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Drug Development & Delivery

May 2016 Vol 16 No 4 www.drug-dev.com

A New Set of Challenges for Biologics

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

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Part# 17307-AW-Rev 1

Drug Development & Delivery

May 2016 Vol 16 No 4

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 Drug Development & Delivery (ISSN) 1537-2898 is published 9 times in 2016, January/February, March, April, May, June, July/August, September, October, and November/December by Drug Delivery Technology LLC, 219 Changebridge Road, Montville NJ 07045. Subscription rates: $120.00 for 1 year in the United States, Canada, and Mexico. $188.00 for 1 year outside the United States, Canada, and Mexico. All subscriptions are payable in US funds, drawn on US banks. Send payment to: Drug Development & Delivery LLC subscription Department, 219 Changebridge Road, Montville NJ 07045. Single copies (prepaid) $20.00, US, Canada, and Mexico; $25.00 in all other countries. Add $5.00 per order for shipping and handling. Periodicals Postage Paid at Montville, NJ 07045-9998 and additional mailing offices. Postmaster: please send address changes to Drug Development & Delivery, 219 Changebridge Road, Montville NJ 07045.

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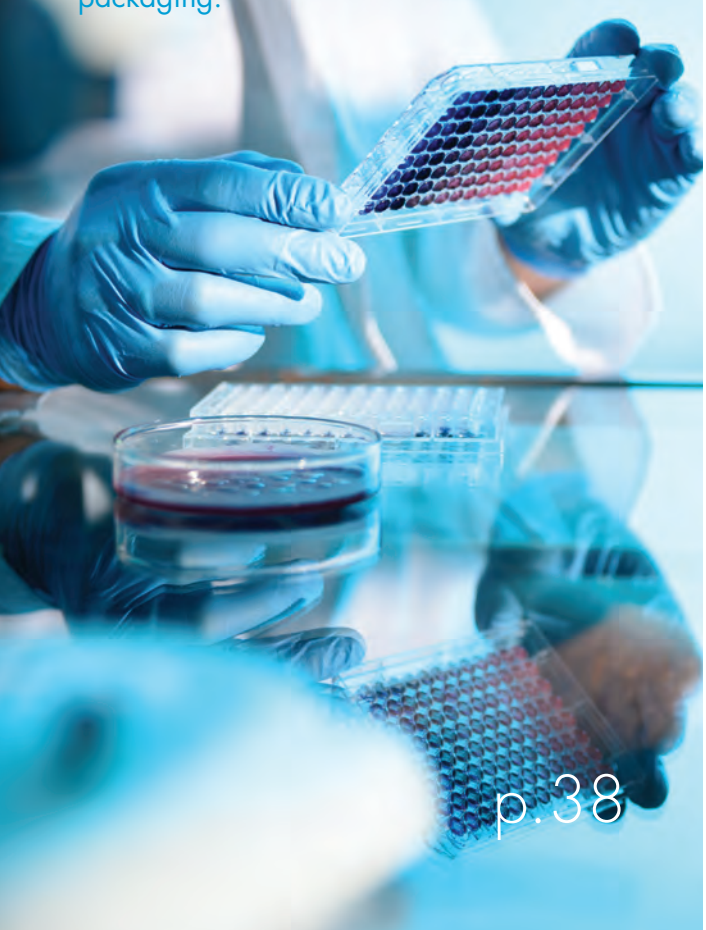
A New Set of Challenges for Biologics

"As the parenteral drug pipeline continues to move from small molecules to complex biologics such as monoclonal antibodies (mAbs) and antibody drug conjugates (ADCs), biological therapies provide unique challenges for parenteral drug delivery, such as volume and viscosity. Other challenges are prevalent as well, including quality concerns, strict regulatory requirements, interaction of prefilled syringes with drugs, manufacturing complexity, combination therapies, and lyophilization. Additionally, aseptic processing of parenterals involves challenges such as protecting the sterility of a product as it moves through each phase of formulation, filtering, filling, and packaging."



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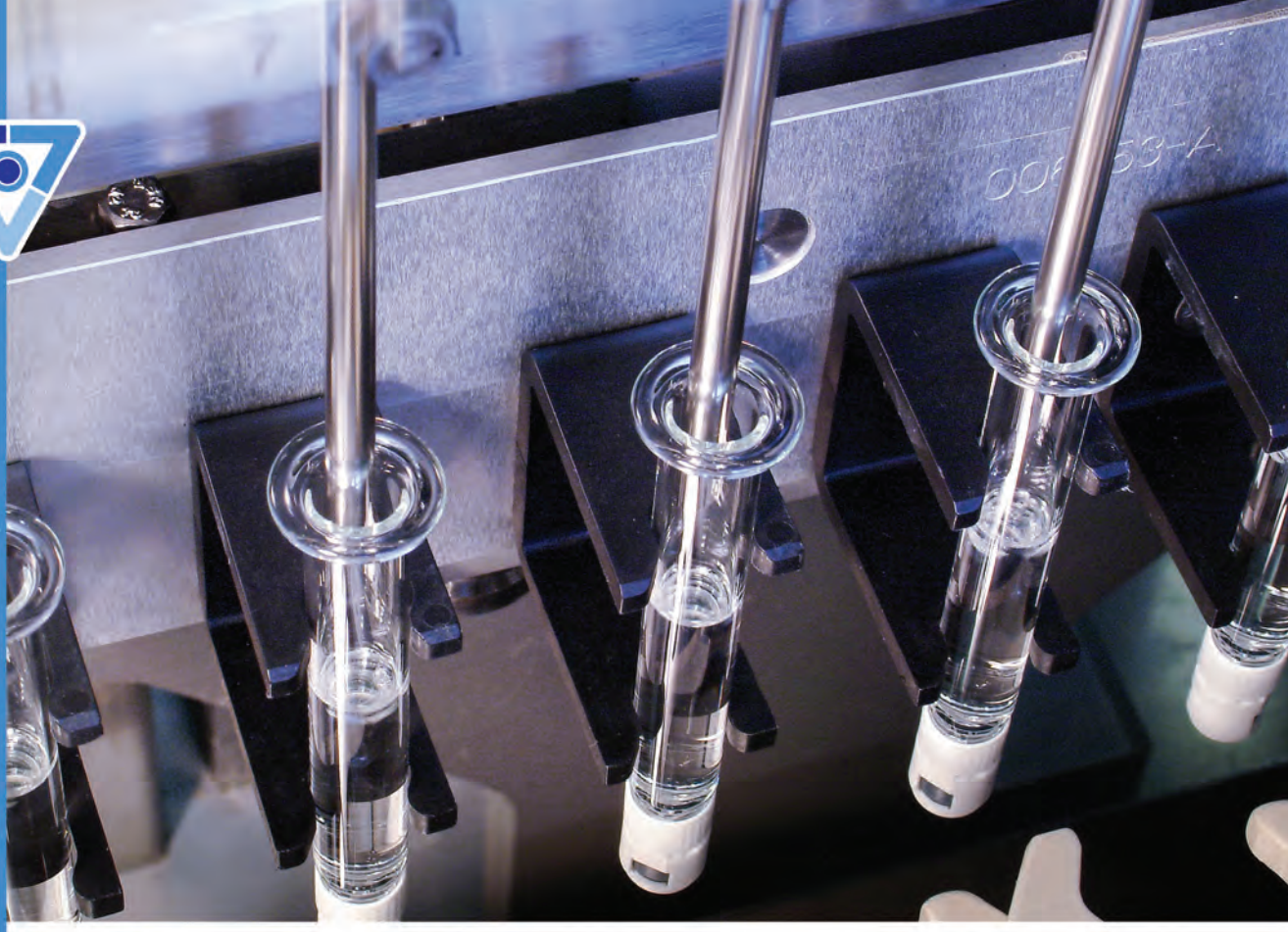

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MorphoSys Licensing Partner GSK Starts Phase II Study

MorphoSys AG recently announced its licensing partner GlaxoSmithKline (GSK) has initiated a Phase II clinical study to investigate the effectiveness and safety of GSK3196165 (previously known as MOR103) in patients with inflammatory hand osteoarthritis (HOA). GSK3196165 is a monoclonal antibody against GM-CSF (granulocyte-macrophage colony-stimulating factor) cytokine, a target molecule for a broad range of inflammatory diseases. The antibody was discovered and engineered by MorphoSys using its HuCAL technology and outlicensed to GSK in 2013.

The European multi-center Phase II double-blind, placebo-controlled study will investigate the efficacy and safety of subcutaneous injections of GSK3196165 in 40 adult subjects with inflammatory hand osteoarthritis. The main objective of the study is to assess the efficacy potential of GSK3196165 on pain in inflammatory HOA. Secondary objectives include the assessment of safety and pharmacokinetics of GSK3196165.

Osteoarthritis is a condition that causes damage to the surface of joints in the body leading to joint pain and stiffness. In some patients it can adversely affect work and normal daily activities.

"We are delighted to see our licensing partner GSK moving GSK3196165 into a clinical Phase II study designed to assess its efficacy and safety in inflammatory hand osteoarthritis, a chronic disease with high medical need," said Arndt Schottelius, Chief Development Officer of MorphoSys AG. "In addition to an ongoing Phase II study in rheumatoid arthritis, this is GSK's second clinical study with GSK3196165 in a therapeutically highly relevant indication. We are excited that our partner is further broadening the clinical development program with this HuCAL antibody discovered by MorphoSys."

In 2013, MorphoSys outlicensed MOR103 (now: GSK3196165) to GSK. Under the terms of the agreement, GSK assumed responsibility for all subsequent development and commercialization activities of the drug candidate. MorphoSys received an immediate upfront payment of EUR 22.5 million. On achievement of certain developmental, regulatory, commercial, and sales-based milestones, MorphoSys will be eligible to receive additional payments from GSK of up to EUR 423 million to total, in addition to tiered, double-digit royalties on net sales. GSK3196165 is a HuCAL-derived antibody against GM-CSF (granulocyte-macrophage colony-stimulating factor) cytokine, a target molecule for a broad range of inflammatory diseases. GSK is currently developing GSK3196165 in two clinical trials in two indications - a Phase IIb study in rheumatoid arthritis (initiated in Q3 2015) and a phase IIa study in inflammatory hand osteoarthritis (started now). MorphoSys has concluded a Phase I study in healthy volunteers, a Phase I/II study in mild-to-moderate rheumatoid arthritis as well as a Phase Ib study in multiple sclerosis.

MorphoSys developed HuCAL, the most successful antibody library technology in the pharmaceutical industry. By successfully applying this and other patented technologies, MorphoSys has become a leader in the field of therapeutic antibodies, one of the fastest-growing drug classes in human healthcare.

New Potential Lung Cancer Biomarkers Identified by The West Virginia University Cancer Institute

Protea Biosciences Group, Inc. recently announced the use of its proprietary bioanalytical technology to achieve the molecular profiling of live tumor cells while they are under treatment.

A team of scientists from Protea and The West Virginia University Cancer Institute presented their results at the American Association for Cancer Research (AACR) Annual Meeting 2016 currently underway in New Orleans. The presentation, titled Mass Spectrometry Imaging Determines Biomarkers of Early Adaptive Precision Drug Resistance in Lung Cancer, identifies molecular changes occurring within drug-resistant lung cancer cells. The research used the company's proprietary mass spectrometry imaging (MSI) workflows to rapidly identify molecular changes occurring within residual tumor cells.

"Drug resistance emergence is a common problem that limits long-term outcome benefits in the era of precision cancer therapy," said Erin Seeley, PhD, Clinical Imaging Principal Investigator at Protea. "We presented the use of our mass spectrometry imaging (MSI) technology to interrogate the biomolecular changes occurring within residual tumor cells under precision treatment with ALK-specific kinase inhibitor treatments. Using Protea's MSI technology, our team discovered several metabolites that were changing over a time course of treatment. Peptides were detected that showed differentiation with over 98% accuracy between treated and untreated xenograft tumors (FFPE); also MSI analysis of frozen tumors allowed for detection of the precision therapy drug, as well as lipids that were changing in expression as a result of treatment."

A common problem in the treatment of cancer is that the tumors become resistant to the drug with which they are being treated. The earlier the resistance is detected, the sooner the patient can be switched to a different therapy, thus increasing their chances of treatment success and cure. The research presented by Protea and WVU scientists at the AACR Annual Meeting profiles the biomolecules being expressed (peptides, lipids, metabolites) in a mouse xenograft model and a cell line model of lung cancer that both show resistance to treatment with a particular class of drugs, known as kinase inhibitors. The ability to rapidly identify the specific molecular changes that occur when a tumor becomes resistant to treatment will help guide the development of improved treatment strategies.

Further studies are planned to validate the use of the biomarkers to identify drug resistance in lung cancer. Protea's mass spectrometry imaging (MSI) technology facilitates rapid interrogation of the molecular changes occurring within tumor cells, generating data within minutes on changes in the production of specific molecules in the tumor cells.

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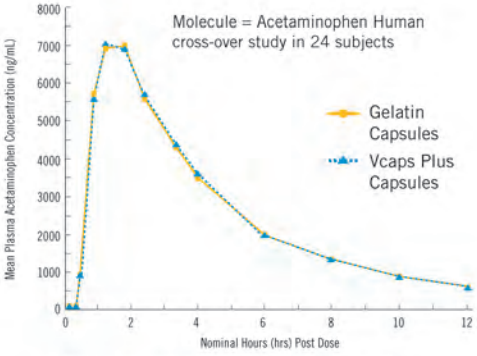

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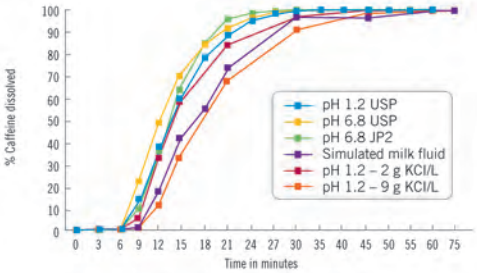

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Patheon Selected by Grünenthal to Develop Drugs Using INTAC Abuse-Deterrent Formulations Technology

Patheon, the leading global provider of pharmaceutical development and manufacturing services today announced it has signed a strategic agreement with Grünenthal, an independent, family-owned, international research-based pharmaceutical group headquartered in Aachen, Germany to serve as its preferred development partner for its products made using Grünenthal's innovative abuse-deterrent formulation technology INTAC.

Patheon was selected to assist with the development of advanced INTAC-based products, including single-entity and fixed-dose combination solid oral dosage forms with immediate and modified release properties. INTAC is Grünenthal's proprietary technology designed to reduce the potential for abuse of controlled substances.

As part of the agreement, Grünenthal has agreed to install specialized equipment in Patheon's Cincinnati manufacturing site. Through their partnership, Grünenthal and Patheon will partner to offer new solutions to the broader pharmaceutical industry. This concept of locating equipment in a Patheon facility – "condo model" – allows clients to benefit from Patheon's process, people and infrastructure to simplify manufacturing.

"This agreement is a tangible example of the deeper, collaborative relationships we are pursuing and winning with clients," said Mike Lehmann, executive vice president, global sales and marketing. "Over the past several years we have built a business to meet the needs of a breadth of clients – from emerging pharma companies to large multinationals.

This collaboration brings together Grünenthal's innovative approach to research and development and the specialized technical manufacturing capabilities of Patheon to bring novel therapies to the marketplace for the patients who need them.

"It is recognized in the healthcare industry that," said Dr. Klaus-Dieter Langner, Chief Scientific Officer Grünenthal Group, "prescription drug abuse is an issue of growing concern in the United States. Typically it is opioids, CNS depressants and stimulants that are the three most established drug classes that are abused. Novel formulation technologies will help reduce that abuse potential."

With its innovative abuse-deterrent formulation technology platform, INTAC, Grünenthal is leading the field with already several FDA-approved opioid products utilizing this unique technology which confers outstanding crush resistance of drug matrix and raises hurdles against prescription drug abuse. Grünenthal considers INTAC to be a leading technology for tamper-resistant opioid products. Grünenthal has expanded the INTAC platform beyond extended release formulations to immediate release as well as modified release dosage forms of single-entity and fixed-dose combination products. This allows Grünenthal to offer this technology now for a broader variety of drugs and abuse- deterrent applications.

Patheon is a leading global provider of outsourced pharmaceutical development and manufacturing services. With approximately 8,700 employees worldwide, Patheon provides a comprehensive, integrated and highly customizable set of solutions to help customers of all sizes satisfy complex development and manufacturing needs at any stage of the pharmaceutical development cycle.

Merrimack Unveils Its Latest Antibody-Directed Nanotherapeutic

Merrimack Pharmaceuticals, Inc. recently announced positive data from preclinical studies evaluating MM-310, an antibody-directed nanotherapeutic (ADN) that encapsulates a newly engineered form of the highly potent chemotherapy docetaxel as a prodrug in an ephrin receptor A2 (EphA2)-targeted liposome. Preclinical data on MM-310 were presented in an oral presentation and three poster sessions at the 2016 American Association for Cancer Research (AACR) Annual Meeting.

"We designed MM-310 to deliver a large and sustained chemotherapy payload of Merrimack's newly engineered docetaxel prodrug within a protective nanoliposome to the tumor site while minimizing exposure to healthy tissues, with a goal of overcoming one of the greatest challenges in cancer treatment," said Walid Kamoun, PhD, Research Team Lead at Merrimack. "We also used our systems approach to choose the EphA2 target as a means of enhancing MM-310's ability to be taken in by tumor cells and to penetrate deep into the tumor core. We are excited by MM-310's preclinical data set and look forward to future clinical evaluation of this latest therapeutic candidate from our ADN platform."

Key findings show that MM-310 demonstrated superior antitumor activity in multiple models compared to free docetaxel and also showed that EphA2 targeted liposomes entered and delivered the cytotoxic to the tumor cell while minimizing exposure to healthy tissues, significantly decreasing traditional docetaxel drug-related side effects, such as neutropenia, in preclinical models. EphA2 receptors are associated with poor prognosis and are shown to be overexpressed in several solid tumors, including prostate, ovarian, bladder, gastric, and lung cancers.

"In an analysis of the docetaxel dose-response relationship, the data strongly suggest that the ability to deliver a higher dose of the traditional chemotherapy may lead to higher therapeutic response but also to higher toxicity. In our preclinical models, MM-310 was associated with fewer hematologic toxicities than free docetaxel and was shown to induce tumor regression or controlled tumor growth," said Daryl Drummond, PhD, Vice President of Discovery at Merrimack. "We believe these data support clinical evaluation of MM-310 across multiple tumor types."

Merrimack is a fully integrated biopharmaceutical company that views cancer as a complex engineering challenge. Through systems biology, which brings together the fields of biology, computing and engineering, Merrimack aims to decrease uncertainty in drug development and clinical validation, and move discovery efforts beyond trial and error. Such an approach has the potential to make individualized treatment of patients a reality. Merrimack's first commercial product, ONIVYDE (irinotecan liposome injection), was approved by the US FDA on October 22, 2015. With four additional candidates in clinical studies, several in preclinical development and multiple biomarkers designed to support patient selection, Merrimack is building one of the most robust oncology pipelines in the industry.

Actinium Announces Selection of Zevacor for Clinical Production & Supply for Pivotal Phase III Trial

Actinium Pharmaceuticals, Inc. recently announced the company has entered into an agreement with Zevacor Pharma, Inc. (formerly IBA Molecular North America, Inc.) for the clinical production and supply of Iomab-B for the upcoming pivotal Phase III SIERRA trial. Pursuant to the agreement, Zevacor Pharma, Inc. will perform the GMP manufacturing, testing, releasing, and distribution of Iomab-B for Actinium's pivotal Phase III SIERRA trial. Iomab-B is a radioimmunotherapy intended to be an induction and conditioning agent prior to a bone marrow transplant for Acute Myeloid Leukemia (AML) patients over the age of 55. Actinium's Iomab-B has received orphan drug designation from the US FDA, and the pivotal Phase III SIERRA trial is expected to enroll 150 patients.

