapeutics. In this article, we have raised examples of focal point diseases that are driving the search for viable pathogen control alternatives, and have raised the important role that midchain and structured triglycerides can play in the effort. ◆

REFERENCES

1. Clifford, J.; Khan, A.; Sharfstein, J. Hearing before the House Committee on Energy and Commerce, Subcommittee on Health. July 14, 2010. Antibiotic resistance and the use of antibiotics in animal agriculture. The authors represented the U.S. Food & Drug Administration, the U.S. Department of Agriculture, and the Centers for Disease Control and Prevention.
2. U.S. Food & Drug Administration. Guidance for Industry 213. December 2013. New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI 209. http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf. (Retrieved Dec. 12, 2016).
3. U.S. Food & Drug Administration. Guidance for Industry 209. April, 2012. The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf. (Retrieved Dec. 12, 2016).
4. Cooper, M.A.; Shlaes, D. Nature 2011, 472, 32. Fix the antibiotics pipeline.
5. Shlaes, D.M. et al. Antimicrob. Agents Chemother. 2013, 57, 4605. The FDA reboot of antibiotic development.
6. Department of Animal Science. MacDonald Campus of McGill University. "Mastitis in Dairy Cows" 2003. https://web.archive.org/web/20030708113702/http://animsci.agrenv.mcgill.ca/courses/450/topics/13.pdf. (Retrieved December 27, 2016).
7. Alternatives to antibiotics: Prevention or treatment of food-producing animals. InnoCentive Challenge ID: 9933897. Waltham, MA: InnoCentive, Inc. Posted December 20, 2016. For an additional example of important pathogen-precipitated cattle diseases, see reference 8.
8. Elanco, Inc. Liver Abscess formation in cattle. InnoCentive Challenge ID: 9933889. Waltham, MA: InnoCentive, Inc. Posted November 17, 2016.
9. Kroll, J.J. et al. Animal Health Res. Rev. 2005, 6, 173. Proliferative enteropathy: a global enteric disease of pigs caused by Lawsonia Intracellularis.
10. Alberton, E.L. et al. Acta Sci. Vet. 2011, 39, 943. Prevalence of porcine proliferative enteropathy associated to Lawsonia intracellularis in pigs slaughtered in Mato Grosso State, Brazil.
11. Boehringer Ingelheim Animal Health GmbH. Ileitis Technical Manual 3.0 2006, Ch. 6.2. Which antibiotics are most effective against ileitis? http://www.thepigsite.com/publications/2/ileitis/93/62-which-antibiotics-are-most-effective-against-ileitis/. (Retrieved Dec. 13, 2016).
12. Muirhead, M.R.; Alexander, T.J.L. Managing Pig Health: A Reference for the Farm, 2nd Ed. Carr, J. (ed.) 5M Publishing: United Kingdom, 2013.
13. Elanco, Inc. Prevention and Control of Enteropathy/Ileitis in Swine. InnoCentive Challenge ID: 9933892. Waltham, MA: InnoCentive, Inc. Posted December 1, 2016. For an additional example of an important pathogen-precipitated cattle disease, see reference 14.
14. Elanco, Inc. Prevention and control of Streptococcus suis infections in swine. InnoCentive Challenge ID: 9933893. Waltham, MA: InnoCentive, Inc. Posted September 8, 2016.
15. Warrell et al. Oxford Textbook of Medicine, 4th ed.; Oxford, UK: Oxford University Press; 2003.
16. Elanco, Inc. Prevention, treatment or control of necrotic enteritis in poultry. InnoCentive Challenge ID: 9933891. Waltham, MA: InnoCentive, Inc. Posted October 14, 2016.
17. Elanco, Inc. Coccidiosis prevention and control in poultry. InnoCentive Challenge ID: 9933890. Waltham, MA: InnoCentive, Inc. Posted December 15, 2016.
18. Thormar, H.; Hilmarsson, H. Chem. Phys. Lipids 2007, 150, 1. The role of microbicidal lipids in host-defense against pathogens and their potential use as therapeutic agents.
19. Jackman, J.A. et al. Molecules 2016, 21, 305. Nanotechnology formulations for antibacterial free fatty acids and monoglycerides.
20. Dayrit, F.M. J. Am. Oil Chem. Soc. 2015, 92, 1. The properties of lauric acid and their signifi-