Iomab-B will be used in preparing patients for hematopoietic stem cell transplantation (HSCT), the fastest growing hospital procedure in the US. The company established an agreement with the FDA that the path to a Biologics License Application (BLA) submission could include a single, pivotal Phase III clinical study, if it is successful. The population in this two-arm, randomized, controlled, multicenter trial will be refractory and relapsed Acute Myeloid Leukemia (AML) patients over the age of 55. The trial size was set at 150 patients with 75 patients per arm. The primary endpoint in the pivotal Phase III trial is durable complete remission, defined as a complete remission lasting at least 6 months, and the secondary endpoint will be overall survival at 1 year.

There are currently no effective treatments approved by the FDA for AML in this patient population, and there is no defined standard of care. Iomab-B has completed several physician-sponsored clinical trials examining its potential as a conditioning regimen prior to HSCT in various blood cancers, including the Phase I/II study in relapsed and/or refractory AML patients. The results of these studies in almost 300 patients have demonstrated the potential of Iomab-B to create a new treatment paradigm for bone marrow transplants by: expanding the pool to ineligible patients who do not have any viable treatment options currently; enabling a shorter and safer preparatory interval for HSCT; reducing post-transplant complications; and showing a clear survival benefit including curative potential.

Iomab-B is a radioimmunoconjugate consisting of BC8, a novel murine monoclonal antibody, and iodine-131 radioisotope. BC8 has been developed by the Fred Hutchinson Cancer Research Center to target CD45, a pan-leukocytic antigen widely expressed on white blood cells. This antigen makes BC8 potentially useful in targeting white blood cells in preparation for hematopoietic stem cell transplantation in a number of blood cancer indications, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), Hodgkin's disease (HD), Non-Hodgkin lymphomas (NHL) and multiple myeloma (MM). When labeled with radioactive isotopes, BC8 carries radioactivity directly to the site of cancerous growth and bone marrow while avoiding effects of radiation on most healthy tissues.

Genomics plc & DNAnexus Collaborate to Develop Solutions for Population-Scale Sequencing Analysis

Genomics plc recently announced it has entered into a research collaboration with DNAnexus, the global leader in cloud-based genome informatics and data management. The companies will work together to improve researchers' ability to analyze population-scale sequencing data.

With DNA sequencing costs continuing to fall, sequencing projects involving tens or hundreds of thousands of people are becoming increasingly common. Such projects include Genomics England's 100,000 Genomes Project, and the Regeneron Genetics Center and Geisinger Health DiscovEHR collaboration, which is the largest private-sector sequencing effort to-date, with the goal of sequencing exomes of 250,000 individuals. At present, there is a variety of informatics challenges facing such projects – from optimizing and improving existing analytical workflows, to large-scale statistical analysis of cohort data, where linking genome sequencing to parameters of health and disease can be limited by differences in the way samples are sequenced and analyzed. Genomics plc and DNAnexus are addressing these limitations by developing solutions to enable accurate and powerful population-scale data analysis algorithms.

Both Genomics plc and DNAnexus are working with the Regeneron Genetics Center, and Genomics plc is a Platform Partner of Genomics England.

"Combined analysis of these huge data sets will enable researchers to extract much more information from large scale studies," said John Colenutt, CEO, Genomics plc. "The longer term goal here is to unlock the potential for researchers to learn more about human biology, in turn leading to better diagnoses and more targeted therapies for patients, and we're pleased to be working with the DNAnexus team towards this goal."

"The DNAnexus Platform has become the leading solution for analysis providers who are seeking a secure, compliant, and scalable environment, on which they can deploy and extend the reach of their product offerings. We believe that working collaboratively with Genomics plc on cutting-edge population-scale data analysis algorithms will help make the promise of population-scale sequencing analysis a reality," added Richard Daly, CEO, DNAnexus.

Genomics was founded by four leading Oxford academics, including Professor Peter Donnelly, Director of The Wellcome Trust Centre for Human Genetics, and Professor Gil McVean, Director of The Big Data Institute. The company has developed a unique platform for genomic data analysis and interpretation, which combines world-leading expertise in statistical analysis and data mining with a unique integrated database linking genotypes and phenotypes.

DNAnexus combines expertise in cloud computing and bioinformatics to create the global network for genomics, operating in North America, Europe, Asia-Pacific (including China), South America, and Africa. The secure, scalable, and collaborative cloud-based DNAnexus Platform helps thousands of researchers across a spectrum of industries – biopharmaceutical, bioagricultural, sequencing services, clinical diagnostics, government, and research consortia – accelerate their genomics programs globally.

Pluristem Continues to Strengthen its Position in Japan; Granted Two Key

Pluristem Therapeutics Inc. recently announced that the Japan Patent Office has granted the Company two key patents addressing: 1) Pluristem's core technology of three-dimensional expansion methods for producing therapeutic cell products derived from placental or fat cells; 2) the use of placenta-derived cells grown with this 3D technology to treat disorders of the hematopoietic system, such as disorders caused by exposure to radiation or chemotherapy, and failed engraftment of hematopoietic stem cell transplants.

Pluristem continues to strengthen its IP position in order to support the current negotiations with pharmaceutical companies in Japan regarding potential partnerships for the development and commercialization of its PLacental eXpanded (PLX) cells. Pluristem recently received clearance for its protocol for a Phase II trial in critical limb ischemia targeting marketing approval in Japan, via Japan's accelerated regulatory pathway for regenerative medicines.

Patent No. 5733894, titled Methods for Cell Expansion and Uses of Cells and Conditioned Media Produced Thereby for Therapy, covers three-dimensional methods of growing adherent placental or adipose cells, and the cells produced by the claimed methods.

Patent No. 5766041, titled Pharmaceutical Composition for Enhancing Subject Hematopoietic System, addresses pharmaceutical compositions containing placental stromal cells grown using 3D culturing methods for supporting engraftment of hematopoietic progenitor cells, thus enabling treatment of disorders of the hematopoietic system by promoting the recovery of the immune system and bone marrow function.

"These latest patent grants in Japan fortify our intellectual property position globally, and specifically in the Japanese market, where we are in active negotiations with potential pharmaceutical partners," said Pluristem Chairman and CEO Zami Aberman. "Our proprietary process and technology for growing placenta-derived cells within a 3D microenvironment make large scale, cost effective cell therapy production a reality, and IP protection of these methods in Japan is a key asset. The use of these cells to treat disorders of the hematopoietic system is an important indication for PLX cells that is now protected in Japan."

Pluristem Therapeutics Inc. is a leading developer of placenta-based cell therapy products. The company has reported robust clinical trial data in multiple indications for its patented PLX (PLacental eXpanded) cells. The cells release a cocktail of therapeutic proteins in response to inflammation, ischemia, hematological disorders, and radiation damage. PLX cell products are grown using the company's proprietary three-dimensional expansion technology. They are off-the-shelf, requiring no tissue matching prior to administration.

Pluristem has a strong intellectual property position; company-owned and operated, GMP-certified manufacturing and research facilities; strategic relationships with major research institutions; and a seasoned management team.

N-of-One Selected by Admera Health to Provide Clinical Interpretation for the OncoGxOne 64-Gene Oncology Panel

N-of-One, Inc. recently announced that Admera Health has selected N-of-One to provide clinical interpretation of their 64-gene oncology panel, OncoGxOne. N-of-One's patient-specific analysis is based on the clinical and scientific evidence linking the results of each patient's molecular tests to therapeutic strategies, including clinical trials. Financial terms of the agreement are not disclosed.

The OncoGxOne is a next-generation sequencing (NGS) panel that detects 64 of the most common mutated genes found in several cancer types. Mutation types detected include single nucleotide variants, insertions and deletions, copy number variants and gene fusions associated with all current FDA-approved targeted therapies and multiple registered clinical trials. Results are delivered in an easy-to-interpret report providing physicians with the information necessary to practice precision medicine in a cost-efficient manner.

N-of-One clinical interpretation provides high-quality analysis of the results of each OncoGxOne test, identifying the most relevant therapeutic options for each patient based on the scientific and clinical evidence.

"We are very pleased to be able to offer N-of-One's patient-specific analysis with our OncoGxOne cancer panel," said James Dermody, PhD, Admera Health Lab Director. "Admera Health's goal of easily integrating into routine clinical practice is supported by partnering with N-of-One. With N-of-One, we can provide oncologists with an Admera Health diagnostic report that is clear, actionable, and based on the latest scientific evidence. We are confident that we can quickly and efficiently provide the very best reports to our customers, so that they can provide the best care possible to their patients."

"N-of-One is excited to be working with Admera Health to deliver a best-in-class, patient-specific solution to the market," added Chris Cournoyer, CEO at N-of-One. "Our objective is to continue to provide the highest quality clinical interpretation to enable clinicians to reap the most value from Admera Health's OncoGxOne panel. Ultimately, the patients and their physicians gain the greatest benefit from our working together."

Admera Health is an advanced molecular diagnostics company focused on personalized medicine, non-invasive cancer testing, and digital health. Dedicated to developing cutting-edge diagnostics that span the continuum of care, Admera Health fulfills unmet medical needs with cost-effective tests and accurate analysis to guide patient care. Utilizing next-generation technology platforms and advanced bioinformatics, Admera Health seeks to redefine disease screening, diagnosis, treatment, monitoring, and management through its innovative, personalized solutions.

N-of-One is the leader in providing patient-specific therapeutic options for precision medicine in oncology by leveraging its world-class team of practicing oncologists and PhD scientists. The N-of-One team, coupled with proprietary technology and processes, enables N-of-One to analyze molecular diagnostic tests required to utilize this data at the point of care. Using N-of-One, laboratories can scale their molecular diagnostic programs with the highest quality clinical interpretation while still saving time and money.

Presage Biosciences Extends Research Collaboration With Takeda

Presage Biosciences recently announced it has entered into a multi-year extension of its November 2014 research alliance with Takeda Pharmaceuticals Company Limited.

The agreement provides Takeda access to Presage's proprietary CIVO technology platform to enable identification of novel oncology drug combinations in solid tumors. Under the agreement, Presage and Takeda will screen a broad array of drug combinations and preclinical models to discover novel combinations and generate data to support clinical decision-making on Takeda's pipeline agents. The agreement includes development and regulatory milestones related to identification of successful novel drug combinations.

"We are pleased to extend our collaboration with Presage and utilize their technology platform to more rapidly understand the impact of drug combinations directly on tumors," said Christopher Claiborne, PhD, Head of the Oncology Drug Discovery Unit at Takeda. "Takeda prides itself on creating novel medicines for patients, and having a committed partner like Presage enables us to continue fulfilling our mission of aspiring to cure cancer."

"It is deeply rewarding to continue our collaboration with Takeda," said Richard Klinghoffer, Chief Scientific Officer of Presage. "Together, the teams at Presage and Takeda are employing the unique potential of Presage's CIVO arrayed microinjection technology to identify novel drug combinations that will hopefully improve the lives of patients with cancer."

CIVO technology is currently being used preclinically to identify effective combinations of drugs. By assessing several combinations in a single living tumor, the CIVO platform is able to characterize and directly compare the influence of multiple biophysical factors, such as immune infiltrate, stromal barrier, and hypoxia on the tumor response.

Presage Biosciences is an oncology company pioneering a radical new drug development approach to assess novel drug combinations directly in patient tumors with its patented CIVO arrayed microinjection platform. The CIVO platform allows for simultaneous assessment of multiple drugs or drug combinations directly in a single solid tumor while still in a patient's body to assess efficacy, resistance, and drug synergies in the tumor's native microenvironment. Presage is using CIVO to develop a portfolio of promising oncology therapies to advance to the clinic, including voruciclib, a clinical-stage oral CDK inhibitor in clinical development for multiple cancer indications. Presage also partners with oncology-focused pharmaceutical companies through strategic alliances to provide data to discover effective drug combinations. Presage is privately held and based in Seattle.

Human Vaccines Project Launches San Diego Research Hub

Four scientific institutions – University of California, San Diego, J. Craig Venter Institute, La Jolla Institute for Allergy and Immunology and The Scripps Research Institute – have teamed up to create the Mesa Consortium, a new scientific hub for the Human Vaccines Project. Under a collaborative agreement, the Mesa Consortium and the Human Vaccine Project aim to transform current understanding of the human immune system and expedite development of vaccines and biologics to prevent and treat many global diseases.

The Human Vaccines Project is a new global initiative that brings together leading research centers, pharmaceutical companies, and state-of-the-art machine-learning methods to tackle the unprecedented mission of decoding the human immune system to accelerate the development of new vaccines and immunotherapies against major infectious diseases and cancers.

The Mesa Consortium will carry out extensive immunological analyses from the Project's clinical research studies designed to answer specific questions about human immunity. The Mesa Consortium will also serve as the Project's bioinformatics core.

"Driven by partnerships with leading academic centers, and enabled by new technologies and a scientific plan focused on solving the main barriers to developing new immune-based interventions, we believe our collaboration with the Project could help to transform global efforts in vaccine and immunotherapeutic development," said UC San Diego Chancellor Pradeep K. Khosla.

"New genetic and immune monitoring technologies are enabling an unprecedented look at the human immune system, and are generating extensive amounts of data," said J. Craig Venter, PhD, Founder, Chairman and CEO of the J. Craig Venter Institute. "When combined with sophisticated bioinformatics analyses, we may soon be able to unlock the principles of how to stimulate and direct immune responses against some of the world's most pressing diseases. We are very pleased to be bringing the Mesa's unparalleled scientific capacity to this global — and potentially transformative — initiative."

The Human Vaccines Project is a non-profit public-private partnership with the mission to accelerate the development of vaccines and immunotherapies against major infectious diseases and cancers by decoding the human immune system. The Project, incubated initially at the International AIDS Vaccine Initiative (IAVI), has a growing list of partners and financial supporters including the Robert Wood Johnson Foundation, John D. and Catherine T. MacArthur Foundation, GSK, MedImmune, Sanofi Pasteur, Crucell/Janssen, Regeneron, Pfizer, Aeras, Vanderbilt University Medical Center, UC San Diego, The Scripps Research Institute, J. Craig Venter Institute and La Jolla Institute for Allergy and Immunology. The Project brings together leading academic research centers, industrial partners, nonprofits, and governments to address the primary scientific barriers to developing new vaccines and immunotherapies, and has been endorsed by 35 of the world's leading vaccine scientists.

Galapagos Initiates Phase IIa Study

Galapagos NV recently announced the start of its exploratory Phase IIa study with GLPG1690 in idiopathic pulmonary fibrosis (IPF) patients, named FLORA, a randomized, double-blind, placebo-controlled study investigating a once daily oral dose of GLPG1690 administered for 12 weeks in 24 IPF patients. Primary objectives of the study are to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690 in an IPF patient population. Target engagement will be measured by LPA in plasma and bronchoalveolar lavage fluid, both at baseline and through 12 weeks of treatment. Secondary objectives include the evaluation of lung function, changes in disease biomarkers, and quality of life. Galapagos expects to complete patient recruitment before end 2016, and to report topline results in Q2 2017. GLPG1690 is a small molecule inhibitor of autotaxin and fully proprietary to Galapagos.

"We identified the autotaxin target using our proprietary target discovery platform and developed molecule GLPG1690 as an inhibitor of this target. GLPG1690 shows promising results in relevant preclinical models for IPF, and there is growing evidence in scientific literature that autotaxin plays a role in this disease. We are pleased to be able to investigate the effect of GLPG1690 in IPF patients and look forward to seeing the results in the first half of next year," said Dr Piet Wigerinck, Chief Scientific Officer of Galapagos.

IPF is a chronic, relentlessly progressive fibrotic disorder of the lungs that typically affects adults over the age of 40. According to an April 2013 GlobalData EpiCast report, the prevalence of IPF is <30 per 100,000 persons in both Europe and the US, and as such, IPF is considered a rare disease. The clinical prognosis of patients with IPF is poor as the median survival at diagnosis is 2 to 5 years. Currently, no medical therapies have been found to cure IPF. The medical treatment strategy aims to slow the disease progression and improve the quality of life. Lung transplantation may be an option for appropriate patients with progressive disease and minimal comorbidities.

Regulatory agencies have approved Esbriet (pirfenidone) and Ofev (nintedanib) for the treatment of IPF. Both pirfenidone and nintedanib have been shown to slow the rate of lung function decline in IPF and are likely to become the standard of care worldwide. These regulatory approvals represent a major breakthrough for IPF patients; yet neither drug improves lung function, and the disease continues to progress in the majority of patients despite treatment. Moreover, the adverse effects associated with these therapies include diarrhea, liver function test abnormalities with nintedanib, nausea, and rash with pirfenidone. Therefore, there is still a large unmet medical need as IPF remains a major cause of morbidity and mortality.

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The Wisdom of Bees: What the Honeybee Can Teach You & Your Company About Making Better Decisions

By: Derek Hennecke, CEO & President, Xcelience

As organizations, we face thousands of decisions every day. Should we buy that new tablet press? Is it time to move into spray dry dispersion? How can we accelerate the proposal process? Should we use epoxy or vinyl on the new lab floors?

There are lots of studies on how we should make decisions, but what I find fascinating is the cognitive studies on how we actually make them. Once you understand what happens in your brain as you weigh your options, you can extrapolate this knowledge and look with fresh eyes at how your CDMO, large pharma, and the industry make decisions.

There are two primary theories that dominate cognitive decision-making theory. The first is the Race Theory. This theory holds that in a race between two competing ideas, the one that gets past the finish line first wins.

Let's say you are driving down an icy road in a thick morning fog. You see a dark shape coming toward you. You know this is a busy street, and you are just as likely to see bikers as cars. One part of your brain starts working on the theory that it's a bike, and another starts developing the theory that it's a car. You will decide what you are looking at based on which chain of neurons moves the fastest; the one which thinks it's a car or the one that thinks it's a bike.

The other theory is the Diffusion Theory. In this theory, your brain is still working on both possibilities, only it's about the accumulation of stimuli rather than the speed of stimuli. The repeated stimulation of neurons in the ventral striatum region of the brain continue on both sides of the decision, like marbles piling up on two sides of a balance, until one hypothesis eventually exceeds a certain threshold, and you make your decision. Yup, that's a bike. Move to the next decision: brake or swerve?

Recent neuroscience research strongly favors the Diffusion Theory over the Race Theory, particularly in binary decisions in which an experiment called the Diffusion-Tensor MRI provides strong support.

HOW THE BEES DO IT

Honeybees are a classic example of Diffusion Theory at the organizational level. Every day, dozens of worker bees go out and look for flowers. As they return, each bee does a little wiggle dance to communicate where the flowers are. Let's imagine that the first bee that returns wiggles about a lush park in bloom in the west. Five more bees arrive with dances about a magnificent botanical garden due east. The next 10 bees can't stop going on about that first park due west. But the hive doesn't decide yet, and good thing. Because after that, many more bees come in and eight out of 10 are absolutely raving about the possibilities in the botanical garden in the east. At a certain point, the threshold is reached, and the hive heads contentedly to find the freshly blossoming 52-acre Brooklyn Botanical Garden. Good choice.

What I find most interesting about the Diffusion Theory is that it doesn't just describe how people and organizations make decisions, but how those decisions might evolve over time, and how long it might take to make decisions.

The threshold is important, because a snapshot at different stages before the threshold is reached might show different impending decisions. If the bees made the decision right away, as the Race Theory suggests, they would have gone to the park as soon as the first bee came back. If they had made the decision a few bees in, they would have leaned toward the Botanical Gardens for a bit, but then settled on the park after all. It took a little time for the majority to tip east, where the preponderance of opinion ultimately led.

If an organization sets its threshold low, decisions will be reached quickly, but the decisions may be wrong. There is a distinct speed/accuracy tradeoff. Decisions that are normally accurate can be reversed under time pressure. Very careful and deliberative decision-makers tend to use a high threshold.

HOW THE ELDERLY DO IT

It's fairly common knowledge that adults over 65 or so take longer to make decisions. The prevailing wisdom is that this is due to cognitive decline, but this may not be the case, according to McKoon and Ratcliff in,

"The Diffusion Decision Model", published in the *MIT Press Novels* in April of 2008. The slowdown is almost entirely due to the older adults' higher thresholds for decision-making, as demonstrated by recent Diffusion Model analyses of two choice data from a number of tasks involving six experiments with 30 or more subjects in each of three age groups per experiment. Older people tend to be more conservative, requiring more information to make a decision.

Is a higher threshold good? Maybe not if you're an air traffic controller, or a trader buying stocks on the floor of the NYSE. The point is that it depends.

HOW ORGANIZATIONS DO IT

While small organizations may have an advantage in nimble decision-making, larger organizations have the advantage in making conservative long-term decisions. They simply have more bees to listen to. We like to de-ride large organizations for their plodding pace and pedantic bureaucracy, but the truth is, insofar as the bureaucracy is geared at securing weigh-in from other departments and knowledgeable decision-makers, taking the time to get all that input can improve decision-making.

FIAT CHRYSLER: IGNORING THE BUZZ COMPLETELY

Of course having lots of bees with lots of stories to tell doesn't mean your CEO will listen to them. Sometimes a strong-willed CEO can chart an independent course. Take Fiat Chrysler's strategy addressing changes in auto demand.

The worker bees have been wiggling madly throughout the auto industry, and their message is well above the thresholds of all the major automakers. The message is threefold: First, there is no new and easy business blossoming in developing markets anymore; that pasture is already heavily populated with bees. Second, the SUV and truck segments that were once the richest flower beds around are no longer as attractive. Violent swings in gas prices and increasingly tough emissions regulations have made this market unreliable. And third, the rise of technology-driven new mobility paradigms, such as Uber car sharing and autonomous vehicles, threatens to overwhelm the traditional model of private ownership that is the foundation of the industry. In bee terms, think of a parking lot full of diggers, pipes, and cement trucks at the edge of the flower bed.

Addressing these issues takes a lot of capital. Car companies need to invest in new technologies, and that puts the little guys like Fiat at a disadvantage. Fiat CEO Sergio Marchionne was all in on tackling these challenges head on last year, when he spent much of his time trying to negotiate a merger to give Fiat the financial clout it needed. No luck.

So when Fiat presented fourth-quarter earnings in January, Marchionne performed a rather sudden about face and proclaimed all the industry's bees to be wrong. Emerging market volumes are irrelevant, he said, because of today's climbing truck and SUV sales. Emissions regulations can be managed by buying credits generated by his competitors with their unprofitable electric car schemes. And mobility paradigms? Futuristic poppycock.

His strategy may well hold up, if only momentarily. Prices at the pump look like they're going to stay where they're at for a while, which is what fuels SUV and truck sales demand.

And yet red flags abound, as the bees attest. By investing in only trucks, SUVs, and luxury brands like Alfa Romeo and Maserati, Fiat Chrysler loses the ability to offer customers a full product line offering. Marchionne claims to be looking for someone to partner with for their sedans, but what would a partnership look like anyway? Are they going to rebadge Mitsubishi sedans as Dodges and Chryslers? And while Marchionne may be right that electric powertrains and autonomous drive are not around the corner, Marchionne is ignoring the mounting evidence that consumers today are looking for slick new futuristic

technologies like lane-change warnings and rear- and side-view cameras the way they used to look for speed and performance.

While I admire his ability to think outside the box, Marchionne needs to be aware that by ignoring the bees completely, he takes a substantial risk. As the other car companies invest billions in new technologies, fuel efficiency, and emission improvements, Marchionne is going all in on a gamble that the automotive industry isn't going to change. Maybe history will prove him right. The bees have been wrong before, though much less often than they are right. Still, I can't help but remember that Chrysler gambled once before on the auto industry not changing. And that didn't turn out so well.

COMBINING HIVES: DECISION-MAKING WHEN LARGE PHARMA MAKES ACQUISITIONS

Large pharma grows by acquisitions. So whenever large pharma takes over a smaller company, the bees in the new acquisition have less voice than they did before. Add to this the "not-invented-here" syndrome, which is a natural human tendency to place less value on external inventions, and the end result is likely to be the cancellation of product lines developed in the acquired company. This may or may not be for the best, but understanding this tendency should highlight the possibility for error in these circumstances. It's important to make sure that good ideas aren't tossed out for the wrong reasons.

AGILITY VS. RELIABILITY – DAILY THRESHOLD TENSIONS AT THE CDMO LEVEL

CDMOs need to be small and agile, allowing them to move quickly and provide for full touch of the owner to client. But there is a tradeoff here. A smaller CDMO has fewer bees to weigh in on a decision, and a shorter process lays the organization open to a higher risk of error. Still, at this stage in the drug development process, speed and agility are widely considered to be paramount.

And yet, CDMO clients also expect reliability, which requires a higher threshold. Reliability and agility are often opposing tensions; sometimes even mutually exclusive. CDMOs must ride and balance this tension on a daily basis.

Here at Xcelience, I believe we have achieved a fairly unique balance. We retain a high degree of speed and agility by maintaining relative independence within the Capsugel umbrella. Yet, I am also learning that there are benefits, sometimes, from doing things the long way. Large organizations have more bees, who have travelled long and far and visited more pastures. We can learn from them. The trick going forward is going to be trying to strike a balance between nimbleness when we need to move quickly, and slower decisions when the situation warrants greater insight. Lots of weigh in and opinions is a good thing, except when it isn't.

TO BEE OR NOT TO BEE: CHOOSING TO USE OR IGNORE THE WISDOM OF BEES

The key to making use of your understanding of Diffusion Theory is not to use it as a prescription for good decision-making, but to use it to understand how decisions are actually made, whether intentionally or not. We can choose a lower or higher threshold, based on our need for speed or reliability. Or we can choose Marchionne's strategy and ignore the bees completely. The important thing is to realize how our decisions are being made, and how that process may affect outcomes. ◆

Derek G. Hennecke
President & CEO
Xcelience

Combination Corner

How to Approach OTS Devices for Your Combination Product

By: Lilli Zakarija, MSME, MBA

In a recent survey[1] of companies in the combination product space, individuals from Quality, Regulatory, and Research & Development were asked about the biggest challenges facing their firms as they strive to comply with the new FDA combination product regulations. One of the pain points they identified was related to confusion around how to handle combination product scenarios where one of the constituents is an off-the-shelf (OTS) medical device. This pain point is a broad statement; however, a myth that is consistently encountered is that OTS devices are already marketed and cleared medical devices by the FDA, and therefore no additional documentation is required. It's perceived as a simple "plug-and-play" scenario. Unfortunately, it isn't quite that simple.

Selecting an OTS medical device to use as a constituent significantly reduces risk and cost compared to developing a new device for the combination product (CP). On the other hand, it does not absolve the combination product manufacturer of the responsibility to show evidence that they have "developed" the correct device constituent. When thinking about device constituent development while using an OTS device, the literal translation of design and development does not apply because the OTS device has already been "designed and developed" and is commercially available. However, in this specific scenario, it applies to the design (selection) and development (qualification) of the device for use with the specific drug and/or biologic.

Confirming the selection and qualification of the OTS device for a CP should still follow the staged device design control process. The level of documentation that needs to be generated compared to a custom device development effort is significantly less, but the benefits of going through the process will yield a robust Design History File (DHF) that touches on the most critical elements of any device development process; including but not limited to requirements, selection of components, risk management activities, and verification and validation testing. Table 1 provides a high-level summary of the device development process (phases and key activities) for a traditional device development effort compared to a scenario where the combination product is utilizing OTS device(s).

The following are three key points to think about when selected an OTS device for a CP, along with a mini-case study that demonstrates the benefits of taking an OTS device through the device design control process.

CONFIRM THE MARKETED OTS DEVICES HAVE AN INDICATION FOR USE THAT ALIGNS WITH INTENDED USE

The OTS devices were developed and cleared or approved by the FDA for a specific intended use. The documentation that the manufacturer has on file supports their indications and use conditions. It may or may not be appropriate for the targeted drug and/or biologic, but confirming this is not the responsibility of the OTS device

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Device Development Design Control Stages				
	Planning	**Design & Development**	**Verification & Validation**	**Manufacturing Transfer & Submission**
Traditional Device	-Develop planning documents -Develop requirements document for device	-Iterate device design -Conduct preliminary benchtop testing -Design freeze	-Conduct design verification and design validation testing to confirm functionality and performance of device design	-Qualify design transfer to manufacturing environment -Submit 510k device file for review
Combination Product: Drug/Biologic + OTS Device(s)	-Develop planning documents -Develop requirements document for system: drug/biologic + device	-Identify potential OTS devices -Conduct preliminary benchtop testing -Design freeze = final selection of OTS device(s)	-Conduct design verification and design validation testing to confirm functionality and performance of drug/biologic + OTS device(s) system	-Summarize key elements of device development process and integrate into BLA/NDA submission

Comparison of Device Development Process for Traditional Device Versus OTS Device for Combination Product

manufacturer. Clearly understanding the boundaries established by the OTS device manufacturer will allow the drug/biologic company to assess potential fit of the identified device.

Mini-Case Study

A company identified an OTS ambulatory pump that had the right flow rate range for the subcutaneous delivery of its proprietary drug product and allowed the patient to be mobile while receiving treatments. A win-win situation (at least on the surface), and the company was planning on moving ahead with this device for commercialization. However, while the device constituent was going through the device development (design control) process for use with the drug, one of the device requirements was that the device label not be contra-indicated for the combination product intended use. In challenging this requirement, it was identified that the ambulatory pump was indicated for intravenous use only, and contra-indicated for subcutaneous use. Reading the fine print identified a big issue and required that the company identify another pump for delivery of its product. The product development process did exactly what it was intended to do – confirm the OTS device chosen met the requirements of the combination product before the product proceeded too far into development or regulatory filing. Had the company not identified the issue, it may have found itself in a situation where it was preparing for a product launch only to have the FDA inform it the information supporting the use of the device constituent is not complete. Should the FDA had missed this discrepancy, the company would have been promoting the device for off-label use.

TRUST BUT VERIFY ANY CLAIMS MADE BY THE OTS DEVICE MANUFACTURER REGARDING THE PERFORMANCE OF ITS PRODUCT

Device manufacturers will provide key data regarding their device performance; however, the test methods and use-case conditions utilized to support their performance claims are typically not provided unless a specific ASTM/ISO standard is cited. But even in this instance, it is difficult to know if their test methods were validated. This level of detail is not typically made available by device manufacturers. As such, when selecting the potential OTS components, one needs to trust the data values that are being provided by the device manufacturer, but take on the responsibility to confirm these performance results - especially in instances where the performance of the drug and/or biologic is heavily dependent on a specific set of device parameters.

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"Confirming the selection and qualification of the OTS device for a CP should still follow the staged device design control process. The level of documentation that needs to be generated compared to a custom device development effort is significantly less, but the benefits of going through the process will yield a robust Design History File (DHF) that touches on the most critical elements of any device development process; including but not limited to requirements, selection of components, risk management activities, and verification and validation testing."

REMEMBER THE OTS DEVICE(S) WERE NOT DEVELOPED WITH YOUR SPECIFIC DRUG/BIOLOGIC IN MIND

Mini-Case Study

A company was in the process of developing the requirements for the delivery of its drug. One key requirement for the device system focused on understanding the total residual volume of the delivery system in order to confirm the patient would receive the required minimum drug dose. The company indicated that when reading the OTS device manufacturer literature and adding up the claimed residual volume values (in this instance, there were multiple devices including a syringe pump and administration set), the total residual volume was acceptable and posed no risk to the patient not receiving the required minimum dose. However, it was recommended that the some benchtop studies be conducted to check if the values obtained under their intended use conditions (ie, a specific volume at a specific flow rate) would align with the published literature. For one of the two device components, the results yielded lower residual volumes than published by the OTS device manufacturer, while the second component yielded residual volumes that were three times higher than published residual volume of 0.2 mL. For a drug that's total delivered volume is low (less than 20 mL per treatment), the difference between 0.2 mL and 0.6 mL of volume not delivered to the patient is significant, not to mention the cost of the drug being left behind. In this instance, the company was able to adjust the fill volume in the drug vial to accommodate the drug loss in the delivery system, and also initiate activities to identify an alternate device constituent that could provide a lower total residual volume.

The OTS device(s) may have been developed as a "generic" device that will satisfy multiple needs and products. The drug/biologic company must understand the device company did not design the device with its specific drug or biologic, or use-case in mind. For example, a pump may present data on flow rate accuracy and/or residual volume; however, that data may have been collected using a limited number of types of liquids. Are those liquids representative of the intended viscosity and density of the intended drug/biologic product?

Mini-Case Study

A company was in the process of qualifying an ambulatory pump for the delivery of its biologic in the homecare setting. It should be noted that this specific biologic had a viscosity that was > 10 cp. A requirement identified for its product was the ambulatory pump could deliver a minimum of 20 infusions on a single battery. The OTS pump manufacturer published information that its device could function on a battery for over 30 hours, which collectively was greater than the time necessary to deliver the desired 20 infusions. This company had a design control process in place for devices utilized in a CP, and it proceeded to conduct testing on a number of different pumps to confirm that for its intended delivery conditions, the pumps could deliver a minimum requirement of 20 infusions on a single battery. During testing, it was identified that some of the pumps were not able to meet the minimum requirement of 20 infusions on a single battery. In addition, the pump-drive mechanism started to fail, highlighting

a pump reliability issue. Conversations with the manufacturer yielded little value, and when testing evolved into understanding the weaknesses of the pump, the OTS device was immediately removed from consideration. The biologic company was starting to go down the path of understanding the design and reliability of the pump mechanism, which was not within the scope of its responsibility for the device and not its area of expertise. While the pump manufacturer indicated that its pump could handle a range of viscosities and flow rates, reality proved to be something different and highlighted that the manufacturer most likely had not done significant amounts of testing under more extreme use conditions.

SUMMARY

The aforementioned reminders seem so obvious, and yet, had these companies accepted information provided by the OTS manufacturer at face value and not developed and challenged their devices to the specific drug/biologic delivery requirements dictated by their product, they would not have uncovered the issues as early as they did. Discovering these issues early avoid the complications that would have surfaced had these OTS devices been released as part of the combination product. Utilizing OTS medical devices for drug/biologic combination products will continue to be a reality especially as devices like patch pumps and technology-integrated pen injectors are introduced. The bottom line is that while OTS devices are already "developed" and on the market, they should still go through the device development design control process from the perspective of the combination product, and then let the design control process determine if the device meets the specific requirements of the CP. Avoiding the design control process altogether for an OTS is NOT an option. ◆

REFERENCE

1. EdgeOne Medical. Report: Highlighting Challenges in the New Combination Product Regulatory Landscape. EdgeOne Medical: Chicago, IL. February 2016.

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

BIOGRAPHY

Lilli Zakarija is Co-Founder and President of EdgeOne Medical Inc, an ISO 13485- certified medical device testing firm and consultancy focused on supporting combination products through the device development (design control) process. Prior to founding EdgeOne Medical, she developed and led the global device engineering function for Baxter's BioScience division (now Baxalta) in support of all its combination (biologic and device) products and single-use, disposable medical devices. Ms. Zakarija earned both her BS in Biomedical Engineering, and Masters in Engineering Management from Northwestern University, and her Executive MBA from Kellogg School of Management.

PROTEIN PHOSPHORYLATION

New Pathways, New Tools: Phosphohistidine Signaling in Mammalian Cells

By: Xiaoyi Xu, MS, Chandreyee Das, PhD, and Michael Sturges, PhD

HISTIDINE PHOSPHORYLATION: A THERAPEUTICALLY IMPORTANT PATHWAY?

Because protein phosphorylation regulates a wide array of cellular processes, many drugs and drug candidates act on kinases and phosphatases to modulate post-translational modifications (PTMs). As of April 2015, the United States Food and Drug Administration (FDA) had approved 28 therapeutic protein kinase inhibitors, the majority of which are being used to treat cancers. Most drug discovery programs are focused on tyrosine, serine, and threonine kinases; however, protein phosphorylation is known to occur on nine different amino acids. Systems in which multiple amino acids are phosphorylated and dephosphorylated may have an evolutionary advantage – regulation by multiple kinases and phosphatases may confer more opportunities to respond to environmental cues and, thus, increase capacity to dynamically tune a response.

Could the phosphorylation of histidine emerge as a therapeutically important pathway in mammals? The phosphorylation of histidine has not been widely studied in mammalian cells, despite its discovery in bovine liver mitochondria.[1] Histidine phosphorylation is well-studied in bacteria and is part of a "two-component" signaling pathway used for chemotaxis and transcription (Figure 1). In prokaryotes, this signaling system is a phosphorelay system typically consisting of two types of proteins: a membrane-bound histidine kinase (HK) and a response regulator (RR). This system is activated when an environmental signal causes a membrane-associated HK to be auto-phosphorylated on a conserved histidine residue. This is followed by the transfer of the phosphate to a cytoplasmic RR protein on a conserved aspartate residue. The phosphorylated RR protein can then function as a transcription factor and activate genes associated with range of cellular processes, such as chemotaxis, stress response, sporulation, antibiotic resistance, etc.[2]

Fungi also possess a similar two-component system, which is more complex than the bacterial system. In the fungal system, the HK and RR proteins are present, as well as a third protein, a histidine phosphotransferase (HPt). In yeast, this protein is known as Phosphorelay intermediate protein Ypd1. The main function of the Ypd1 protein is to facilitate the transfer of phosphate from the histidine kinase to response regulator proteins.[3] Another key difference between the bacterial and fungal two-component systems is the number of phosphorylation events that occur (Figure 1). In fungal systems, there are four phosphorylation events that happen on the three proteins. First, the HK protein is auto-phosphorylated on a histidine present in its histidine kinase domain. This event is followed by a transfer of the phosphate group to an aspartate on the receiver domain of the HK protein. A third phosphotransfer event occurs in which the phosphate group is transferred to the histidine phosphotransferase domain on the Ypd1 protein. Finally, a fourth transfer occurs in which the phosphate group is transferred to an aspartate on the RR protein. This can result in either the activation or

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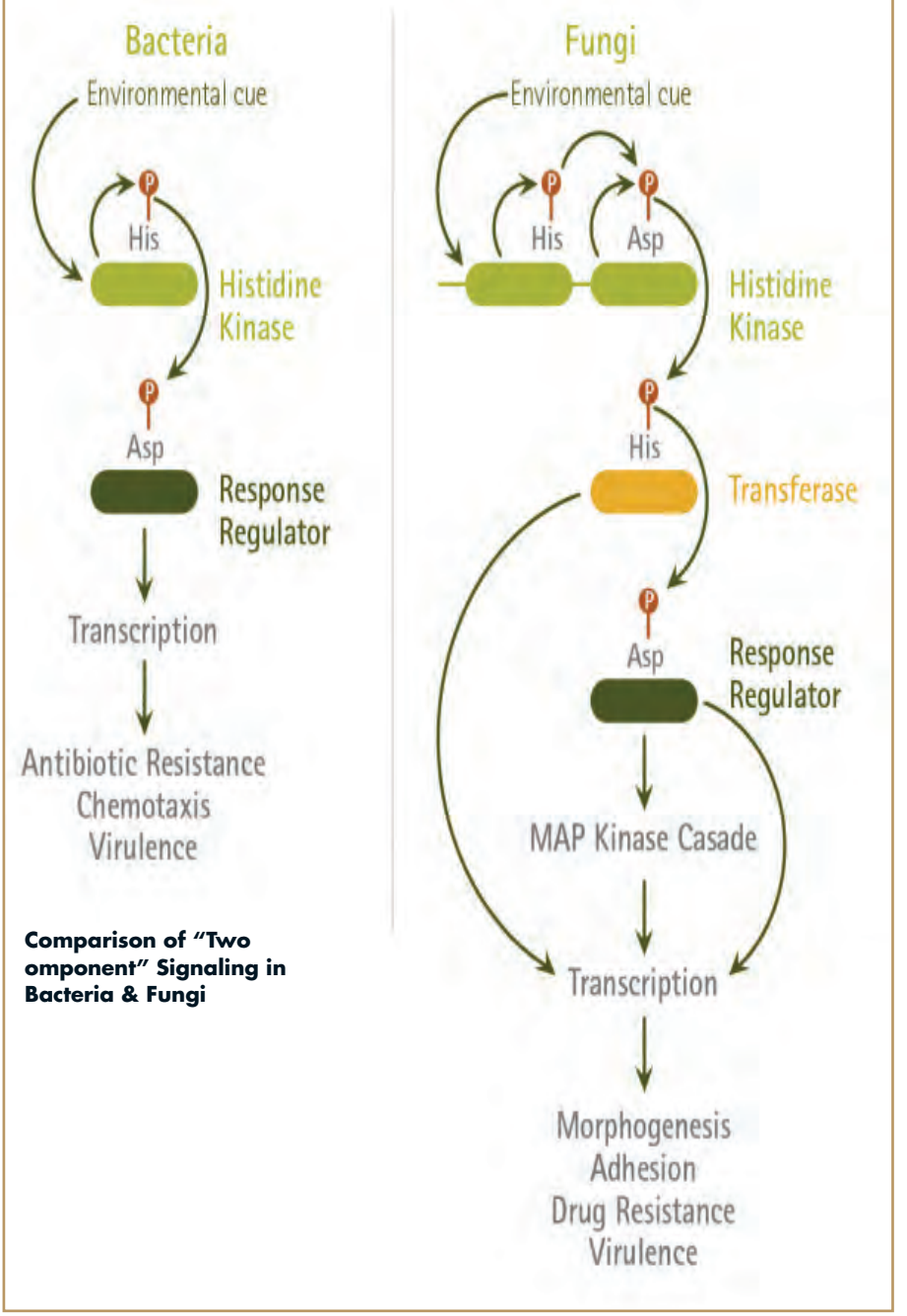
downregulation of specific sets of genes, depending on the system and the specific sets of proteins involved.