cance in coconut oil. Clark. J.R. Botan. Gaz. 1899, 28, 289.
21. Thormar, H. Antibacterial Effects of Lipids: Historical Review (1881 to 1960), in Lipids and Essential Oils as Antimicrobial Agents; Hoboken, NJ: John Wiley & Sons, Ltd; 2011.
22. Cunningham, A.S. J. Pediatr. 1977, 90, 726. Morbidity in breast-fed and artificially fed infants.
23. Downham, M.A.P.S. et al. Br. Med. J. 1976, 2, 274. Breast-feeding protects against respiratory syncytial virus infections.
24. Winberg, J.; Wessmer, G. Lancet 1971, 1, 1091. Does breast milk protect against septicaemia in the newborn?
25. Adebonojo, F.O. Clin. Pediatr. 1972, 11, 25. Artificial vs. breast feeding: relation to infant health in a middle class American community.
26. Welsh, J.K.; Skurrie, I.J.; May, J.T. Infect. Immun. 1978, 19, 395. Use of Semliki Forest Virus to identify lipid-mediated antiviral activity and anti-alphavirus Immunoglobulin A in human milk.
27. Welsh, J.K.; May, J.T. J. Pediatr. 1979, 94, 1. Anti-infective properties of breast milk.
28. The lipolytic cleavage mechanism leading to lipid (triglyceride) antimicrobial activity, in vivo, was first observed by Canas-Rodriguez and Smith. (a) Canas-Rodriguez, A.; Smith, W. Biochem. J. 1966, 100, 79-82. The identification of the antimicrobial factors of the stomach contents of suckling rabbits; (b) Smith, H. J. Pathol. Bacteriol. 1966, 91, 1-9. The antimicrobial activity of the stomach contents of suckling rabbits. Discussed in: Isaacs, C.E. et al. J. Infect. Dis. 1986, 154, 966. Membrane disruptive effect of human milk: inactivation of enveloped viruses.
29. Isaacs, C.E. et al. Arch. Dis. Childhood 1990, 65, 861. Antiviral and antibacterial lipids in human-milk and infant formula feeds.
30. Thormar, H.; Isaacs, C.E.; Brown, H.R.; Barhatzsky, M.R. Antimicrob. Agents and Chemo. 1987, 31, 27. Inactivation of enveloped viruses and killing of cells by fatty acids and monoglycerides.
31. Kabara, J.J. et al. Antimicrob. Agents Chemother. 1972, 2, 23. Fatty acids and derivatives as antimicrobial agents.
32. Kabara, J.J. et al. Lipids 1977, 12, 753. Antimicrobial lipids: Natural and synthetic fatty acids and monoglycerides.
33. Kabara, J.J. J. Soc. Cosmet. Chem. 1978, 29, 733. Structure-function relationships of surfactants as antimicrobial agents.
34. Kabara, J.J. Nutr. Rev. 1980, 38, 65. Lipids as host-resistance factors of human milk.
35. Kabara, J.J. J. Am. Oil Chem. Soc. 1984, 61, 397. Antimicrobial agents derived from fatty acids.
36. Isaacs, C.E. Thormar, H. 1991. The role of milk-derived antimicrobial lipids as antiviral and antibacterial agents. In: Advances in experimental medicine and biology: immunology of milk and the neonate. Mestecky, J.; Ogra, P.L., eds. New York, NY: Plenum Press, pp. 159-165.
37. Isaacs, C.E. et al. J. Nutr. Biochem. 1992, 3, 304. Addition of lipases to infant formulas produces antiviral and antibacterial activity.
38. Isaacs, C.E. et al. Nutr. Biochem. 1995, 6, 362. Antimicrobial activity of lipids added to human milk, infant formula, and bovine milk.
39. Decuypere, J.A.; Dierick, N.A. Nutr. Res. Rev. 2003, 16, 193-209. The combined use of triacylglycerols containing medium-chain fatty acids and exogenous lipolytic enzymes as an alternative to in-feed antibiotics in piglets: concept, possibilities and limitations. An overview.
40. Bergsson, G. et al. APMIS 2001, 109, 670. Killing of Gram-positive cocci by fatty acids and monoglycerides.
41. Kelsey, J.A.; Bayles, K.W.; Shafii, B.; McGuire, M.A. Lipids 2006, 41, 951. Fatty acids and monoacylglycerols inhibit growth of Staphylococcus aureus.
42. Petra, Š. et al. Eur. J. Lipid Sci. Technol. 2014, 116, 448. Formulation, antibacterial activity, and cytotoxicity of 1-monoacylglycerol microemulsions.
43. Zhang, H. et al. Int. J. Food Microbiol. 2009, 135, 211. Antimicrobial activity of a food-grade fully dilutable microemulsion against Escherichia coli and Staphylococcus aureus.
44. Zhang, H. et al. Int. J. Pharm. 2010, 395, 154. Characterization and antimicrobial activity of a pharmaceutical microemulsion.
45. Fu, X. et al. Int. J. Pharm. 2006, 321, 171. Physicochemical characterization and evaluation of a microemulsion system for antimicrobial activity of glycerol monolaurate.
46. Fu, X. et al. J. Food Process Eng. 2009, 32, 104. Enhancement of antimicrobial activities by the food-grade monolaurin microemulsion system.
47. Thormar, H. et al. App. Environ. Microbiol. 2006, 72, 522. Stable concentrated emulsions of 1-monoglyceride of capric acid (monocaprin) with microbicidal activities against the food-borne bacteria Campylobacter jejuni, Salmonella spp., and Escherichia coli.
48. Bergsson, G. et al. Antimicrob. Agents Chemother. 2002, 20, 258. Bactericidal effects of fatty acids and monoglycerides on Helicobacter pylori.
49. Hilmarrson, H.; Thormar, H.; Thrainsson, J.H.; Gunnarsson, E. Poultry Sci. 2006, 85, 588. Effect of glycerol monocaprate (monocaprin) on broiler chickens: An attempt at reducing intestinal Campylobacter infection.
50. Aurousseau, B.; Thivend, P.; Vermorel, M. Annales de Zootechnique 1984, 33, 219-234. Influence of replacement of part of the tallow in a food by tricaproqne or tricapryline in association with coconut oil on the growth of young preruminant calves.
51. Diereck, N. et al. Livestock Prod. Sci. 2002, 75, 129-142. The combined use of triacylglycerols (TAGs) containing midchain fatty acids (MCFAs) and exogenous lipolytic enzymes as an alternative for nutritional antibi
otics in piglet nutrition. I: In vitro screening of the release of MCFAs from selected fat sources by selected exogenous lipolytic enzymes in simulated pig gastric conditions and their effects on the gut flora of piglets.
52. Diereck, N. et al. Livestock Prod. Sci. 2002, 76, 1-16. The combined use of triacylglycerols (TAGs) containing midchain fatty acids (MCFAs) and exogenous lipolytic enzymes as an alternative for nutritional antibiotics in piglet nutrition. II: In vivo release of MCFAs in gastric cannulated and slaughtered piglets by endogenous and exogenous lipases; effects on the luminal gut flora and growth performance.
53. Bergsson, G. et al. Antimicrob. Agents Chemother. 1998, 42, 2290. In vitro inactivation of Chlamydia trachomatis by fatty acids and monoglycerides.
54. Lampe, M.F. et al. Antimicrob. Agents Chemother. 1998, 42, 1239. Killing of Chlamydia trachomatis by novel antimicrobial lipids adapted from compounds of human breast milk.