While not as well-characterized, histidine phosphorylation has been detected in eukaryotic systems.[4-5] Recent evidence suggests phosphohistidine signaling is involved in the regulation of key cellular processes in mammalian cells.[5] In support of this assertion, two mammalian histidine protein kinases have been identified. These protein kinases are known as NME1 (Nucleoside diphosphate kinase A or Nm23-H1) and NME2 (Nucleoside diphosphate kinase B or Nm23-H2). Recent data are consistent with roles for these enzymes in a variety of cellular processes including mammalian signal transduction,[6-8] cancer biology,[9,10] differentiation, development, apoptosis, cytokinesis, and dynamin-mediated endocytosis.[11,12]

Some phosphohistine-containing proteins that are substrates of NME1 and NME2 have been recently identified. One of these is SK4, a calcium-activated potassium channel expressed in mammalian blood vessels, whose expression is correlated with the proliferation of endothelial cells in cardiovascular disease.[13] SK4 can be reversibly phosphorylated at His358, enabling the fine regulation of vascular cell proliferation.[14] Another study identified the calcium channel, TRPV5, as a protein regulated by histidine phosphorylation by NME1.[6] When phosphorylated at His711, the TRPV5 channel shows increased activity, as shown by patch clamp experiments. More calcium enters TRPV5-expressing cells in NME1 wild-type background compared to cells in which NME1 has been knocked down. The study's authors, however, cite "technical problems with our assays, as well as reagents that are available to detect histidine phosphorylated proteins" as reasons for not being able to collect more detailed information regarding the histidine-mediated regulation of TRPV5.[6]

FIGURE 1

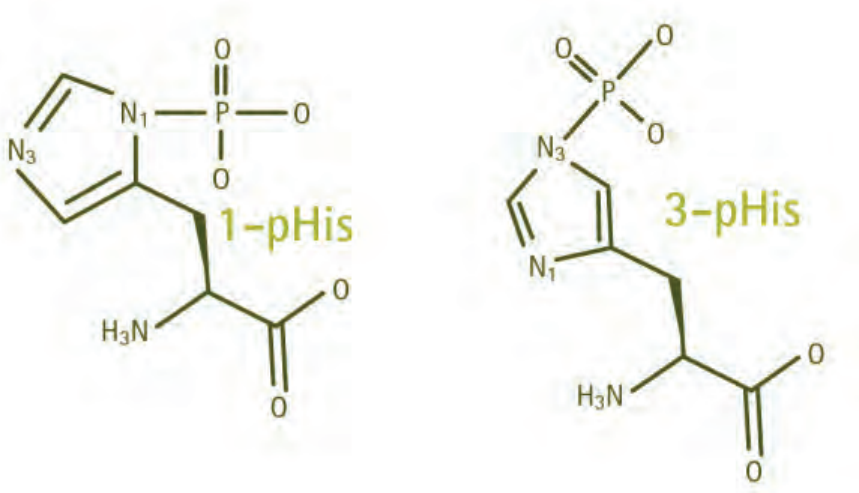


Comparison of "Two omponent" Signaling in Bacteria & Fungi

OBSTACLES TO DETECTING HISTIDINE PHOSPHORYLATION

One reason detecting histidine phosphorylation has been so difficult is that the modification is thermodynamically less stable than phosphorylation of serine, threonine or tyrosine. Compared to phosphorylation of hydroxyl groups, which exhibit ΔG of hydrolysis ranging from -6.5 to -9.5

FIGURE 2



Isomers of histidine allow phosphorylation at the N1 or N3 position. N1 phosphohistidine can be specifically detected by Anti-N1-phosphohistidine, clone SC1-1 (Cat. No. MABS1330), and clone SC50-3 (Cat. No. MABS1341). N3 phosphohistidine can be specifically detected by Anti-N3-phosphohistidine, clone SC39-6 (Cat. No. MABS1351), and clone SC56-2 (Cat. No. MABS1352).

kcal/mol, the phosphorylation of histidine has a ΔG of hydrolysis ranging from -12 to -14 kcal/mol[4]. Furthermore, under the acidic conditions in which phosphoproteins are frequently purified, the kinetic stability of phosphohistidine is lower than that of other modifications.[4] Thus, histidines often become dephosphorylated during preparation for mass spectrometry and acidic staining of polyacrylamide gels, and other manipulations. Phosphoserine and phosphothreonine are sometimes purified using chromatography in which the stationary phase is conjugated to metal ions; however, because both phosphorylated and unphosphorylated histidine can bind to many metal ions, this method has been less fruitful for phosphohistidine detection.

Progress in understanding the cellular function of phosphohistidine has been further hampered by the lack of specific antibody detection reagents for this modification. Creation of these reagents using phosphohistidine peptides as an immunogen has proven challenging due to the instability of phosphoramidate bonds resulting in the destruction of the immunogen before a strong immune response can occur. The effort was even called "devilishly hard" by Kee and Muir.[15]

ANTIBODIES AGAINST PHOSPHOHISTIDINE: THE GOOD, THE BETTER & THE BEST YET

Recently, pan-phosphohistidine antibodies were generated using nonhydrolyzable synthetic analogs of phosphohistidine.[16,17] For the first of these antibodies, peptides containing phosphohistidine were recognized with only ten-fold higher sensitivity than peptides containing phosphotyrosine.[16] The cross-reactivity with phosphotyrosine was even greater when assessed using bovine serum albumin-conjugated (BSA) phosphotyrosine and phosphohistidine.[17] The second pan-phosphohistidine antibody showed less, but still significant, crossreactivity with phosphotyrosine in the context of a bovine serum albumin conjugate.[17]

Additionally, and even more significantly, these antibodies were unable to distinguish between the N-1 and N-3 phosphoisomers of histidine. One unique feature of histidine is that phosphohistidine can be phosphorylated at either the N-1 or N-3 nitrogen of the imidazole ring (Figure 2). This is because at physiological pH, the imidazole ring of histidine can have its proton at either nitrogen. Thus, in biological systems, two tautomers exist, resulting from phosphorylation at either N1 (1-pHis) or N3 (3-pHis) positions (Figure 2).

Both the crossreactivity with phosphotyrosine and the inability to distinguish between phosphoisomers present a challenge to researchers wishing to detect phosphohistidine in proteomics studies of eukaryotes more complex than yeast.

To better understand the role of phosphohistidine signaling in mammalian systems, antibodies that have the following properties are needed:

- Sequence-independent detection of phosphohistidine
- Isomer-specific antibodies that reliably discriminate between 1-pHis or 3-pHis
- No cross reactivity with phosphotyrosine
- The ability to work in a variety of applications, such as Western blotting, immunofluorescence and immunoaffinity purification

With these specific goals, a team of Salk Institute researchers, led by Tony Hunter, engaged in a project to generate a set of monoclonal antibodies with these properties. Their success in generating these highly specific and isoform-specific monoclonal antibodies was recently reported in *Cell*.[18]

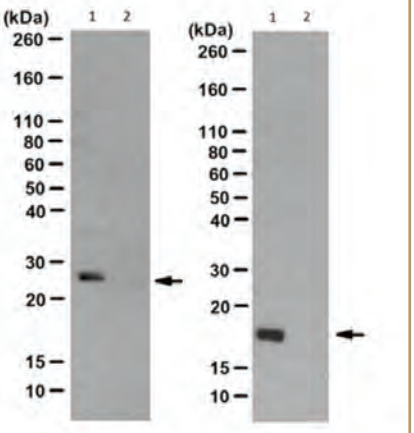
To get around the issue with the stability of the phosphoramidate bond, the Hunter lab created degenerate peptide libraries that incorporated non-hydrolyzable phosphoryl-triazolylalanine (pTza) histidine analogs into the peptide sequence. For the generation of isoform-specific antibodies, two separate degenerate peptide libraries containing either 1-pTza or 3-pTza were used for immunizations. The resulting antisera were initially screened using dot blots against the immunizing peptides to identify isomer-specific sera. Sera with the right specificity profile were further characterized by Western blotting using proteins phosphorylated *in vitro* using NME1/NME2 (generates 1-pHis modified proteins) or PGAM (generates 3-pHis modified proteins), with heat-induced dephosphorylation as a negative control (Figure 3). Anti-N3-phosphohistidine detected 3-pHis phosphorylated PGAM (phosphoglycerate mutase, ~25 kDa) in a non-heat-inactivated sample but not in a heat-inactivated sample. Similarly, anti-N1-phosphohistidine antibody detected 1-pHis phosphorylated NME1 (~18 kDa) in a non-heat-inactivated sample but not in a heat-inactivated sample.

Hybridomas were generated and screened to yield multiple isoform-specific monoclonal antibodies.To demonstrate that the resulting monoclonals detected pHis in a sequence-independent fashion, each of these monoclonal antibodies was screened using pTza peptides of a defined sequence. This was followed by screening with cell lysates to demonstrate that these antibodies are capable of detecting endogenous pHis proteins. The specificity for phosphohistidine and lack of cross reactivity to pTyr was also evaluated using both pTyr peptides and cell lysates. Neither the 1-pHis nor the 3-pHis monoclonal antibodies generated showed any cross reactivity to pTyr.

WHAT THE NEW PHIS ANTIBODIES REVEAL

In their *Cell* publication, the Hunter lab presented data from both immunofluorescence and immunoaffinity purification experiments.[18] Using the monoclonal antibodies developed for this study, they evaluated the biological role of the phosphohistidine modification in a manner not previously possible and reported some interesting findings relative to the two isoforms of phosphohistidine. Specifically, immunofluorescence using 1-pHis antibodies was localized to the outer membrane of phagosomes. Phagosomes are vesicles that are formed when the cell membrane closes completely around a particle, for the purposes of nutrition or cellular defense; this pHis localization pattern is consistent with the previous finding that histidine kinases may regulate membrane trafficking.[11] In contrast, immunostaining with 3-pHis antibodies suggested involvement in the cell cycle with the N-3 phosphoisomer associated with centrosomes, spindle poles, and the midbodies of cells in late telophase.

FIGURE 3



Western blots show that Anti-N3-phosphohistidine detects 3-pHis phosphorylated PGAM (phosphoglycerate mutase, ~25 kDa) in a non-heat-inactivated sample (lane 1, left panel) but not in a heat-inactivated sample (lane 2, left panel). Similarly, anti-N1-phosphohistidine antibody detects 1-pHis phosphorylated NME1 (~18 kDa) in a non-heat-inactivated sample (lane 1, right panel) but not in a heat-inactivated sample (lane 2, right panel).

To identify specific proteins containing the pHis modification, immunoaffinity purification was performed, followed by mass spectrometry. This work identified 280 different proteins containing the 1-pHis modification and 156 proteins with the 3-pHis modification. This diversity of proteins that are uniquely associated with either the 1-pHis or 3-pHis isoform suggests a role for phosphohistidine in a variety of cellular processes. Mass spectrometry analysis of the 3-pHis proteins was consistent with the immunofluorescence data, with several of the 3-pHis proteins identified being associated with the cell cycle.

The work of the Hunter lab has resulted in the generation of an important set of reagents. The existence of these phosphohistidine monoclonal

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antibodies will pave the way for more detailed studies of the role of histidine phosphorylation in mammalian systems. Studies using these reagents can help better define the emerging roles of phosphohistidine in areas such as signal transduction, cancer, differentiation, development, and apoptosis.

Making these reagents readily available to the scientific community will help drive this understanding. MilliporeSigma has licensed the Hunter lab's phosphohistidine antibodies to make them easily available to the research community. It is expected that the broad availability of these reagents will open up the study of histidine phosphorylation to a broad segment of researchers, and uncover new paradigms in cellular signaling.

THE FUTURE OF PTM RESEARCH

The methods by which the new phosphohistidine antibodies were developed may guide researchers to developing antibodies to other post-translational modifications and "challenging" epitopes. After all, there are other amino acids that can be phosphorylated (albeit unstably) by protein kinases: cysteine, glutamate, aspartate, and lysine. Most recently, chemists at Xiamen University reported developing a structural analog of phosphoarginine, using the same general synthetic scheme as used by the Hunter lab, with the goal of using this analog as a hapten immunogen for raising anti-phosphoarginine antibodies.[19] We do not yet fully understand the importance of phosphorylation of these other amino acids is in eukaryotes; however, the development analytical methods adapted for neutral or basic pH, combined with the development of novel antibodies, can help answer that question. Affinity-based enrichment of proteome samples using specific phosphoamino acid antibodies can then be combined with advanced mass spectrometry methods and analysis software that are optimized to fragment and identify PTM-bearing peptides, further aiding the discovery of new PTM sites, kinase substrates, and sophisticated cell signaling networks.[20]

Once studies reveal a critical number of therapeutically promising targets bearing a particular phosphoamino acid, one would expect a subsequent emergence of drug discovery and development programs targeting the regulation of this PTM. In the case of histidine phosphorylation, several small molecule inhibitors of bacterial histidine kinases have been developed as antibiotics.[21] Further study of mammalian histidine kinases may reveal the utility of these scaffolds as starting points for targeting therapeutically relevant pathways in humans. ◆

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BIOGRAPHIES

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Dr. Chandreyee Das is a Senior Content Development Specialist at MilliporeSigma, researching trends and technologies in the preparation and analysis of proteins and small molecules in complex samples. She earned her PhD in Chemistry and Chemical Biology at the University of California, San Francisco, studying the structural determinants of RNA-protein interactions, and was a Ruth L. Kirschstein Postdoctoral Fellow in the department of Molecular Oncology at the Dana Farber Cancer Institute.

Dr. Michael R. Sturges served as a Senior Product Manager at MilliporeSigma from 2009 to 2015. He is currently at SGI-DNA, a Synthetic Genomics company. For the past 14 years, he has worked in the bioscience industry in marketing and product development. This experience is complemented by more than 12 years of hands-on scientific research at both academic and commercial organizations. Dr. Sturges earned his PhD at the University of California, Santa Cruz, and completed his postdoctoral studies in the Department of Pediatrics in the laboratory of Dr. Charles Roberts, Jr. at Oregon Health and Sciences University. Dr. Sturges is currently applying his experience and knowledge of genomics, proteomics, and molecular biology to drive the development and commercialization of novel technologies that enable research and discovery.

Special Feature

Prefilled Syringes & Parenteral Contract Manufacturing: Biologics Present a New Set of Challenges

By: Cindy H. Dubin, Contributor

Parenteral drug delivery is the second largest segment of the pharmaceutical market and accounts for nearly 30% of the market share. Currently, around 3.5 billion prefilled syringes are produced each year and that number is growing between 9-10% annually. The *Future of Alliances and Partnerships in the Prefilled Syringes Market to 2020* forecasts that the global market for prefilled syringes will hit $6.6 billion in 2020, up from $3.9 million in 2014.[1]

The surge is being attributed to an increasing geriatric population, increasing demand for vaccines, increasing prevalence of chronic diseases, and technological advancement in prefilled syringes. In addition, the demand for point-of-care administration and regulations regarding needlestick injuries are driving the growth of the global prefilled syringes market.[2]

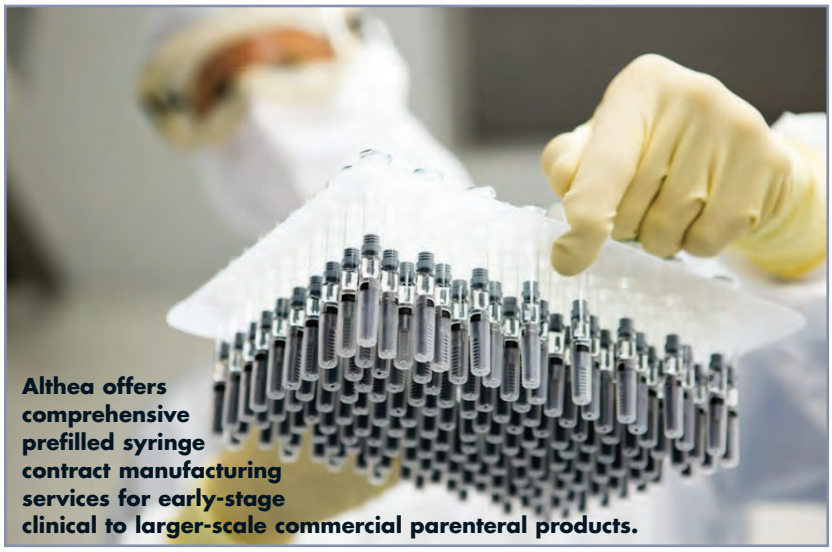
There is also a shift in demand for biologics and biosimilars. In fact, nine of the top-10 drugs available in prefilled syringes are now biologics and the majority of these are used for treating chronic diseases such as diabetes, rheumatoid arthritis, and multiple sclerosis.

As the parenteral drug pipeline continues to move from small molecules to complex biologics such as monoclonal antibodies (mAbs) and antibody drug conjugates (ADCs), biological therapies provide unique challenges for parenteral drug delivery, such as volume and viscosity.

Other challenges are prevalent as well, including quality concerns, strict regulatory requirements, interaction of prefilled syringes with drugs, manufacturing complexity, combination therapies, and lyophilization. Additionally, aseptic processing of parenterals involves challenges such as protecting the sterility of a product as it moves through each phase of formulation, filtering, filling, and packaging.

Due to the complexities of syringe manufacturing, the contractor market is growing. According to Frost & Sullivan, sterile parenteral contract services make up about 82.8% of the total sterile CMO market. This includes small-volume

West's prefillable syringe components help to ensure consistency of delivery.