BIOGRAPHY

Dr. Ryan Littich is Innovation & Special Programs Manager at ABITEC Corporation. He is responsible for the development of solution-driven lipid excipient technology and applications. Professionally, he draws on experience within a VC-backed biotechnology start-up, having led new product development in an organization commercializing Nobel Prize-winning catalyst technology to transform natural triglycerides into fine and specialty chemicals. He is a classically trained synthetic organic chemist with a foundation in the de novo synthesis of medicinally relevant, complex natural products. He earned his BA in Chemistry from Ferris State University, and his PhD in Synthetic Organic Chemistry from the University of Texas at Austin.

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

Technology & Services Showcase

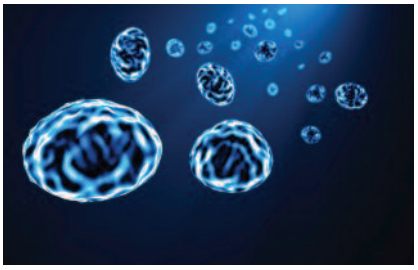
CDMO Services

ALTHEA

THE POWER TO MAKE®

Althea is a fully integrated, contract development and manufacturing organization providing clinical and commercial product development services. Althea offers cGMP drug product filling in both vials and syringes, and production of microbial-derived recombinant proteins and plasmid DNA. In conjunction with these manufacturing operations, Althea offers comprehensive development services, including upstream and downstream process development, analytical development, lyophilization cycle, complex formulation, product release and ICH-compliant stability testing. In addition, Althea offers a proprietary formulation technology platform, Crystalomics®, and an innovative recombinant protein expression technology called Corynex® technology. Althea is the manufacturing partner that delivers the relentless dedication and support our clients need. For more information, visit Althea at **www.altheacmo.com.**

Nanoparticle Formulations



Ascendia Pharmaceuticals is a contract development and manufacturing (CDMO) company offering services for formulation development of poorly soluble drugs and other challenging development programs. Our formulation options include nanoemulsions, amorphous solid dispersions, nanoparticles, liposomes, and oral controlled release. These technologies are suitable for oral, topical, or injectable dosage forms. NanoSol is our technology for production of nanoparticle formulations. Ascendia has the capability to make nanoparticles from native drug crystals using ball milling, or lipid-based nanoparticle composites for lipophilic drugs. When the nanoparticle is delivered to the body there is greater surface area for dissolution, and by using enhancers in the formulation higher bioavailability can be more readily achieved. Ascendia can optimize nanoparticle formulations and produce clinical trial materials for first-in-man studies. For more information, contact Ascendia at (732) 640-0058 or visit **www.ascendiapharma.com.**

Sampling System

With a proven ability to collect accurate representative samples, maintain bioreactor sterility, and generate real-time product quality data, the Modular Automated Sampling Technology (MAST™) system is a breakthrough for bioprocessing. Developed through a focused 5-year development program in collaboration with 10 of the world's largest pharmaceutical companies, MAST brings product quality attribute control one step closer to reality. For more information about MAST, visit **http://mastsampling.com/.**

Platform Technology

CAPTISOL®

Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 8 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.com.**

BIO International Convention

The Global Event for Biotechnology

BIO PARTNERING OPENS APRIL 2017

ONE ON ONE PARTNERING™ Powered by BIO

Meet thousands of executives and leaders from these companies with **BIO One-on-One Partnering™**:

DOUBLE HELIX

abbvie · AMGEN · Bristol-Myers Squibb · Genentech *A Member of the Roche Group* · Johnson & Johnson · MERCK

HELIX

Lilly · Pfizer · SANOFI

JUNE 19-22, 2017 • SAN DIEGO, CA • CONVENTION.BIO.ORG • #BIO2017

Technology & Services Showcase

OptiForm® Solution Suite

Catalent's OptiForm® Solution Suite was launched in 2015 and combines both predictive and high throughput screening tools to identify the most stable and efficient drug form for small molecules. By matching the best drug delivery technologies to each developmental molecule, optimal preclinical PK materials can be delivered in just 12 weeks. OptiForm Solution Suite Bio extends the rapid screening technology platform to include macromolecules and the identification of suitable non-invasive methods of drug delivery for biological drug products. Expanding the scope to encompass macromolecules, OptiForm Solution Suite Bio employs Catalent's OptiGel™ Bio and Zydis® Bio advanced formulation technologies, and uses a parallel screening model, based on rigorous science and best-in-class formulation expertise, to deliver in vivo study material in as little as three weeks. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com**.

Full-Service CDMO

CordenPharma is your full-service CDMO partner in the Contract Development & Manufacturing of APIs, Drug Products, and associated Packaging Services organized under 5 technology platforms: Peptides, Oligonucleotides, Lipids & Carbohydrates, Injectables, Highly Potent & Oncology, Small Molecules, and Antibiotics. With multiple cGMP manufacturing facilities across Europe and the US, CordenPharma experts translate your complex ideas into high-value products at any stage of development. CordenPharma provides proprietary peptide, lipid, carbohydrate, and oligonucleotide technologies for cGMP-compliant products and services. We additionally specialize in the manufacturing and containment of highly potent peptide APIs (with exposure limits as low as 1 ng/m^3), highly potent formulations (solid forms), cephalosporins & penicillins (oral & sterile), oncology drug products (oral & sterile), and packaging. For more information, visit CordenPharma at **www.cordenpharma.com.**

On Body Delivery System

Enable Injections' on body delivery system (OBDS) delivers high-volume, often viscous drugs subcutaneously for patients to conveniently and discreetly inject at home, work, or on the move. The design is based upon over 12 years of research in minimizing injection pain with a strong emphasis on the end-user and Human Factors. The platform consists of a single injector up to 5-ml, 10-ml, 20-ml, 30-ml, 40-ml, 50-ml capacity - and associated transfer system. One of the three transfer systems (Syringe, Vial, or Fully Automated Reconstitution) is combined with each injector to provide the user with a simple disposable package. This package transfers the drug from the original container closure to the injector in a few intuitive steps. For more information, visit Enable Injections at **www.enableinjections.com.**

High-Performance Micronizer

The PinMill-Lab is a high-performance micronizer designed for pulverizing hard or crystalline products to D90 > 10 m. It is deal for processing small-scale laboratory batches of 50 g > 2 kg. It can also be used for pilot-scale production up to 50 kg/h. The unit's compact design facilitates quick setup and easy integration. Easily interchangeable on a Tri-Clamp flange; the head can be confined with either a rigid or a flexible isolator; its inlet directly integrated with a volumetric dosing system. The head, easily cleanable, can also be sterilized. Up to 99% product recovery due to the innovative design of the milling chamber. Milling head is available for operation in ATEX Zones 1/ 21. For more information, visit Frewitt at **www.frewitt.ch.**

Technology & Services Showcase

CMC Services

FRONTAGE
YOUR DRUG DEVELOPMENT PARTNER

Ensure comprehensive product analysis with Frontage's team of experienced analytical scientists. We specialize in analytical method development, validation and transfer for product development and clinical trial materials (CTM) manufacturing support, as well as commercial product release and stability testing. Our services are designed to help sponsors throughout the drug development process in their effort to fully characterize drug substances, developmental formulations and commercial drug products. Our facilities house a wide range of the latest analytical instrumentation for a comprehensive array of methods. And, we continually keep pace with technology to ensure compliance with evolving regulatory and market requirements. Our development team can solve your analytical challenges efficiently. For more information, contact Frontage at (610) 232-0100 or visit **www.frontagelab.com.**

Fast Track to Clinical Trials

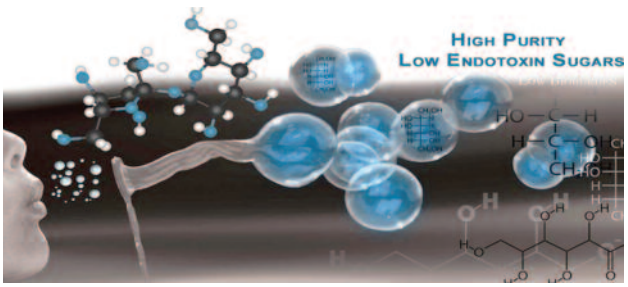
metrics contract services

With more than 140 successful FTIM fast track to clinical trial studies and materials completed, **Metrics Contract Services** understands what it takes to deliver this challenging and critical service. We offer a commitment to a 16- to 24-week timeline from receipt of a well-characterized NCE to shipment of clinical materials, plus specialized equipment, like our Xcelodose 600 micro dosing system, and a standardized internal process to ensure both speed and accuracy. For more information on our Fast Track to Clinical Trials services, visit **www.MetricsContractServices.com.**

Drug Delivery Solutions

With over 1,500 people and 4 plants across two continents, **Nemera** is a world leader in the design, development and manufacturing of drug delivery solutions for the pharmaceutical, biotechnology, and generics industries.
Nemera leverages decades of experience in the devices sector, from full solution development to pure contract manufacturing, through customized solutions. Nemera's expertise covers several modes of delivery: Ophthalmic (multidose, preservative-free eyedroppers), Nasal, Buccal, Auricular (pumps, valves, and actuators for sprays), Dermal & Transdermal (airless and atmospheric dispensers), Parenteral (auto-injectors, pens, safety devices, and implanters), and Pulmonary (pMDIs, DPIs). Over 5 million diabetics and 10 million asthmatics use every day the devices manufactured by Nemera. For more information, contact Nemera at information@nemera.net or visit **www.nemera.net.**

Specialized Products & Services



Pfanstiehl is a leading cGMP manufacturer of parenteral grade excipients and highly potent APIs. Pfanstiehl develops and manufactures high-purity, low-endotoxin (HPLE) carbohydrates such as trehalose, sucrose, mannitol, galactose, and mannose utilized as injectable excipients for the stabilization of proteins, mAbs, and vaccines. These HPLEs are also used as supplements for industrial cell culture, cell therapy, and cryopreservation media. Pfanstiehl also works closely with some of world's largest multinational pharmaceutical and biopharmaceutical firms, as well as with virtual pharmaceutical companies, to synthesize proprietary and commercial compounds in quantities ranging from grams to MT quantities. Manufacturing and development occur at Pfanstiehl's a 13-building campus located near Chicago, IL. For more information, visit us at **www.pfanstiehl.com.**