Althea offers comprehensive prefilled syringe contract manufacturing services for early-stage clinical to larger-scale commercial parenteral products.

parenterals (vials, ampoules, and syringes), which make up the majority of sterile CDMO services with 88.9% of market share. The sterile parenteral manufacturing subsegment is expected to reach a market size of $6.5 billion by the end of 2016.[3]

In this exclusive *Drug Development & Delivery* report, syringe developers and contract manufacturers discuss how they are overcoming the challenges discussed above and provide a look at some advancements in prefilled syringe technology.

Althea—Keeping Up With the Increased Preference for Prefilled Syringes

During the last few years there has been tremendous growth in sales and units of prefilled syringe versus other injectable dosage forms. Althea prepared for this favorable market condition by investing in a new syringe line, which became commercially approved last year. "Our capacity utilization has increased substantially over the past year and we have seen a marked increase in the number of biosimilar/biobetter-based drug programs," says Don Paul Kovarcik, Technical Marketing Specialist, Althea. "We anticipate this trend to continue as more branded drugs go off patent."

Initially in the biologics segment, vials were the gold standard. After conducting trials, the developer would switch to prefilled syringes just before commercial launch, explains Mr. Kovarcik. In cases where clients use alternative primary container systems, Althea works with them to ensure they are compatible with automated filling systems.

Recently, however, many developers have decided to simply start out using prefilled syringes. "Because of this change, Althea has started to do a lot more prefilled syringe work much earlier in the development process and sometimes even in the preclinical stage."

Critical to prefilled syringes is manufacturing high-quality product the first time. Manufacturing success is dependent on a robust and reproducible process. To this end, Althea has been advocating for its pharmaceutical partners to bring forward their prefilled syringe programs in the earlier stages of development. "That way we can identify any gaps in the production processes, which allows us sufficient time to work through any issues prior to clinical studies and commercial launch," says Mr. Kovarcik.

Aptar Stelmi—Elastomeric Closure Systems for Sensitive Injectables

Aptar Stelmi designs and manufactures elastomeric closures: stoppers for vials, and prefilled syringe and cartridge components such as plungers, needle shields, and tip caps for all parenteral applications. The most recent addition to its product portfolio is the PremiumCoat™ coated serum stopper designed for the protection of sensitive and high-value drugs, including biopharmaceuticals.

Based on an approved, pure,

With Aptar's PremiumCoat serum stoppers, a barrier film covers the drug contact area. (Photo courtesy: Aptar Stelmi)

state-of-the-art formulation, the surface of the elastomer is coated during manufacturing with an ETFE film. This coating acts as a barrier to many of the extractables and leachables that can be released from the elastomer. As a result, compatibility of the drug and the closure is improved. The first design released in 2015 was the 20mm coated stopper, and a 13mm coated stopper will soon be available.

Catalent Pharma Solutions—Helping Clients Comply with cGMPs for Devices

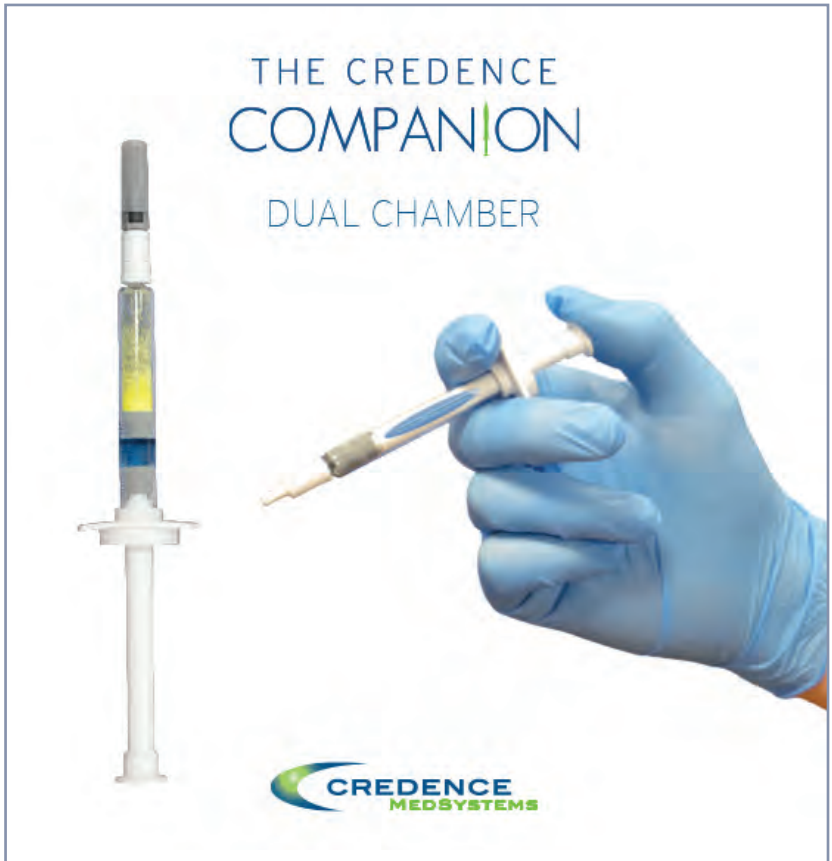
A notable trend in the market for sterile injectables has been toward self-injection or autoinjector devices, which have become increasingly popular over the past few years as a means of improving patient compliance and helping prevent needlestick injuries. Catalent has actively supported customers in this market segment by implementing the necessary steps to fully comply with Current Good Manufacturing Practice regulations for devices (21 CFR 820 (cGMP)) from a quality and regulatory assurance viewpoint.

"These regulations require a focused approach, with design reviews performed across the different parties involved: the assembly site, the final customer, primary component supplier, autoinjector parts supplier, and the machine manufacturer," says Wim Blendeman, Director New Product Introduction, Advanced Delivery Technologies at Catalent. "These reviews are important to determine the Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and to put final design controls in place in order to supply the final product reliably."

The majority of the investment in a typical project is made prior to starting the assembly process and the design is checked and verified prior to starting clinical assembly. Using information gained through the executed process, In-Process-Controls (IPCs), Acceptable Quality Limits (AQLs), Process Control Limits (PCLs), and process reviews need to be implemented and checked for effectiveness. These data must also be supported by a risk assessment and facilitate the drafting of a User Requirement Specification (URS) for a fully automated assembly line. "Due to the precise and unique nature of the autoinjector market, equipment is, in most cases, specifically designed to support each type of autoinjector," says Mr. Blendeman.

Credence MedSystems—Addressing the Need for Innovation in Reconstitution Safety Devices

The growth of biologic parenterals in the commercial and pipeline portfolios of drug manufacturers has been well documented. These biologics are



The Credence Companion Dual Chamber simplifies the task of mixing two separated components into a single user step while providing passive needlestick safety.

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often formulated as powders, in lyophilized or spray-dried form, when unstable in solution. Additionally, there are an increasing number of applications requiring separation of two liquid components during storage. Because of this, the number of drugs that require reconstitution or mixing at the point of injection has increased.

The conventional approach to reconstitution includes multiple vials, syringes, needles, and/or vial access components, and an arduous mixing and administration process that contribute to inefficient workflow, dosage errors, wasted drug product, and needlestick exposure, explains John A. Merhige, Chief Commercial Officer, Credence MedSystems. The industry has seen attempts to improve upon this approach with vial mixing devices and multi-chamber syringes and cartridges.

"While the dual-chamber offerings that are available or in development have been evolving, there remain limitations with regards to efficient manufacturability, supply chain availability, cost, usability, and safety that have placed barriers on adoption," he says. "With the delivery of healthcare moving from formal medical settings to the home, and medications increasingly being administered by self injectors, the industry is in need of an injection system that allows those complex biologics requiring point-of-care mixing to be injected easily and safely by less experienced users."

To address this market need, Credence MedSystems has developed and recently introduced its Companion Dual Chamber Reconstitution Safety Syringe technology. "The Companion Dual Chamber shares the *Innovation Without Change* design philosophy that is seen across Credence's other safety syringe systems, maximizing the usability and safety of the device while minimizing the change from existing primary package components and supply chain dynamics," says Mr. Merhige.

The Companion Dual Chamber simplifies the task of mixing two separated components into a single step. The user advances the plunger rod as in a conventional injection, creating a newly formed center channel through the standard stopper, and allowing the contents of the rear chamber to pass into the front chamber where they are combined together for mixing.

Beyond the simplification of the mixing process, the Companion Dual Chamber provides important safety and usability features. A pre-attached needle reduces yet another user step, but also provides the key to an integrated passive safety system; the user simply completes the injection (marked by an end-of-dose click) and then the needle automatically disappears through the stoppers and into the plunger rod and syringe barrel. The syringe cannot be reused and is now rendered safe for disposal.

Existing approaches to dual-chamber devices all use some combination of customized primary package components: bespoke glass barrels with external or internal bypasses, stoppers with specialized internal channels or wiper blades, etc. "These customized components drive high costs, long lead times, captive supply chains, and the potential for product failure and complaints stemming from a dependency on primary package components that do not have a proven history in the field," says Mr. Merhige.

The Companion Dual Chamber uses a standard, uniform diameter glass barrel (syringe or cartridge), standard stoppers, and standard needle shields from well-known component suppliers. Additionally, the Dual Chamber is glue-free, eliminating any risk of interaction between glue and the drug product.

"The combination of single-step mixing, end-of-dose cues, passive needlestick safety, and reuse prevention makes the Companion uniquely suited to enable a broader utilization of point-of-use mixing devices in the home and healthcare provider markets," he says.

Enable Injections—Wearable Devices Make Biologic Self-Administration Possible

Recent discussion in the industry has centered on reducing overall healthcare costs by eliminating waste associated with excess drug that is thrown away. For example, many biologic drugs must be infused

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The Enable OBDS features improvements in materials and safety features for in-home delivery of large molecules.

intravenously by a healthcare professional, typically at a hospital. Healthcare costs could be significantly reduced, compliance increased, and patient convenience vastly improved if patients could safely and easily self administer such drugs subcutaneously at home without the aid of a healthcare professional, believes Mike Hooven, CEO and President of Enable Injections.

To that end, Enable Injections is developing a new class of wearable on-body drug delivery devices capable of delivering higher volumes and viscosities with minimal discomfort.

The new generation of wearable injectors feature improvements in construction materials, injections process, and safety features, meant to overcome the challenges of delivering large-molecule and high-volume biologics. For example, Enable Injections' on-body delivery system (OBDS) is designed with a proprietary S.E.T. (sequential elastomeric toroid) mechanical drive system. The force required to deliver the drug does not change with the volume, and the needle size is the smallest available, typically 31g.

"Advancements with wearable injectors offer the opportunity to revolutionize biological therapy treatments, especially those treating chronic conditions that struggle to attain positive clinical outcomes due to patient adherence," says Mr. Hooven.

While the Enable OBDS is not yet approved or commercialized, independently conducted User Preference studies demonstrate a high acceptance of the technology by patients and caregivers, says Mr. Hooven. "Obtaining this information provides confidence that development of larger volume biologics for in-home use will not be an impediment to product uptake and acceptability."

Gerresheimer Medical Systems—Customized Solutions for Biotech Drugs

The specific requirements of biologics development and production, the obligation to better understand the final product, as well as the latest revision of the FDA Combination Product Guidance have resulted in the more complex qualification of prefillable syringes as the container closure system for new products, says Claudia Petersen, Global Director Business Development Medical Systems, Business Development, Gerresheimer Medical Systems. To address these trends, she believes close and early interaction in the product development cycle between the packaging and/or formulation development departments and the supplier is key to increasing patient compliance.

To date, most development-stage and marketed biopharmaceuticals are either monoclonal antibodies or recombinant proteins, each with specific requirements/sensitivities, and need to be administered by injection. "Protein-based drug products have complex requirements that demand customized prefilled syringe solutions," she says.

Custom drug delivery devices with prefilled syringes are a must in the parenteral market because of the vast number of parenteral drugs that exist. That's why Gerresheimer offers a comprehensive portfolio of high-quality products in glass and cyclical olefin polymers (COP), and adapts the syringe system to the customer's

individual requirements profile.

"Gerresheimer is one of a few companies in the world to offer its customers both glass and COP syringes," says Bernd Zeiss, Medical Systems, Technical Support Manager at Gerresheimer. COP's barrier properties effectively protect the content of the syringe. COP is also transparent, which means that COP syringes are similar in appearance to glass syringes. This transparency makes it easy to visually check the content for clouding, particulate, and other defects. COP syringes can be used as a primary packaging for biotechnologically derived drugs.

Gerresheimer's ClearJect (COP) syringe with needle is transparent like glass for visually checking content.

"These are some of the most expensive drugs on the market and highly susceptible to external influences. They are manufactured in high-tech processes and involve complex development and production methods," says Mr. Zeiss. "The very precise injection molding process permits more exact tolerances than the freeforming process used for glass syringes. Exact geometries are very important if the syringe is destined for use in an autoinjector. These exact geometries also reduce the syringe's dead volume so that less drug residue is left inside the syringe after use. This is a persuasive argument for manufacturers of expensive drugs."

Nemera—A New Version of a Proven Device to Address Safety and Biologics

Since the early 2000s, prefilled syringes have gained popularity due to their ease of use, improved user safety, and the reduction of potential dosage errors. Self-administration, at-home administration, and the rise of biologics are the main drivers of this growth. Indeed, needlestick injuries remain a global concern with more than 3 million exposures to blood every year, according to the World Health Organization. In order to overcome those problems, regulation/recommendations have been established to improve users' conditions. As a consequence, devices such as safety devices for prefilled syringe or autoinjectors have emerged.

While 1ml prefilled syringes are the common primary container, over the last years—with the rise of biologic drugs—larger volume containers (2.25ml) have emerged. Those biologics have raised new challenges. "Indeed, on one hand, biologics are adding complexity to the parenteral segment due to the nature of the drug (more viscous and with larger filling volume), while on the other hand biologics are targeting patients suffering from chronic diseases who have to self inject," says Adrien Tisserand, Global Category Manager at Nemera.

In response, Nemera has developed a 2.25ml version of Safe'n'Sound®, an open, adaptable, and customizable platform of add-on passive safety devices for prefilled syringes to help prevent needlestick injuries. As a passive safety device, the safety feature activates automatically at the end of the injection, easing the use.

User interface has been integrated from the beginning in the design and development of the device, integrating many ergonomic features: a large thumb pad surface

Nemera's Safe'n'Sound® is a 2.25ml customizable platform that addresses the challenges of administering biologics.

to smooth the injection; large built-in finger flange to facilitate handling; a round shape for more comfortable handling; and a spring located at the syringe flange position to provide good visibility of the tip of the syringe and enable inspection of the drug, even with low-filling volume drugs. An optional add-on ergonomic extended finger flange has also been developed to improve the handling, gripping, and comfort for the user.

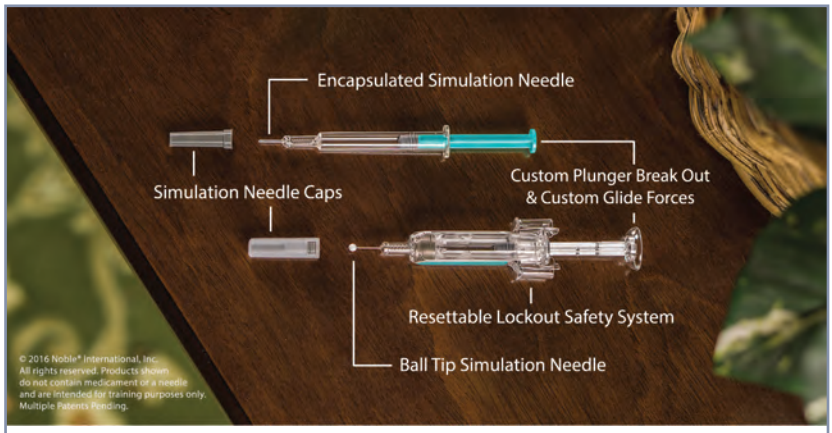
Safe'n'Sound has been designed to give flexibility to the laboratories being an open and customizable platform. Indeed, Safe'n'Sound is compatible with syringes of different filling volume (1ml and 2.25ml), flange type, and suppliers. "The device provides pharmaceutical companies flexibility on their dosage formulation, and an innovative safety device solution to equip small- and large-volume drugs while responding to patients' needs in terms of ease of use and safety," says Mr. Tisserand. "Moreover, Safe'n'Sound is a patented, 510(k) cleared product, which can be sold worldwide."

Noble—Providing a Positive Patient Onboarding Experience

The demand for prefilled syringes continues to grow as more patients are being required to self-administer medications, such as the increasing number of biologics and biosimilars entering the market. As these products continue to augment and launch into new therapeutic sectors, training and education will remain a critical success factor that will determine a patient's ability to safely and effectively use prefilled syringes and adhere to therapy, explains Paul Sullivan, Associate Director of Business Development at Noble.

Noble is a full-service, patient-centered product development and manufacturing company that specializes in onboarding and device training. Noble works closely with pharmaceutical and biotechnology companies to develop educational and training solutions designed to provide positive patient onboarding experiences, reduce errors, and improve patient outcomes.

"There are psychological factors that self-injection patients face, such as anxiety and confidence," says Mr. Sullivan. "Over the past decade, advancements in the industry have given us a better understanding of patient adherence and the benefits of training and education. The



Training and educating users about prefilled syringe use and safety have been shown to improve patient compliance, according to Noble.

traditional patient educational materials have proven to be ineffective, as studies reveal 78% of the patient population lacks proficient health literacy[4], resulting in treatment barriers for prefilled syringe users."

Mr. Sullivan adds that training devices have been shown to be effective for improving patient outcomes and adherence.

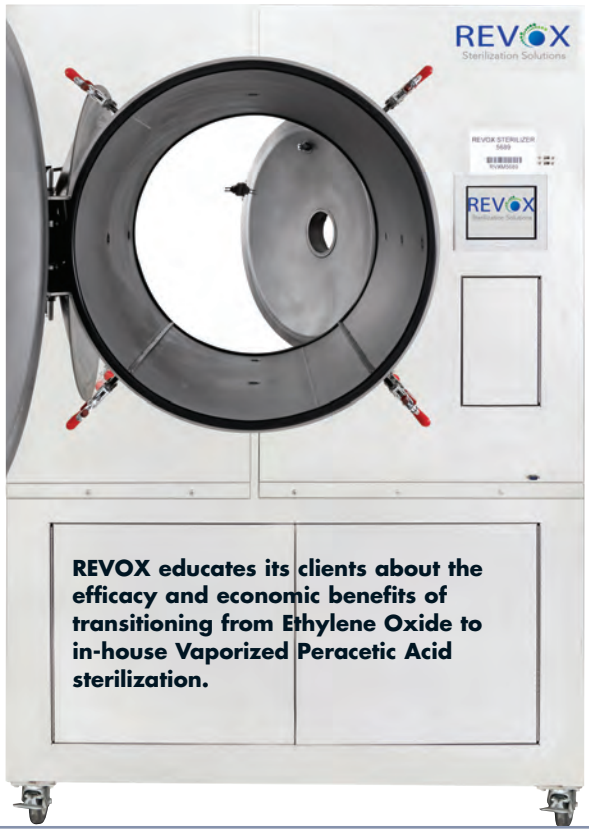
Findings also reveal patients who use a training device are more compliant.[5] Novel training technologies like simulation needles help promote positive onboarding experiences and empower patients to lead healthier lives.

"In the modern era of patient-centric care, products that are able to provide superior onboarding and patient experiences will be well positioned to reduce patient errors, while improving patient satisfaction and outcomes," he says.