Technology & Services Showcase

Global Data & Analytics

PharmaCircle is a leading provider of global data and analysis on the pharmaceutical, biotechnology, and drug delivery industries. PharmaCircle's premier database delivers an integrated scientific, regulatory, and commercial landscape view with unprecedented access to hundreds of company, product, and technology attributes. PharmaCircle connects product and pipeline information for drugs and biologics with formulation and component details, and provides due diligence level data on nearly 6,000 drug delivery technologies and devices. Drug label comparison tools and full-text document search capabilities help to further streamline research. No other industry database matches PharmaCircle's breadth of content and multi-parameter search, filtering, and visualization capabilities. To learn more, email contact@pharmacircle.com, call (800) 439-5130, or visit **www.pharmacircle.com.**

Dosage Form Innovation

UNITHER PHARMACEUTICALS

NEW WAYS FOR YOUR PRODUCTS

Unither Pharmaceuticals is a unique development and manufacturing partner for proprietary and generic dosage forms, and a global leader in single-unit dose technologies, such as sterile blow-fill-seal, and liquid and powder stick-packs. As a global company serving over 80 countries from manufacturing operations in both Europe and North America, Unither Pharmaceuticals offers a range of innovative single-unit dosage forms and delivery systems that can differentiate products and extend product lines for OTC and Rx products. Unither's focus is delivering medicines that are convenient, affordable, and easy to use. Unither technology benefits patients by offering improved dosing safety and compliance with pre-measured, correct dosing that reduces the risk of medication errors. For more information, visit Unither at **www.unither-pharma.com.**

Development Services

UPM Pharmaceuticals®
Formulating Your Future™

UPM Pharmaceuticals is an independent, award-winning contract development and manufacturing organization (CDMO). The Bristol, TN-based CDMO serves the pharmaceutical and biotechnology industries with its offering in tablet, capsules, and semi-solid dosage form manufacturing – including DEA controlled substances (CII-CV) and a controlled humidity suite. Experienced personnel at UPM can provide high-quality pharmaceutical drug development services that include formulation development, cGMP manufacturing and packaging, analytical method development and testing from concept through commercialization all in one 476,000-sq-ft facility. UPM is characterized by its strict sense of quality, timeliness, sound scientific fundamentals, and affordability with which they complete all projects to ensure success to clinic/market. For more information, contact UPM Pharmaceuticals at (423) 989-8000 or visit **www.upm-inc.com.**

Integrated Delivery Systems

West is a leader in developing and manufacturing pharmaceutical delivery systems. The company has unique technologies in self-injection systems, including the SmartDose® electronic wearable injector and the SelfDose® injector, that enable patients to self-administer injectable medicines at home. West is also collaborating with HealthPrize Technologies on a connected health offering that is designed to improve and reward medication adherence with unique technologies. The offering integrates HealthPrize's Software-as-a-Service medication adherence and patient engagement platform into injectable drug delivery systems, providing biopharmaceutical companies and their patients with an end-to-end connected health solution. For more information, contact West at (800) 345-9800 or visit **www.westpharma.com.**

SAMPLE PREPARATION MARKETS

Automation & Application Trends Drive Growth in Sample Preparation Markets

By: Christi Bird, Senior Industry Analyst & Associate Fellow in Frost & Sullivan's Life Sciences & Transformational Health Team

INTRODUCTION

Sample preparation remains one of the largest challenges and bottlenecks in research, but is crucial to the success of downstream applications. The sample quality that emerges from preparation tasks, like nucleic acid or protein isolation and purification, pipetting, and other liquid-handling requirements, can greatly impact the accuracy of research. If these tasks are not preformed properly, they can impair entire projects and cost laboratories thousands of research dollars in having to duplicate work, or worse yet, waste precious samples that cannot be restored. Given the higher scrutiny on research data accuracy; stricter quality standards in applied markets like clinical testing, forensics, and food and beverage testing; and a greater focus on laboratory efficiency, labs continue to move toward automated sample preparation methods. Instruments for automated nucleic acid purification and isolation (NAPI), liquid handling, and library preparation for next-generation sequencing (NGS) are gaining popularity in response. In addition to delivering higher quality prepared samples, advantages of these systems over manual tasks include the reduction of human error, significantly less hands-on time required, speed, increased throughput, reproducibility, reliability, and increased laboratory efficiency.

While automation has been standard in many organizations for years, including most pharmaceutical and biotechnology settings, many laboratories viewed automation as an unaffordable, expensive luxury item. Why buy an expensive instrument when graduate students and lab technicians can accomplish it cheaply in a manual fashion? However, the launch of more affordable benchtop sample preparation instruments along with greater scrutiny on research accuracy, driven by an increase in scientific publication retractions, are two of the reasons that view has started to change. Meanwhile, downstream application trends are constantly evolving, driving new product development in upstream sample preparation and often increasing sample throughput. Automation and application trends are the main drivers across the liquid handling and nucleic acid purification markets, keeping these seemingly mature markets growing steadily at single digits. Here, we discuss the many factors impacting these sample preparation markets and examine market metrics.

COST FACTORS MAKING AUTOMATION MORE AFFORDABLE

Human error, contamination, low purity quality, and inconsistent yield are major problems associated with manual sample preparation, particularly nucleic acid purification. These issues can cause inaccuracies in data and experiments to be discarded with all relevant reagents, should data errors occur. The demand for more accurate data, the desire to eliminate costly errors, and the need to keep standards consistent across samples are driving more labs to seek automated sample preparation instruments. In drug discovery applications, this reduction of variation enables easier identification of hits and decreases the number of false positives in an expensive assay downstream. Accuracy upstream increased through automated methods can achieve better results downstream, reducing the need for multiple runs to verify results.