REVOX—Sterilization Can Mean the Difference Between Success & Failure

Biologics and more complex delivery devices are sensitive to the high temperatures associated with traditional sterilization processes. The REVOX vaporized peracetic acid (VPA) sterilization process is conducted at room temperature (21°C), allowing full sterilization of the device without affecting the drug.

"Sophisticated delivery systems like combination devices require greater simplicity for the patient and the manufacturing process, which in turn requires the integration of diverse components with variable suitability to standard sterilization processes," explains Mason Schwartz, Operations Manager and Co-inventor of REVOX. "High temperature sterilization methods often necessitate separation of components and assembly either post-manufacturing or with the patient. With more than 100 materials tested for compatibility with the REVOX VPA process, the product can be fully assembled pre-sterilization."



REVOX educates its clients about the efficacy and economic benefits of transitioning from Ethylene Oxide to in-house Vaporized Peracetic Acid sterilization.

Elevated temperatures in the sterilization process may affect the medication itself. And "surface sterilization" with lower temperature methods is often more challenging than the term implies, he says. "With the goal being sterilization of every component of the device while not touching the drug, the method needs to have the capability of penetrating mated surfaces, such as the threads on a plunger-to-stem assembly, while providing variable controls to limit the penetration to just short of reaching the drug itself."

Add to this the issues such as strict regulatory requirements, recalled prefilled syringes, manufacturing complexity, and the cost associated with prefilled syringes. "All of this demonstrates the obvious preference and potential advantages, from various standpoints, to have a combined, single device for medication delivery," says Mr. Schwartz. "If vial/syringe packaging was 'good enough,' manufacturers wouldn't be challenging that status

quo with the costs and risks associated with prefilled syringes. The sterilization method used on prefilled syringes can be the difference between success and failure."

From a cost standpoint, depending on the standing infrastructure of a manufacturer, contracted sterilization is the standard sterilization process. REVOX enables on site, in-line sterilization that can significantly reduce per unit costs associated with sterilization.

Sometimes cost savings aren't enough to make a convincing argument. Mr. Schwartz recalls one client that wanted to launch its product as a prefilled syringe. However, project timeline pressures were intense. "We demonstrated the feasibility of REVOX VPA sterilization of the prefilled syringe, but the client didn't want to trade off an on-time launch with potential delays associated with a novel sterilization method of a prefilled syringe."

Another client, however, saw the "writing on the wall" in terms of the ever-lowering Ethylene Oxide (EtO) residual standards. As the residual limits are lowered, the WIP (work in process) time and volumes increase with the need for greater EtO post-processing aeration times. "We continue to work with this client to demonstrate the efficacy and economic benefits of transitioning from EtO to in-house VPA sterilization."

Mr. Schwartz continues: "We are seeing a tremendous increase in the need for sterilization of advanced combination and prefilled syringes. We've seen commercialization plans compromised with vial versus prefilled syringe packaging simply because of traditional sterilization constraints."

SCHOTT Pharmaceutical Systems—Polymer Syringe Eases Viscous Drug Delivery

With regards to syringe manufacturing, significant achievements have been made in recent years. This leads to an overall reduction of cosmetic defects (which otherwise could have an impact on filling operations) and enhanced mechanical strength of the syringe. For example, syringe barrels can be produced with tighter dimensions, which ensures a better fit with safety devices; tungsten residues and siliconization can be controlled in a better way, the latter by diving nozzle technology, resulting in a uniform distribution of the silicon oil inside the barrel; and highly automated handling of the syringe during production helps to further reduce defects.

"Looking ahead, patient comfort and safety will become even more prevalent," says Anil Busimi, Director Strategic Marketing and Innovation, SCHOTT Pharmaceutical Systems. "A very important point is drug container interaction and the determination of extractables and leacheables (E&L).

To address this, SCHOTT introduced a new prefillable polymer syringe, designed to improve the safety and stability of sensitive drugs. The product, SCHOTT TopPac® SD, offers new features for a reduced E&L profile, such as an inert COC (cyclic olefin copolymer) barrel that releases no ions or heavy metals; cross-linked silicone for barrel lubrication that reduces the amount of subvisible particles and still ensures optimal functionality; and the syringes are sterilized with an ETO (Ethylene Oxide) method, rather than irradiation.


TopPac® Rigid Cap is a new closure system for prefilled polymer syringes from SCHOTT Pharmaceutical Systems.

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To address the topic of patient comfort, a new syringe (TopPac SD) was designed with one of SCHOTT's clients to make the application of hyaluronic acid safer and more comfortable. "Given that hyaluronic acid is highly viscous, doctors need to apply a great deal of injection force when they use conventional luer lock syringes to give the injections," explains Mr. Busimi. "It is not uncommon for that to cause patients to feel pain. In extreme cases, the high pressure can even disconnect the needle hub from the syringe and, in a worst-case scenario, lead to breakage of the luer lock adapter. For that reason, highly viscous drugs (HVD) require packaging that allows a consistent gliding/injection force. The newly designed syringe comprises a smaller inner diameter, as well as optimized siliconization. This ensures that the plunger slides evenly with low injection force and that the medication can be administered in precise dosages. The syringe also features an integrated luer lock that prevents leakage, breakage, and needle pop off."

SCHOTT also added new closure systems for its prefilled syringe portfolio. "These rigid caps ensure the integrity of the container, yet can easily be opened by healthcare professionals or patients," he says. "The closure adds a great deal of flexibility to our customers' supply chain, and speeds up time to market for new or already existing drug products."

Vetter—Tackling the Challenges of Package Design and Material

Large (bio-)pharmaceutical companies often focus their efforts on core competencies, such as late-phase development and drug marketing. To improve their efficiency in these areas, they are making efforts to reduce and simplify their network of different service providers. "Whenever possible, they purchase a solution that equates to 'one-stop-shopping,'" says Bernd Stauss, Senior Vice President Pharmaceutical Production/Engineering, Vetter Pharma-Fertigung GmbH & Co. KG.

But it's not just single sourcing in partners that matters to pharma. An all-in-one concept is also appealing with regard to prefilled syringe technology and the issue of lyophilization. Dual-chamber systems offer advantages in this sector. The Vetter Lyo-Ject® dual-chamber syringe is designed for sensitive drugs that will not degrade in a lyophilized state. The actual active ingredient is lyophilized in one chamber, while the other chamber of the syringe contains a solvent that is mixed with the active substance immediately before application.

"This all-in-one concept enables a long shelf life as well as easy handling. This also means higher yields of your active product ingredient and precision in dosing," says Mr. Stauss.

In addition to package design, packaging material plays an important role. For instance, Mr. Stauss says it can be a challenge to determine the right amount of silicone that will enable the correct movement of the plunger rod while avoiding any form of interaction between the silicone and the drug substance.

Consider this real-life example. High-value products are often based on very complex compounds. This means that these compounds demand a high degree of accuracy on the filling line. As a manufacturer, Vetter has to deal with the increased sensitivity to manufacturing processes and environmental conditions. One highly sensitive API required very small fill volume in a syringe device. "Small filling volumes create an increased demand on all production areas, including process design, technical equipment, and packaging material," he explains. As such,

All-in-one simplicity: Dual-Chamber Syringe Vetter Lyo-Ject® for lyophilized drugs.

packaging material and processes needed to be adapted to meet the requirements of this product.

"Reaching the right amount and correct application technique of the silicone coating the syringe is but one example of the challenges we face in fill/finish projects like this one," says Mr. Stauss. "Comprehensive project management is also needed to handle such a project successfully, taking into consideration the needs of both the product and the customer."

West—Delivering Delivery Differentiators for Biologics and Combination Products

Last year saw the first FDA-approved biosimilar. Advanced drugs, like biologics and biosimilars, require sophisticated packaging and drug delivery systems, and the market has responded with offerings that address this new need. In the case of biosimilars, with many companies competing for the same therapy, the mechanism of administration can be a key differentiator. West's contribution to this evolution has included Daikyo Crystal Zenith® cyclic olefin polymer (COP), which is used to produce a technologically advanced COP containment and delivery system. Crystal Zenith is proven to complement biopharmaceuticals and other complex, high-value medicinal products because it addresses the need for clear, biocompatible material that helps mitigate the chemical interaction and breakage risks inherent in glass, says Mike Schaefers, Vice President, Global Product Management and Marketing Operations, West Pharmaceutical Services, Inc.

"For injectable biosimilars currently in the pipeline, it will be important to examine drug delivery options that can improve the patient experience while ensuring, when possible, a delivery format with which patients are familiar and comfortable," says Mr. Schaefers. "Together, device and drug manufacturers can work seamlessly as partners to provide innovative solutions that help mitigate risk, encourage patient adherence, and enhance value."

Focusing on enhancing quality from early development through commercialization, West adopted Quality by Design (QbD) concepts in the design and manufacturing of packaging components. QbD delivers an improved, data-driven output, providing superior product and process understanding that minimizes risk, emphasizes patient-critical quality requirements, and enhances drug product effectiveness. For example, West's NovaPure® plungers incorporate functional performance parameters like gliding and breakloose forces, which are very important to ensure consistent injectable drug administration when syringes are used in combination with an injection device.

And when it comes to the popularity of combination products, drug manufacturers are more heavily relying on companies like West to offer insight into the regulatory process related to components. "Our expertise around how drugs may interact with the delivery systems can help to avoid regulatory delays, increase safety and expedite the process of getting combination products to market," says Mr. Schaefers.

Additionally, combination products have also brought to the forefront the importance of flexible manufacturing, which enables drug companies to quickly transition fill lines from vial format to cartridge to prefilled syringes, depending on the needs of the injectable medicine.

Finally, the popularity of combination products has raised the bar in terms of developing drug containment and delivery systems that are safer and enhance the patient experience. "West strives to manufacture packaging and delivery systems that are easy-to-use, minimize discomfort, and work in a way that is compatible with patients' lifestyles, as they need to easily assimilate these devices into their daily routines." ◆

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PULMONARY DELIVERY

Pulmonary Delivery of Insulin to Treat Diabetes - A Debacle

By: T.R. Shantha, MD, PhD, FACA

INTRODUCTION

Diabetes is a disease in which the body does not produce and/or properly use insulin, ie, insulin resistance. According to the American Diabetes Association, 20.8 million people in the US - or 7% of the population - have diabetes. One out of every 10 healthcare dollars spent in the US goes to treat diabetic patients. The treatment of type I and some cases of type II diabetes is with subcutaneous insulin injections. It is associated with lack of compliance due to the pain of multiple daily injections, especially in type I juvenile diabetics. Hence, there is an enormous demand for insulin that can be administered without painful shots. Development of such an insulin delivery system would open the way to a multibillion-dollar market, while also making diabetics more treatment-compliant.

Let us look at why the lungs are a preferred target route of many therapeutic agents, including insulin. The human lungs have a combined surface area of 50 m^2 to 100 m^2 (1,076 ft^2 compared to 2 m^2 or 22 ft^2 of skin) exposed from within and to the surroundings for a multitude of infections and adverse environmental conditions besides air to supply life-supporting oxygen and removal of carbon dioxide. If all of the capillaries surrounding the lungs' alveoli were unwound and laid end to end, they would extend for about 992 kilometers (616 miles). Both lungs contain approximately 2,400 kilometers (1,440 miles) of airways and 274-790 million alveoli (estimated by counting their openings at the level of the free septal edges, where they form a two-dimensional network) involved in gas and liquid exchange and transport of liquids delivered to the alveoli to the blood.[1,2] Hence, the alveoli and its associated vascular network is sought after as a method of delivering many therapeutic agents, including insulin, to systemic circulation for treating various pulmonary and systemic afflictions, such as diabetes. Delivery of corticosteroids, bronchodilators, and therapeutic agents to treat cystic fibrosis of lungs and many others are very effective, and much desired, but not insulin.

The search for a non-injectable form of insulin continues, and the diabetic population all over the world is exploding, needing insulin and other anti-hypoglycemic agents. Fear of needles and the inconvenience of insulin injections have created a market for alternative methods of treating diabetes needing insulin injections to control blood sugar. An apparent breakthrough arrived with the development of a preparation that required no needles; instead insulin could simply be inhaled (Figure 1).

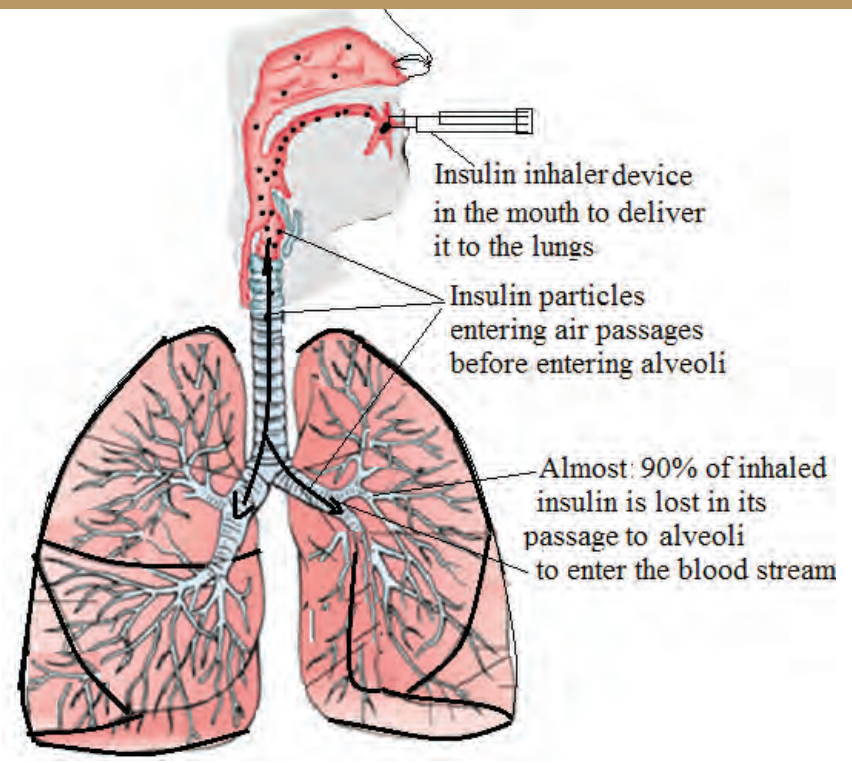
While the FDA has deemed this novel insulin preparation safe and effective, many questions regarding its long-term health effects remain unresolved. After I published the article on the cancer-causing effects of inhaled insulin using the device called Exubera, Pfizer withdrew the drug from the market, took a $2.5-billion dollars loss.[2-4] This is not the end of the story - they also reported the development of lung cancer (Figure 2) in six patients who used Exubera to treat their diabetes, as we predicted.[3,4] Their withdrawal was timely and saved hundreds of diabetics using inhalation insulin from developing lung

cancer.

Now what is the problem? On June 27, 2014, the FDA approved AFREZZA®, a novel, rapid-acting insulin in powder form with a special, smaller delivery device (compared to the original bulky device of Exubera abandoned by Pfizer). After Pfizer withdrew the drug, another pharmaceutical company and developer of this method of insulin delivery spent more than $1 billion dollars to develop this special form of insulin and its miniaturized delivery system. It is obvious the FDA did not look at the ill effects of inhaled insulin. We have sent our publications to the FDA and diabetic agencies, including the developer of this mode of administration of insulin; still it was ignored. We sent the latest publication to all the agencies responsible for the approval and the drug companies marketing it under license, including Sanofi-Aventis US LLC. Finally, the law firm representing Sanofi-Novartis sent a notice informing the developer of Afrezza, terminating the agreement because the prescription levels of Afrezza failed to meet modest expectations.[8] Could it be they realized the long-term negative health effects by its long-term use, such as cancer, as we reported in our articles, and its legal implications?[1-4]

Though both drug giants (Pfizer and Sanofi) dropped marketing inhaled insulin based on a failure to meet their modest expectations, we believe that one can assume they realized the carcinogenic effects of inhaled insulin as we reported in many publications, and with multiple litigations against the product and the company that markets it. Inhaled insulin, in addition to being anti-diabetic, is carcinogenic when inhaled.[1-4]

FIGURE 1

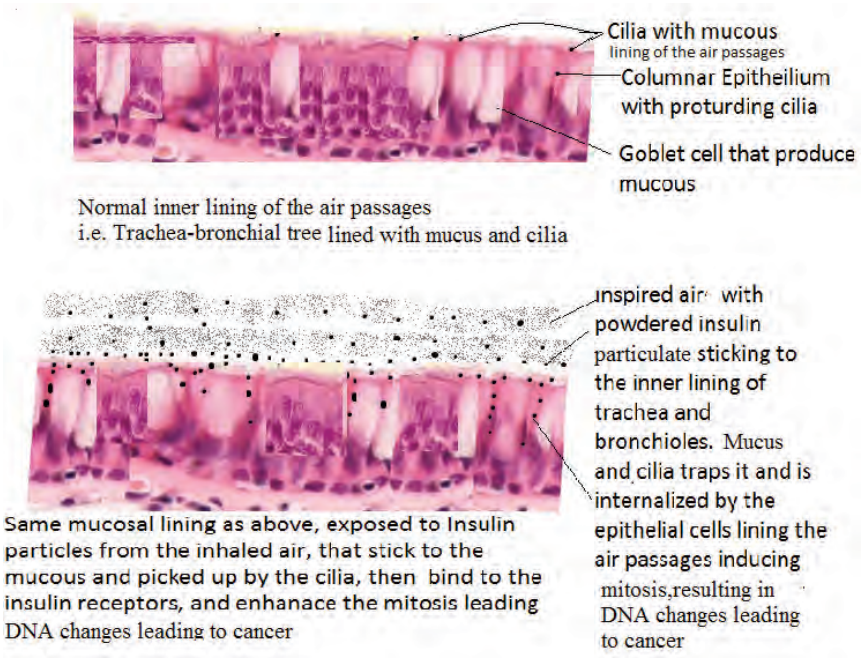


The air passages for the delivery of insulin to alveoli by inhalation. Note insulin particles have to travel extensive air passages (about 1,440 miles) and escape billions of villi lining the air passages to reach millions of lung alveoli - the site of entry of insulin to circulation. Hence, only a small percentage of insulin reaches the alveoli to enter systemic circulation to reduce blood sugar.

After Pfizer and Sanofi dropped marketing pulmonary delivery of insulin, the developer of this inhaled insulin established a new collaboration and license agreement with Receptor Life Sciences.[7] The newly formed entity covers the development of multiple inhaled therapeutic products to treat chronic pain, neurologic diseases, and inflammatory disorders in addition to this product. Our stand on the pulmonary delivery of insulin has not changed, and we hope the developer and promoters abandon this mode of insulin delivery. They need to remember what Albert Einstein said on such an effort "Insanity: doing the same thing over and over again and expecting different results."

Then what is the problem of this mode of delivery of insulin one may ask? There are many problems with this mode of delivery as previously described.[1-4] The respiratory passages within the lungs, in addition to the skin, are the only organs in the body that are constantly and directly open to the external environment, exposing them to epidemiological, environmental, occupational, personal, and social factors (close congested living) and their related diseases as exemplified by tuberculosis, pneumoconiosis, black lung disease, and others.[5] The main problem with inhaled insulin is that the majority of insulin particles stick to the air passages before they reach the lung alveoli to be absorbed to the systemic circulation to reduce the blood sugar with dire consequences, such as induction of cell

FIGURE 2



The mucosal lining of the air passages lined with cilia and mucous, to which the insulin particles stick to the lining on their way to alveoli as shown in the lower diagram. They then get attached to the cell linings and then insulin receptors, where they are internalized and stimulate mitosis of these air passage cell linings. This results in DNA changes (due to repeated multiple rapid divisions of cell linings) and tumor genesis.

mitosis in normal and metaplasic cells leading to cancer. It is estimated less than 10% of the inhaled insulin reaches the lungs to exert the anti-diabetic therapeutic effects, and the rest of it sticks to the air passages, resulting in this disastrous outcome.