Therefore, when labs assess the cost of products, labor, project time, and increase in the funding timeline cycle associated with errors in sample preparation, reliable automated methods become more affordable.

Furthermore, the development of low-to-mid throughput "personal" benchtop nucleic acid instruments, liquid handlers, and library prep instruments at lower price points have greatly expanded the accessibility of automation. These instruments have lower throughputs and complexity, yet are sufficient for many of the lower-throughput applications that run less than 24 samples a day and allow labs to gain the benefits of automation without the high price tag. As more options are launched and prices decline, labs will adopt these instruments more extensively. These affordable systems are changing the view that sample preparation instruments are luxuries; now they are seen as standard equipment labs need in order to deliver quality data and keep up in their fields.

DOWNSTREAM APPLICATION TRENDS DRIVING NEW PRODUCT DEVELOPMENT & GROWTH IN UPSTREAM SAMPLE PREPARATION

The needs of downstream applications and assays drives sample preparation and liquid handling needs upstream. Thus, as laboratories adopt new applications, they often require new tools on the front end of the workflow, which can translate to purchases of new instruments and reagents to accommodate the changing needs. Some of the fast-growing applications driving changes in the sample preparation market and the need for automated sample preparation include next-generation sequencing, single cell analysis, circulating cell-free DNA and tumor cell analysis, biologics drug discovery, pharmacogenomics, mass spectrometry, cell biology, food and beverage testing, agricultural research, environmental testing, and molecular diagnostics testing. The uptake of these popular and fast-growing applications is informing new product development in sample preparation, increasing sample throughput, and expanding the need for automation.

Within the life sciences industry, application trends shift over time, and new applications are constantly being developed. These application changes generate the need for new products, helping to generate organic growth for competitors. In addition, they create opportunities for competitors to differentiate from other suppliers, and in some cases, specialize in a niche market. For instance, a first-to-market competitor with a purification kit or specialized instrument for a new emerging application has an incredible opportunity to gain an early market stronghold in that niche. For instance, in the nucleic acid purification kit market famously dominated by Qiagen, MO BIO Laboratories carved out a market-leading niche in environmental research, particularly in soil and microbial isolation kits. It was no surprise when Qiagen subsequently acquired MO BIO in late 2015. Ultimately, those companies at the forefront of application changes have the best chance to launch early, successful products that help them carve out niches in the sample preparation markets.

Previously, the majority of liquid-handling portfolios were application universal, meaning they were not designed for, or optimized to, a specific downstream application. Now that the market has many universal products across various throughputs, technologies, speeds, and capabilities, companies are looking for other ways to differentiate. Throughout the past few years, competitors started to launch application-specific nucleic acid purification instruments and liquid handlers. This has occurred on a small scale within the NAPI market, with instruments such as Promega's Maxwell CSC and Maxwell 16 both optimized for IVD use, and Hamilton's Genomics STARlet and Forensic STARlet Workstations targeting genomics and forensics, respectively. In the liquid-handling market, companies have already targeted even more specific applications, such as next-generation sequencing, molecular biology, and cell biology. Perkin Elmer's Sciclone NGSx and Zephyr molecular biology workstations, Eppendorf's epMotion 5070 CB system for cell biology, and Tecan's Fluent cell biology system are examples of recently launched application-specific instruments. Many new product launches throughout the next 5 years will be application specific or technology specific to popular and quickly growing fields. These instruments would offer optimized protocols for particular applications, with vendors providing application support to customers.

In addition to driving product development among competitors, this trend is likely to be the source of new entrants in the market. Companies that develop downstream growth technologies or assays are well positioned to develop upstream sample preparation tools. They may develop such products on their own, but are more likely to partner with or acquire current liquid-handling or NAPI competitors.

Furthermore, several M&A moves throughout the past few years in the life science tools industry have centered on next-

"These market factors are helping drive considerable growth in automated sample preparation markets. In 2015, the US Nucleic Acid Purification and Isolation Instruments Market was forecast to surpass $200 million in revenue generation for market competitors. Moving forward, the market is forecast to grow at a compound annual growth rate (CAGR) of 8.1% between 2014 and 2021, reaching $328.0 million in 2021. More than 15 companies competed in the NAPI instruments market in 2015. The most recognized competitors are Qiagen, Thermo Fisher Scientific, and Promega, yet several other big-name life science tools companies play within this space, including Beckman Coulter, Eppendorf, Hamilton, Perkin Elmer, and Roche."

generation sequencing. Many have involved large companies purchasing emerging sequencing technology startups to potentially launch sequencers that would compete with Illumina and Thermo Fisher Scientific (ie, Life Technologies; the top two providers in NGS. These past acquisitions include Qiagen's acquisition of Intelligent BioSystems, Roche's acquisition of Genia Technologies, and Bio-Rad's acquisition of GnuBIO. It is likely that several additional acquisitions of sequencing start-ups will occur given the numerous entrepreneurial companies aiming to develop the next big sequencer. If any of these start-ups are successful in launching competitive sequencers, they will likely consider expanding their offerings along the sequencing workflow. Much like Illumina-acquired nucleic acid purification provider Epicentre, these sequencing companies may look to NAPI competitors as potential acquisition targets or partners. As these sequencing start-ups are likely to take several more years to launch sequencers and become established, M&A and partnerships with NAPI companies are likely to pick up in the long-term. Thus, as a high-growth application, it is expected to see NAPI companies positioning their products toward the NGS industry, increasing their chances of M&A or partnership down the line, in addition to benefiting from strong growth.

AUTOMATED SAMPLE PREPARATION MARKET METRICS

These market factors are helping drive considerable growth in automated sample preparation markets. In 2015, the US Nucleic Acid Purification and Isolation Instruments Market was forecast to surpass $200 million in revenue generation for market competitors. Moving forward, the market is forecast to grow at a compound annual growth rate (CAGR) of 8.1% between 2014 and 2021, reaching $328.0 million in 2021. More than 15 companies competed in the NAPI instruments market in 2015. The most recognized competitors are Qiagen, Thermo Fisher Scientific, and Promega, yet several other big-name life science tools companies play within this space, including Beckman Coulter, Eppendorf, Hamilton, Perkin Elmer, and Roche. Qiagen dominates with its QiaSymphony portfolio of instruments, particularly in the molecular diagnostics industry, with the entire line selling about 250 instruments per year. Qiagen's QiaCube is the leading spin column-based NAPI instrument. Thermo Fisher Scientific and Promega differentiated from Qiagen early in market inception by using magnetic bead technology for their instruments. Now most competitors use magnetic bead technology due to its amenability to being automated and its throughput scalability. Laboratories running 12 to 24 samples a day can get away with using a spin column-based instrument, while greater throughput levels veer toward automation through magnetic bead chemistry. Moving forward, optimization to specific applications, the abil-

ity to provide workflow solutions and pricing are likely to be the major competitive factors within the NAPI instruments market.

Meanwhile in the US Liquid-Handling Market, the combined automated robotic workstations and low-to-mid throughput automated tools segments were forecast to reach $383.0 million in 2015 and grow at a CAGR of 5.4% between 2014 and 2021. The combination of these markets is expected to surpass a half-billion in revenue in the US by 2021. More than 15 companies competed in the US automated robotic workstations market in 2015 and over 25 competed in the low-to-mid throughput range of instruments. Tecan, Eppendorf, Hamilton Robotics, Beckman Coulter, Perkin Elmer, Thermo Fisher Scientific, and CyBio/Analytik Jena are the top competitors within these markets. Tecan is the long-held market leader in the high-throughput automated robotic workstations market with a very broad portfolio of liquid handlers along the spectrum of throughputs and laboratory needs, as well as a well-established installed base worldwide. The low-to-mid throughput automated liquid-handling tools market is much more fragmented than the high-throughput market, with more competitors and a wide range of product offerings. However, Eppendorf's epMotion line of benchtop instruments is perhaps the most widely recognized and used in the industry. The low-to-mid throughput "personal" benchtop liquid-handling market has been an attractive segment for existing competitors to expand their portfolios to reach new customer bases, as well as for new market entries. These instruments are less complex to develop than robotic workstations, making this an easy entry point for automated liquid handlers. Competitors in the liquid-handling market are expected to compete on ease of use, flexibility, task integration, and customization capabilities moving forward.

SUMMARY

Sample preparation remains a critical task in many research and testing workflows across biopharmaceutical, basic research, clinical, and industrial applications. While the market lacks the hype and excitement of NGS, CRISPR/Cas9, or the microRNA and epigenetics boom several years ago, the sample preparation market will always be a slow and steady gainer on an already large market size. Downstream applications will always evolve, researchers will always dream of larger cohort studies, standards and requirements will always get stricter instead of more lenient, and automation will always improve and become more accessible. These factors will consistently result in new product development and greater sample throughputs, ultimately driving growth along the spectrum of sample preparation markets. ◆

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

BIOGRAPHY

Christi Bird is a Senior Industry Analyst and Associate Fellow in Frost & Sullivan's Life Sciences and Transformational Health Team. She has a broad range of expertise in the Life Sciences, specializing in the Life Science Research Tools and Laboratory Products and Services Markets. She holds 11 years of research and consulting experience managing projects spanning market intelligence, competitive benchmarking, emerging markets, and customer research, among others. Prior to joining Frost & Sullivan, she held a Project Management Analyst role at the National Institute of Health's National Human Genome Research Institute. Ms. Bird earned her BS in Biology and English from Georgetown University in Washington, DC. For more information on Frost & Sullivan's Global Life Sciences Practice and offerings, or the market mentioned within this article, please reach out to Kayla Belcher, kayla.belcher@frost.com, Corporate Communications Associate for Frost & Sullivan, North America.

ONLY THREE WEEKS LEFT

REGISTER NOW!

Drug-DevConference.com

2ND ANNUAL

Innovation Networking Summit &

TABLE-TOP EXHIBITION

MAY 4-5, 2017

HILTON HOTEL

PARSIPPANY, NJ

For more details and to reserve your table-top and sponsorship, contact:

John Kiesewetter
T: 541-338-0022
E: jkiesewetter@drug-dev.com

Ralph Vitaro
T: 973-263-5476
E: rvitaro@drug-dev.com

Drug Development
& Delivery

CONFERENCE SPEAKERS

Keynote Speaker
Donald Sebastian, PhD
President & CEO, New Jersey Innovation Institute & Senior Vice President, Technology & Business Development, New Jersey Institute of Technology

Keith Horspool, PhD
VP of Material & Analytical Sciences, Boehringer Ingelheim

Jeffrey Bacha, MBA
Chairman & CEO, DelMar Pharmaceuticals

Finn Bauer, PhD
Director of R&D & Head of Solid Formulations, MilliporeSigma

Scott Brown, MS
Executive Director, Device Development, Merck

Nila Das, PhD
Senior Research Investigator, Bristol-Myers Squibb

Martin Eastgate, PhD
Director, Chemical & Synthetic Development, Bristol-Myers Squibb

Mahen Gundecha, MBA
Head of Alliance Management, Sandoz Inc. (Novartis Group)