The issue that needs to be addressed is how to deliver insulin into the alveoli directly without a majority of it being deposited on the air passages on its way to the alveoli. So far, no such method has been developed, and it may be an impossibility especially due to the presence of billions of tentacles (cilia) on the surface of the cells lining the air passages that pick up any particulate matter from the breathed air that passes by, such as insulin particles of inhaled insulin of Afrezza, before they reach the alveoli as shown in Figure 3.

The problem with the inhaled form of insulin is that it is effective only when the administered dose is more than three or even up to ten times the amount given by subcutaneous injection, because little more than 10% of the inhaled insulin reaches the alveoli to produce a hypoglycemic effect. The interval between the administration of insulin and the onset of glucose-lowering activity is about 10 to 20 minutes. Given its rapid onset of activity, inhaled insulin is suitable for pre-prandial (before meal) but not for a long-term basal (baseline) use. Tight glucose control, however, may come at a price.

One area of potential concern regarding inhaled insulin is the possible effect on the tissues that it comes in contact with on its way to the alveoli, such as the linings of the mouth, throat, tongue, cheeks, gums, tonsils, trachea, bronchial tree, vocal cords, larynx, nose and nasal air sinuses, and olfactory mucosa (which has a direct connection to the brain). Even the modified dry form of special insulin delivered through the special delivery unit makes it no different. The powdered insulin will stick to the aforementioned breathing passages to the lungs before it reaches the alveoli to enter the blood. It is a known fact that insulin induces division of cells called mitogenic wherever it is deposited. Furthermore, because insulin is a growth factor, there is also the potential concern that inhaled insulin could support aberrant cell growth, and potentially even trigger and support cancer and change precancerous lesions to cancers. The report of the development of six cancer cases after using Exubera, an inhalation delivery method, tells us that no matter what kind of insulin you deliver, the powder insulin particulates stick to the naso-oro-laryngo-trachea-bronchial tree. The majority of the special insulin delivered through Afrezza (human insulin) will be sticking to these structures before it reaches the alveoli and will act as mitogenic, turning some cells to cancer. It is a known fact that the cancer cells and pre-cancer cells have numerous insulin receptors compared to normal healthy calls, which lock the inhaled insulin, taken inside the cells and thus stimulating further multiplication of these cells (Figure 3) by supplying more glucose as the energy, and turning some of them to cancer growth.[4]

Research has noted that those with elevated blood sugar due to type II diabetes and other conditions are more prone to develop certain types of

cancers than the healthy population. Numerous cancers, and even non-cancerous fibrous tumors, have more than the normal amount of insulin receptors to facilitate the entry of large amounts of glucose into the tumor cells to support their energy needs, thus promoting their growth, multiplication, and spread - it is no different in trachea-bronchial air passages.

Hence, the important possible threat about treatment with inhaled insulin is therefore the potentially increased risk of lung cancer, which has been already reported by Pfizer.[4] Studies of human bronchial epithelial cells suggest that insulin-receptor activation is in itself insufficient for malignant transformation. However, once malignant transformation has been induced by other agents (environmental, coal miners, smoking, age related, trachea, and bronchial afflictions, etc), the insulin receptor pathway with attachment of inhaled insulin promotes rapid malignant progression of these cells.[1-5] Because almost 90% of the inhaled insulin comes in direct contact with so many tissues before it reaches the lung alveoli, it is crucial that future research examines its impact on normal, pre-cancerous, and cancerous cells of the naso-oro-pharyngeal-tracheal-bronchial respiratory and digestive systems.

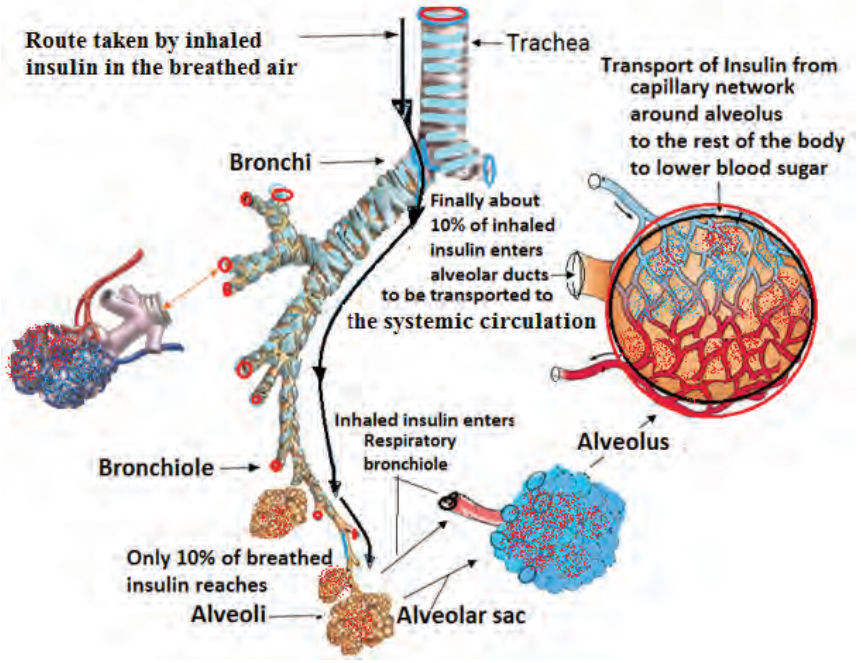
POTENTIAL HEALTH RISKS OF INHALED INSULIN THERAPY

Questions about carcinogenic effects that inhaled insulin has shown in a small number of cases using similar methods like the one recently approved by the FDA still do not remain resolved about the potential health risks of inhaled insulin. The documented and possible health risks of insulin inhalation and oral route of administration are explained by us in our extensive article.[1-4, 6, 8-10] Due to potentially increased tumor incidence in the tissues of the respiratory tract, and as previously mentioned, Pfizer withdrew inhalation insulin from the market and reported six cases of lung cancer in the users after its withdrawal.[4,8]

Exubera rode a wave of anticipation that it would free patients from the need for daily painful injections. Regrettably, that wave was either not big enough or crashed on the rocks of safety and price concerns before it could be fully used as an alternate choice to injections. This may explain why Afrezza, arguably an improvement on Exubera, has not been able to reach even the level of prescriptions and sales achieved by Exubera. There is no longer any wave of excitement and anticipation for an inhaled insulin.

As reported by Josef Bassart in the March 2016 issue of this publication (Afrezza – Another Lesson for Drug Delivery Professionals?) on pulmonary delivery "the lung is not like the skin, the nose, or even the stomach." He appropriately pointed out that "Insulin delivery to the skin offers a number of safety benefits. It presents a large surface area that permits delivery sites to be rotated, and it is also easily inspected for tolerability and safety issues by the health professional and the patient.[6] In a worst-case situation, sections of skin can be removed and repaired with grafts. Insulin delivery to the lung is a bit of a black hole. Selective delivery to distinct areas of the lung is hard to accomplish, rotating pulmonary delivery sites is hard to imagine, and assessing ongoing safety can only be performed through

FIGURE 3



The route taken by inhaled insulin to reach the alveoli as shown in the diagram. It depicts the anatomical and histological route taken by the insulin before it reaches the alveoli and systemic circulation to reduce blood sugar.

"One area of potential concern regarding inhaled insulin is the possible effect on the tissues that it comes in contact with on its way to the alveoli, such as the linings of the mouth, throat, tongue, cheeks, gums, tonsils, trachea, bronchial tree, vocal cords, larynx, nose and nasal air sinuses, and olfactory mucosa (which has a direct connection to the brain). Even the modified dry form of special insulin delivered through the special delivery unit makes it no different. The powdered insulin will stick to the aforementioned breathing passages to the lungs before it reaches the alveoli to enter the blood."

indirect testing.There is no simple 'look and-see' approach to head off more serious problems."[6]

With large-scale prolonged use of inhalation insulin, this will become more apparent with increased tumors of the nasal sinuses, nasopharyngeal cavity, laryngeal and respiratory tracheobronchial passages, as well as the esophagus.

Oral-rectal insulin delivery, according to a published report, also cannot be used to treat insulin-dependent diabetes due to similar health risks.[8,9] These authors reported the possibility of more gastrointestinal tumors due to prolonged use of insulin and its mitotic effects. We know that the lining of the gastrointestinal mucosa is highly mitotic and sheds completely every 7-10 days. These cell linings are replaced by other newly formed cells from the crypts, which are highly mitotic and become even more mitotic with oral insulin, ultimately leading to increased incidences of GI tumors. The true health risks of pulmonary, oral, and nasal delivery of insulin to treat diabetes could take a long time to reveal themselves, as has occurred with other drugs, such as Vioxx® (an anti-inflammatory), Avandia® (an oral anti-diabetic drug), and Phenphen diet drugs and other such therapeutic agents. In addition to the eye-opening health risks of inhaled or oral insulin, it is more expensive than other insulin preparations.

FUTURE OF INSULIN DELIVERY & DEVELOPMENT OF ANTI-HYPOGLYCEMIC AGENTS

There are many concerns about the promises of pulmonary delivery of insulin.[1-7,10] The future of insulin delivery other than the pulmonary route with the fewest side effects with almost painless delivery may come from the following:

1. Transdermal delivery of insulin with a physical approach to facilitate its uptake without using needles and/or a special method to absorb the insulin from the patch.
2. Development of a human gene that transforms pancreatic ducts or other stem cells into insulin-producing islets (already named Human Proislet Peptide-HIP).
3. Development of an insulin pump or microdermal needles to deliver insulin under the skin.
4. Development of methods to activate and induce primordial β stem cells in the pancreas' insulin-producing islet cells or their primordial cells.
5. To ease the painful delivery of insulin by injections, development of a transmucosal and transdermal delivery insulin patch as described in US Patent Publication 2009/0304776 Al.
6. Development of a local anesthetic patch to deliver insulin shots painlessly and make the patients more compliant when insulin injections are needed as described in US Patent

Publication 883487 B2 and 883488 B2.

7. Other therapeutic hypoglycemic agents that are akin to insulin, but need not be injected to lower the blood sugar, administered sublingually, transdermally, and by other routes.

The market for new anti-diabetic therapeutic agents and their painless delivery is enormous. It is a multibillion dollar market open to such products. I am sure the drug companies and research scientists are in a race to develop safer methods other than the pulmonary and oral routes to deliver insulin to control elevated blood sugar to treat the ravages of diabetes, which has become an epidemic, though a controllable endocrine disease in the current century. This is the only endocrine disease in medicine that ravages millions of humans, resulting in millions of disability and premature deaths (costing billions of dollars in healthcare cost). Though the hormone responsible for diabetes was discovered in 1921 by Frederick Banting, and used on humans for the first time in January 1922 in Toronto, Canada, on a 14-year-old boy, Leonard Thompson, a type I diabetic teen was the first person to receive insulin by injection. Dr. Banting won the Nobel Prize in physiology in 1923 for insulin discovery. We are still battling how best to deliver this life-saving hormone to save millions of diabetics, though many billions of dollars have been spent on route of insulin delivery projects since the first insulin injection was given 94 years back, and still it is delivered under the skin, by injection - not by inhalation. ◆

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BIOGRAPHY

Dr. T.R. Shantha has been a member of the faculty of Emory University school of Medicine, Medical College of Georgia, Grady Memorial Hospital, Georgia Baptist Hospital, and is presently a visiting professor at JJM Medical College. He has published more than 100 research articles since 1962, in peer-reviewed reputable journals, including Nature (7 papers), Science, NEJM, J Urology, Anesthesia, Anatomy, Exp. Eye Research, American J of Physiology, etc. He discovered Terbutalene as a treatment for Priapism, which is now used all over the world as the first line of treatment in the emergency rooms and by urologists. He has won numerous awards for his academic contributions, including AMA and GAPI distinguished physician awards. He was one of the nominees for the Nobel Prize in Physiology and Medicine in 2007 for his and Dr. Bourne's research work on the membranes of the nervous system discovered at Emory University. His work is quoted in many medical textbooks and research literature. He has more than 56 patent applications, many published and issued. He is presently working on the treatment of Alzheimer's and Parkinson's disease, and has received two patents in the past 6 months for the treatment of sleep apnea. He has developed many innovative therapies, utilizing traditional and alternative methods for the treatment of cancers and many other incurable diseases. He has published 4 books on the brain and one on the breast from Emory University and Yerkes Primate Research Center of Emory University. At present he is working on 3 books which will be published in the forth coming year.

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Drug Development
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Bruce K. Redding, Jr.
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Transdermal Specialties, Inc.

Transdermal Specialties: A New Dimension in Transdermal Drug Delivery

Of the multitude of drugs that can be delivered transdermally, only about 25 compounds have found market. All are low molecular weight drugs usually lower than 500 Daltons. Larger compounds have generally been unable to be employed in transdermal delivery in which GI-By-Pass is the primary goal. As a result, it takes more research, longer clinical times, and food interaction studies to get a compound from concept to the medicine cabinet. In the United States, the average is 12 years, that is, if it makes it at all. Only 5 in 5,000 drugs that enter preclinical testing progress to human testing; 5 of these drugs that are tested in people are approved. The chance for a new drug to actually make it to market is thus only 1 in 5,000. Not very good odds. Transdermal Delivery can reduce that timeline and investment to as little as 3 years through a transdermal routing as opposed to a GI route. Therefore, there is a need for expanding the number of compounds that can be delivered transdermally. Transdermal Specialties, Inc. (TSI) has been a pioneer in Active Transdermal Delivery Systems since 2009 and has developed a new

ultrasonic-based delivery system that has the promise to significantly increase the number of compounds that can be delivered transdermally, from 1 to 125,000 Daltons in molecular weight. The U-Strip™ is currently being employed to provide transdermal insulin, but there are over 175 target compounds on the list. Structurally, because Transdermal Insulin is now entering Phase III trials, the company has created a subsidiary, Transdermal Global, whose sole focus is diabetes care applications. The parent company, TSI, is currently developing central nervous system applications for the U-Strip Delivery technologies, one of which will enter Phase II clinical trials in 2016. *Drug Development & Delivery* recently spoke with Bruce K. Redding, Jr, CEO and Founder of TSI, about the importance of developing this new tool for enhanced drug delivery, but also a means to reduce the time-to-market for new formulations while also expanding the number of drugs that can be delivered transdermally.

Q: Can you provide our readers some background on Transdermal Specialties?

A: TSI is developing a new form of Active Transdermal Patch system for the delivery of both small and large molecule drug delivery. In particular, our lead product is a Transdermal Insulin Patch for the treatment of diabetes. No Needles. Having completed Phase I and II clinical stages, the company is preparing for a 1,100 patient trial to complete the Phase III program with 500 subjects in the United States and 600 subjects globally. The US component of the Phase III program will involve 5 Super Clinics, each treating over 10,000 type 2 diabetics. Located in Broomall, PA, just outside of Philadelphia, TSI employs 22 researchers and technicians, and expects to add another 30 to its roles for the international program. Production capacity for the Trans-Insulin™ patch is now over 1 million patches per week and conducted at our plant in Charlotte, NC. The company plans to introduce this technology at the American Diabetes Association's annual Scientific Sessions, June 10-14, 2016, in New Orleans. See us at booth No. 116, where we will demonstrate the effectiveness of the U-Strip patch system upon type 2 volunteers in real time.
In addition, the company is involved in a number of strategic relationships to adopt our delivery technology to the delivery of both small and large drugs through strategic research arrangements. This program is called the drug screening program and has already resulted in 3 successful non-insulin drugs now being planned for human clinicals in 2016.

Q: How does TSI's technology function, and why is it unique?

A: **Cutting Edge Technology** – The U-Strip is an active transdermal delivery system using a patented alternating ultrasonic waveform process to temporarily dilate the skin pores, expanding the pore size from 50 to 110 microns in just a few seconds. This process enables large molecule drugs to permeate through the skin (stratum corneum) into the dermis and then into the blood stream. The ultrasound signal does not generate cavitation or heat like conventional ultrasound and is composed of two waveforms: Ultrasound Sawtooth Waveforms

"TSI is developing a new form of Active Transdermal Patch system for the delivery or both small and large molecule drug delivery. In particular, our lead product is a Transdermal Insulin Patch for the treatment of diabetes. No Needles. Having completed Phase I and II clinical stages, the company is preparing for a 1,100 patient trial to complete the Phase III program with 500 subjects in the United States and 600 subjects globally. The US component of the Phase III program will involve 5 Super Clinics, each treating over 10,000 type 2 diabetics."

enlarge the pore size, while Square Waveforms push the drug through the expanded pores into the dermis. Designed originally for insulin delivery, there are more than 175 additional compounds that cannot normally be delivered through the skin, but are candidates for the U-Strip system. This method of drug delivery is unique and does not rely upon skin permeation, which is restricted to drugs below 1,000 Daltons. With the U-Strip system, we have delivered compounds as large as 75,000 Daltons transdermally.

Market Target – The target market is type 2 diabetics, which account for 95% of all diabetes sufferers. Globally, this translates to 209 million type 2 diabetics versus 11 million type 1 diabetics. This is an underdeveloped market with most type 2 on a regimen of oral medicines. Many endocrinologists believe that type 2 would be better off through a regular dosing of insulin instead of relying on Metformin, Glucophage, and other medications because they are inconsistent in maintaining healthy glucose levels and could have long-term serious side effects.

Q: Can you please discuss your development status to date?

A: The kick-off product is the Trans-Insulin system, which completed a 24-hour; 12-subject clinical trial of its miniaturization program.

The U-Strip System involves 4 main components:
Insulin Patch, which uses an absorbent pad construction, the first on-off transdermal patch. The patch snaps onto the transducer coupler and can contain as much as 150 units of insulin, enough for a 2-day supply for most diabetics, and is disposable.

Transducer Coupler, which snaps onto the Patch.

The Ultrasonic Applicator consists of a transducer device that generates ultrasonic transmissions to dilate the pores, enabling large molecule drugs, such as insulin, to enter the blood stream and a keypad to operate and control the dosage level and frequency. The system is worn by the patient and is completely portable.

Battery - A 9-volt battery provides portable power for multiple-day treatment regimens.

The U-Strip system may be worn on the arm, over the abdomen, or on any part of the body. A control device is placed over the insulin patch. This device regulates the dosing schedule for basal and bolus insertions of insulin to maintain the glucose levels of the diabetic patient at a healthy level. The insulin patch is designed to hold a 2-day supply of insulin.

Key advantages of the U-Strip/Insulin system include:

- Very rapid glucose reduction. Volunteers average between 10 and 30 mg/dl reduction in just the first 5 minutes
- Steady glucose reduction to healthy normal range, 95-115 mg/dl followed by glucose stabilization
- Defeats glucose spikes post meal
- Diagnostic & Self Correction

- Dose reporting to physician via the Internet
- Dose tracking memory
- Improved compliance
- Improved disease treatment and management
- Totally non-invasive: needle-free, no catheters

Q: What is the next critical milestone for TSI?

A: The Phase III trial for the insulin system is about to start in 4 nations. Once that data is in, the next critical milestone will be regulatory submission and commercialization for the insulin system. Initially, the target market is type 2 diabetics, to be followed by type 1, and then an insulin patch for children. Along the way through our drug screening program, we will be testing other pharmaceutical compounds for ultrasonic transdermal delivery. Through cooperative research and strategic alliance relationships, we will actively work to expand the number of drugs that can be delivered transdermally, from less than 30 today, to 175 investigations within the next 3 years. Already we are working our way through CNS indications and soon will be investigating arthritis and cardiac care applications.

Q: Will you offer co-development programs with interested potential partners?

A: Yes, we are active in both internal areas beyond insulin, and we do have co-development partnering opportunities for future drug programs. Our drug screening program is expected to generate other opportunities for expanded transdermal applications. First, we treat the target compound for 8 hours using our alternating ultrasound transmission. If no damage, we move to patch development and liberation tests, followed by cadaver skin permeation studies. The whole drug screening investigation can take as little as 3 months. If the compound fails along the way, the partner has invested only in laboratory screening services. If we pass the drug screening program, human clinicals are next, and partners are offered strategic alliance options. As each opportunity manifests itself, we may create separate focus divisions or affiliations to bring those products to market. Right now, insulin has spun to a dedicated subsidiary under Transdermal Global. The CNS, arthritis, cardiac, and oncology products may each be similarly situated

depending upon the needs of potential partnerships.

Q: What are the future plans for the enterprise?

A: Insulin is number one on the runway. As previously mentioned, we have created a subsidiary, Transdermal Global, to focus only upon diabetic care products, starting with the type 2 glucose control system, the U-Strip controller, and the low profile Trans-Insulin™ Patch. That subsidiary will be manned by professionals with diabetes care as their sole focus. Essentially, we are placing all of our diabetes researchers, marketing, and clinical teams under one focus - diabetes care. I am a full believer that emergent companies need to have a focus and thus we have placed our diabetes care unit under one roof. Transdermal Global is forming now and expects to enter Phase III clinical trials later this year. A major goal for this year beyond the Phase III trials is to expand our current pilot patch production facility to 1 million patches per week. Meanwhile, the parent company TSI, will continue its product development activities to explore the use of this patented technology to both speed the regulatory review process by avoiding the GI tract, and to expand the number of compounds that can be delivered transdermally. Our R&D teams are working upon several CNS applications, some internally sponsored, and some already with strategic partners. We are now entertaining potential research and strategic partners who may wish to have their compound tested for enhanced transdermal delivery via the U-Strip technology. For inquiries, contact Bruce K. Redding, Jr at (484) 479-3240 or bkredding@transdermalspecialties.com. ◆

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LYOPHILIZATION

A Lyophilization Scale-Up Model: Lessons Learned & Best Practices

By: Enrico Corona

INTRODUCTION

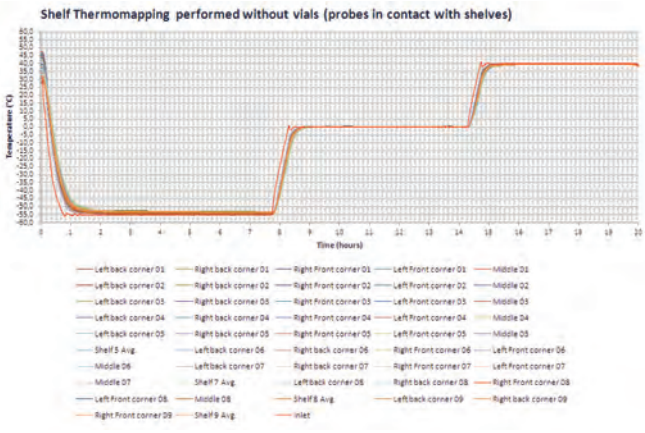
Freeze-drying or lyophilization – which is used to convert solutions of biopharmaceuticals into solids by removing the solvent, typically water, for the purpose of improving long-term storage stability – poses challenges in scale-up from the laboratory to manufacturing.

Lyophilization is one of the most expensive pharmaceutical unit operations, with overly conservative freeze-drying cycles, resulting in long processing times that increase the cost of production. Long lyophilization cycles are also less robust, with an increased potential for equipment failure. Freeze-drying cycles should be optimized to minimize drying time without adversely affecting product quality. Lyophilization runs that affect cost include plant capabilities, as well as raw and primary packaging materials. Full scalability between laboratory and production lyophilization units allows for the development or optimization of freeze-drying cycle parameters that yield significant cost savings.

For example, scalability between the pilot lyophilization unit of the pharmaceutical development services (PDS) department at Patheon's site in Ferentino, Italy, and the LyoMax units located in the site's good manufacturing practice (GMP) area was established using the following steps for maximum efficiency:

- Comparison of the technical specification of the freeze-dryers
- Comparison of the downloaded digital data of the lyophilization cycle performed at pilot scale and at production scale
- Shelf temperature mapping without load
- Shelf temperature mapping with full lyophilization load
- Sublimation rate test
- Comparison of critical quality attributes related to lyophilization performance

FIGURE 1



Shelf thermomapping performed without vials (probes in contact with shelves)

KEYS TO SCALABILITY

Performance of laboratory and production units must be very close in terms of shelf and condenser minimum temperature, shelf and condenser cooling time, ultimate

vacuum, vacuum pump down capacity and shelf temperature uniformity. Based on Patheon's experience, the surface area of the condenser, shelf area, and the size of the laboratory and production units' condenser opening must closely correlate to obtain acceptable scalability.

It is important to determine the ratio of condenser surface area to shelf surface area, and the ratio of shelf surface area to the size of the opening leading to the condenser for lab and production scale dryers. These ratios are very similar for all of our lyophilization equipment, despite the large range in dryer shelf capacities. The closeness of these ratios suggests similar capabilities of the condenser openings to handle the ice vapour during primary drying.

Shelf temperature mapping with no load was performed to verify the uniformity of temperature across the shelves. A star pattern model with temperature probes inserted inside the copper plate at the four corners and in the middle of each shelf was used. Temperature profiles are shown in Figure 1.

Temperature mapping was then repeated with a lyophilizer fully loaded with vials containing a placebo solution (Figure 2).

Thermocouples were placed inside the vials using the same star pattern model consisting of four corner vials and one center vial for each shelf used when mapping the empty shelves. The probed corner vials were placed as closely as possible to the corner of the lyophilizer shelf within an exterior row of vials.

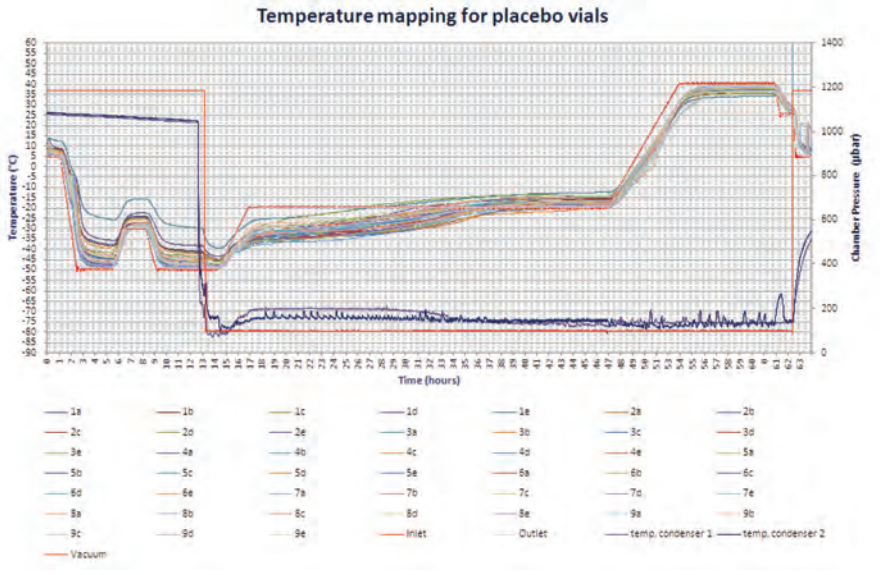
Thermocouples were attached to the rim of each corner tray on shelves 1 and 2 to measure the air temperature approximately 1 cm above the shelf (Figure 3). Thermocouples were also put on the upper interior portions of the door and wall to record surface temperatures.

During inspection, vial location by tray was maintained, making it possible to determine the approximate shelf location for any vials rejected for improperly formed cakes.

Air temperature above the shelves was also measured to investigate the effects of radiation. While conduction is responsible for heat transfer from the shelves to the bottom of the vial, radiation is responsible for heat transfer from the walls and the door of the lyophilizer. Radiation is more pronounced in lab units, resulting in the "edge effect," where edge vials dry faster than center vials.

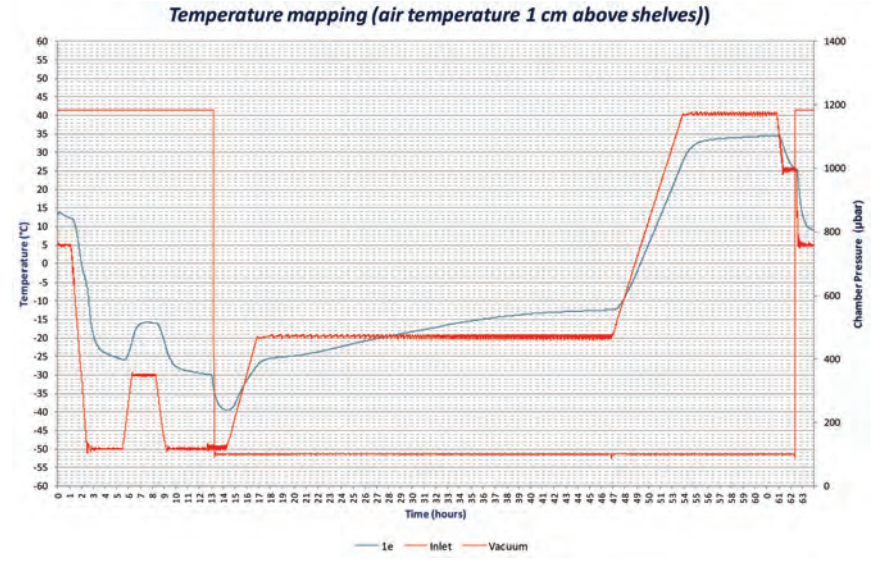
Heat transfer uniformity can be improved by introducing an inert gas,

FIGURE 2



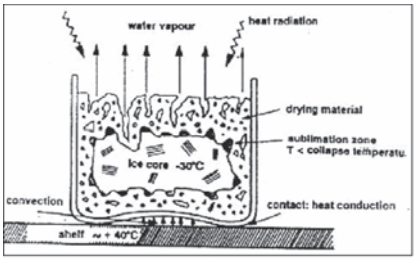
Temperature mapping for placebo vials

FIGURE 3



Temperature mapping (air temperature 1 cm above shelves)

FIGURE 4



Heat transfer during sublimation

such as nitrogen. Gas molecules facilitate heating of the container walls and heat conduction through the container, which increases the amount of heat applied to the product.

Heat transfer coefficient is measured by performing vial sublimation tests, using the same lyophilization parameters as the production and laboratory units (Figure 4). Frozen water shows maximum sublimation rate because of the absence of the product mass transfer resistance.

In these tests, ISO 10R vials were filled with 5 mL of water for injection (WFI), loaded into the freeze-dryer, and frozen at -30°C. Sublimation was then initiated after pulling a vacuum of 100 µbar and raising the shelves' temperature to 10°C. After 3 hours, the process was interrupted, and the remaining ice was allowed to thaw.

Selected vials were weighed before loading the lyophilizer, and at the end of the drying step, vials were fully stoppered and weighed. The amount of water lost during sublimation was calculated and compared between equivalent positions in each freeze-dryer (Figures 5 & 6). A faster sublimation rate corresponds to a higher heat transfer.

The weight loss due to frozen water obtained in the lab unit ranged between 87% and 105% of that in the production freeze-dryer, showing an acceptable comparability in terms of sublimation performance.

LYOPHILIZATION CYCLE PERFORMANCE

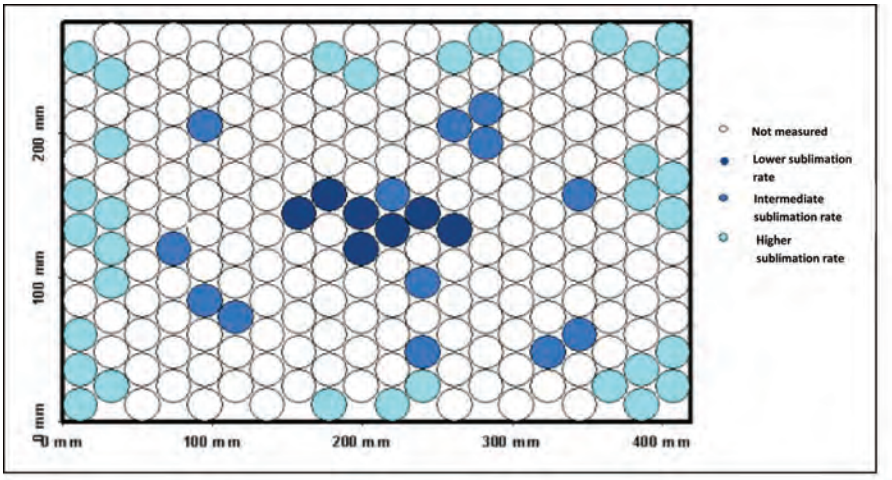
Downloaded digital data from lyophilization cycles performed in the pilot and GMP units were compared. Average deviation from temperature set point and average vacuum value were calculated for each step, along with minimum and maximum deviation from the temperature and vacuum set points.

Comparison of several critical quality attributes related to the lyophilization process for products manufactured at pilot scale and at-scale was also completed, including appearance of the lyophilized product and the reconstituted solution, pH, reconstitution time, residual moisture, content by HPLC, and related substances.

Analytical data were comparable at both pilot scale and GMP scale. The results for residual moisture indicated that the lyophilization process was uniform throughout the lyophilizer chamber at both scales. The moisture mapping line graph for the GMP unit is shown in Figure 7.

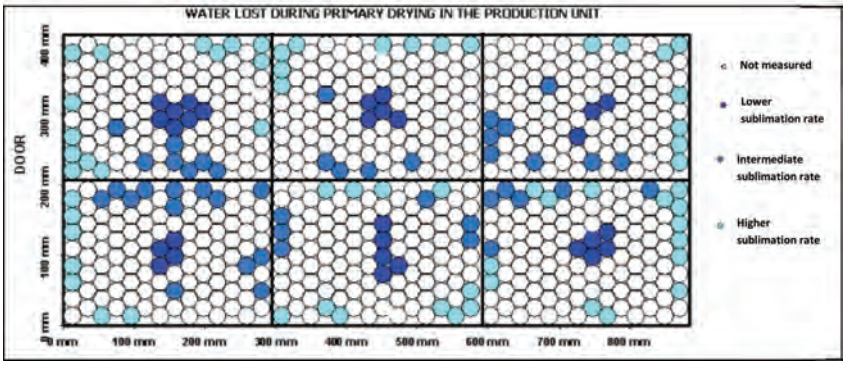
The results for the assay and related substances indicated that the lyophilization process was uniform throughout the lyophilizer chamber and had no adverse impact on the product at any freeze-dryer location at either scale. Lyophilized products appear to have

FIGURE 5



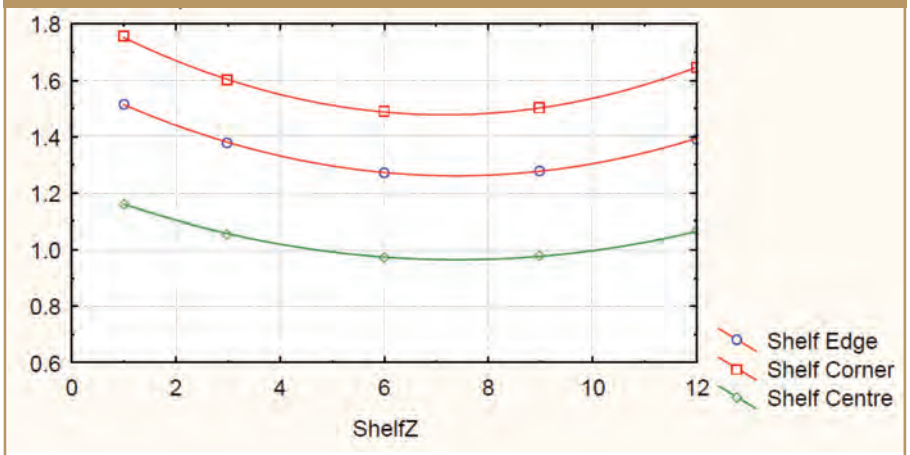
Water lost during sublimation test in the laboratory unit

FIGURE 6



Water lost during sublimation test in the GMP unit

FIGURE 7



Moisture mapping for the GMP unit

similar reconstitution times and residual moisture contents.

CONCLUSION

These results established confidence that lyophilization in the LyoMax units in the GMP area of Patheon's Ferentino site, yielded products that achieved predefined specifications and quality attributes, based on parameters tested in the PDS department's pilot unit. The side-by-side comparison of digital data collected from lyophilization of lab batches and batches manufactured in the GMP area showed that the performance of the freeze-dryers are within an acceptable control range.

The variations around the target set point have a negligible impact on the products, and the experiments clearly demonstrated the scalability of the equipment. While the batch to-batch consistency was high, as measured by a number of analytical properties, especially those sensitive to lyophilization, acceptable product characteristics were maintained during scale up from lab scale to production freeze-dryers.

From these results, it can be concluded that just as both laboratory and commercial scale equipment can be maintained at a comparable state of control, products can be reliably made using either scale of equipment – confirming the scalability of the processes. ◆

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BIOGRAPHY

Enrico Corona serves as Director in PDS for formulation and process development at Patheon Italia – Ferentino site. He earned his Bachelor of Science in Medicinal Chemistry and his additional Bachelor of Science in Pharmacy from Rome University "La Sapienza". Upon graduation in 1996, he joined the Pharmacy Research and Development Division of Intervet, where he was involved in the formulation of sterile liquid and semi-solid products. He joined Patheon in February 2003. While at Patheon, he has been active in the development of new liquid and lyo parenteral formulations for preclinical and clinical and for the marketplace. He conducts lyophilization cycle development and presides over scale-up to fill finish sterile suite. He can be reached at enrico.corona@patheon.com

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External Delivery

Lead Your Company, Don't Over Manage It

By: John A. Bermingham

John A. Bermingham is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America.

For many years, I have witnessed a continuing discussion on the question of, "what's the difference between leadership and management?" Or is there one? I believe that while there are crossover points between the two, there is a difference. Let me focus on management to explain.

There are five functions of management: controlling, planning, organizing, staffing, and directing. These are hands-on management responsibilities. Yes, leadership is responsible for ensuring these functions take place, but the direct responsibility for each function lies with the management team.

Here is an example of an actual situation that a company faced. We'll call it the ABC Company. The ABC Company won a bid to install various energy-saving systems on school buildings in San Diego. The projected revenue was just under $8 million with an operating profit of $750,000. Goals and benchmarks were established with timelines, problems were identified, and solutions agreed upon with the entire plan detailed on Microsoft Project. The project budget was established, and the necessary headcount was identified with requisite skill sets.

Training sessions for the install team were scheduled, an incentive bonus was introduced, and a per-diem expense plan was set for employees who would be working away from home for an extended period. Action plans were developed and distributed, the requisite lines of communications were established, and a weekly review meeting schedule was established.

The installation project was completed in slightly less than 1 year, which was on schedule. All segments of the project passed inspections, and the lead contractor was pleased with ABC's performance. Following the completion of the project, the finance group ran an income statement on the project, which showed the revenue as projected at nearly $8 million, but the operating income showed a $1.2-million loss versus a pro forma profit of $750,000. A negative swing of almost $2 million!

The Board became involved in the examination of why this happened due to the surprise loss of what should have been a nice profit. Apparently, because of the internal and external publicity of this project, the CEO became directly involved in managing the project hands-on rather than leading. He made all of the decisions over and around the managers on the project, all of whom were highly competent in their functional areas. When they disagreed with decisions made by the CEO, they were ignored. No matter how much they tried to manage the project, they were overrun by the CEO.

It was strongly believed throughout the company, as well as by the Board, that had the CEO led rather than try to directly manage the project, the outcome would have been very different. So it is important you understand that leaders lead, not manage. When a CEO takes the position that he or she has to directly manage a project or other situation because they cannot delegate it, what they are really saying is that they do not have the right manager(s) in place. Not leading because you are managing is a path to a potential disaster. ◆

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