Tom Johnson
Senior Director, Life Science Solutions, Exostar

Conrad F. Mir
President & CEO, Calmare Therapeutics

Kurt Nielsen, PhD
President, Lupin

Peter Pekos, MSc
President & CEO, Dalton Pharma Services

Mathias Romacker, MA
Senior Director, Device Strategy, Pfizer

Laurie Smaldone, MD
COO & CSO, NDA Group AB

Ronald L. Smith, PhD
Scientific Assoc. VP, Pharmaceutical Sciences, Merck Research Laboratories

Cornell Stamoran, PhD
Vice President, Strategy for Catalent, Inc., & Co-Chair, Catalent Applied Drug Delivery Institute

Lilli Zakarija MSME, MBA
Co-Founder/ President, EdgeOne Medical

GOLD SPONSORS

ADARE Pharmaceuticals™

Catalent APPLIED DRUG DELIVERY INSTITUTE

Catalent®

GATTEFOSSÉ

PharmaCircle™ The Information You Need At Your Fingertips

SGW | Pharma MARKETING

SILVER SPONSORS

LifeSciencePR

BRONZE SPONSORS

CRODA

EVONIK POWER TO CREATE

ASCENDIA PHARMA

TABLE-TOP EXHIBITORS

Adare Pharmaceuticals
Ascendia Pharma
Captisol
Catalent
CordenPharma
Croda
DPT Labs
EdgeOne Medical
EG-GILERO
Eutech Scientific Services
Evonik
Fareva
Fuji Chemical Industries
Gattefosse
InKemia Green Chemicals
LifeSciencePR
Lyophilization Technology, Inc.
Metrics Contract Services
MonoSol Rx
Nitto Avecia Pharma Services
Pace Analytical Services
PharmaCircle
SGS Life Sciences
SGW Pharma B2B
Siegfried
SiO2 Medical Products
SMI
Transdermal Specialties
UPM Pharmaceuticals
URSATEC
Yonwood Packaging
Yukon Medical

April 2017 Advertiser Index

COMPANY	PAGE	PHONE	WEBSITE
Althea	9	888-425-8432	www.AltheaCMO.com
Ascendia Pharma	13		www.ascendiapharma.com
BIO International Convention	63		www.convention.bio.org
Capsugel Dosage Form Solutions	2	862-242-1700	www.capsugel.com
Captisol	3	orders@captisol.com	www.captisol.com
Catalent Pharma Solutions	76	1-888-SOLUTION	www.catalent.com/optiform
Controlled Release Society	67	#CRSboston	www.controlledreleasesociety.org/CRSboston
CordenPharma	5		www.cordenpharma.com
CPhI North America	55	Schedule.cphinorthamerica.com	www.cphinorthamerica.com/register
Frewitt	14		www.frewitt.com
Frontage	31	sales@frontagelab.com	www.frontagelab.com
Innovation Networking Summit	4,18,19, 72,73	973-263-5476	www.drug-devconference.com
Metrics Contract Services	11	252-752-3800	www.metricscontractservices.com
Nemera	15	information@nemera.net	www.nemera.net
SGW Pharma	75	973-299-8000	www.SGWpharma.com
Pfanstiehl	16	847-623-0370	www.pfanstiehl.com
PharmaCircle	24-25	1-800-439-5130	www.pharmacircle.com
Unither Pharmaceuticals	12	585-475-9000	www.unither-pharma.com
UPM Pharmaceuticals	17	423-989-8000	www.upm-inc.com
West Pharmaceutical Services	7	800-345-9800	www.smartdose.com

Coming in May

TOPICS

Pre-filled Syringes
Parenteral Contract Manufacturing
Bioavailability Enhancement
Lyophilization Manufacturing
Clinical Research
MDI Characterization
Solvent-Less Film Coatings

For More Information About Advertising Contact:
John Kiesewetter – T: 541-338-0022 Email: jkiesewetter@drug-dev.com
Ralph Vitaro – T: 973-263-5476 Email: rvitaro@drug-dev.com

Developing a formula for your brand's **SUCCESS.**

At SGW Pharma Marketing, we never lose sight that branding a technology or service is more engaging when you make a real connection with people. Our formula blends the "human factor" into each of our brand-building strategies.

Whether you're talking to R&D scientists, business development professionals, or C-level executives, we focus on creating tailored messaging to each group and delivering it via a wide range of services.

With 27 years of consumer and B2B pharma experience, you can count on us to deliver innovative solutions that make a difference. That's why the top pharmaceutical companies choose SGW Pharma.

Contact us: 973-263-5289, lnosti@sgw.com or visit us online at sgwpharma.com

SGW | Pharma MARKETING

Your brand's formula for success.

BRANDING • DIGITAL • WEB DESIGN • PRINT • OUTDOOR • TV • VIDEO • PUBLIC RELATIONS

Introducing OptiForm® Solution Suite Bio. Our integrated offering enables rapid screening of your biomolecule's potential for a non-invasive delivery route. With our advanced formulation technology platforms and parallel screening model based on rigorous science and best-in-class formulation expertise, getting the answer is easy, fast and cost effective.

- **EASY** INTEGRATED WITH TWO ADVANCED TECHNOLOGIES: OPTIGEL™ BIO AND ZYDIS® BIO
- **FAST** PARALLEL SCREENING IN AS LITTLE AS 3 WEEKS
- **COST EFFECTIVE**

DEVELOPMENT DELIVERY SUPPLY

Catalent. More products. Better treatments. Reliably supplied.™

US + 1 888 SOLUTION (765-8846) **EU** + 800 8855 6178 catalent.com/optiform