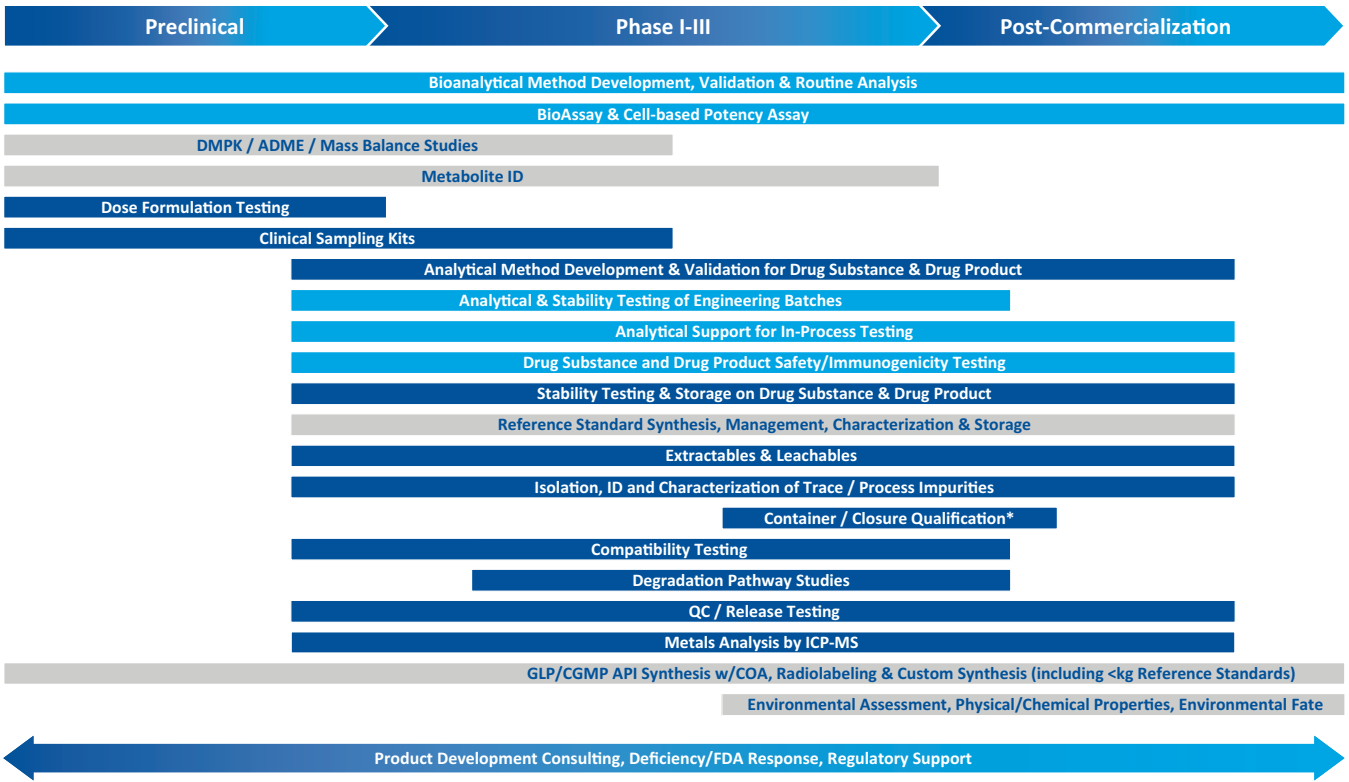
Drug Development Services



*ABC may outsource this service to a qualified vendor.

KEY

- Small Molecule
- Large Molecule
- Small & Large Molecule

visit abclabs.com
or call 855.538.5227

abc better insight better outcomes

Drug Development & Delivery

May 2015 Vol 15 No 4 www.drug-dev.com

Prefilled Syringes & Manufacturing: Meeting Future Needs

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

Sagarika Bose, PhD
Design & Evaluation of a Polymer-Based Prefillable Syringe for Biopharmaceuticals With Improved Functionality & Performance

James Brady, PhD
The Role of Flow Electroporation in Vaccine Development

Marshall Crew, PhD
The Birth of Physical Pharma: 1920-1960

IN THIS ISSUE

INTERVIEW WITH **SOLIZE CORPORATION'S** DIRECTOR YOSHIKI MATSUDA

Introducing

SoluPath *Flex*™

A new low solubility solution

The Customizable, Fixed-Price Solution to Rapidly Improve Solubility

Never before has it been so fast and simple to overcome solubility challenges. With SoluPath *Flex*™, you'll have access to the choices and scientific expertise you need to meet your unique needs.

- Full array of solubility technologies and services.
- Hand-pick the services for your molecule and business.
- Know all costs, timelines and API requirements in advance.
- Consult with a solubility expert at the earliest stages.
- Plan, quote and launch project in days.
- Rapid results from dedicated equipment and teams.

Only with SoluPath *Flex*™ can you accelerate development with a solubility enhancement solution custom tailored to meet the specific requirements of your molecule, timeline and budget. Plus, you can finalize your plan with a solubility expert in just one meeting.

Get exactly what you need, and get it faster with SoluPath *Flex*™

+1 866.PATHEON • www.patheon.com • doingbusiness@patheon.com

Patheon
Performance the World Over®

Insulet Corporation

Tried, tested, **trusted.**

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

The Drug Delivery Manager

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

The Drug Delivery Pod

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

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

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

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

Drug Development & Delivery

May 2015 Vol 15 No 4

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

CORDENPHARMA

Experts taking care.

Full-Service, Fully Committed.

Linking together a legacy of expertise.

CordenPharma experts link your complex ideas with full-service solutions to create high-value products at any stage of development. Through our global network of cGMP facilities and technology platforms, CordenPharma is your partner in the Contract Development & Manufacture of **APIs, Drug Products** and associated **Packaging Services**.

CordenPharma Technology Platforms

- **Peptides / Lipids / Carbohydrates**
- **Highly Potent**
- **Antibiotics**
- **Injectables**
- **Small Molecules**
- **Oncology**

Find Your Expert:
www.cordenpharma.com/contact-us

Visit us at the upcoming

Pharma Outsourcing
May 18-19, 2015
Frankfurt, Germany

Bio
Stand 3326
June 16-18, 2015
Philadelphia, PA USA

www.cordenpharma.com

CordenPharma

Europe
Phone: +49 6202 99 2299

North America
Phone: +1 800 868 8208 or +1 781 305 3332

Future Needs

"The introduction of advanced technologies and application of specific know-how for parenteral drug delivery, such as polymer-based prefillable syringes and the application of a novel silicone oil-free system (i-coating™ technology), can address many of these issues and challenges effectively."

p.36

Table of Contents

When **Performance** Matters Most

West
By your side
for a healthier world™

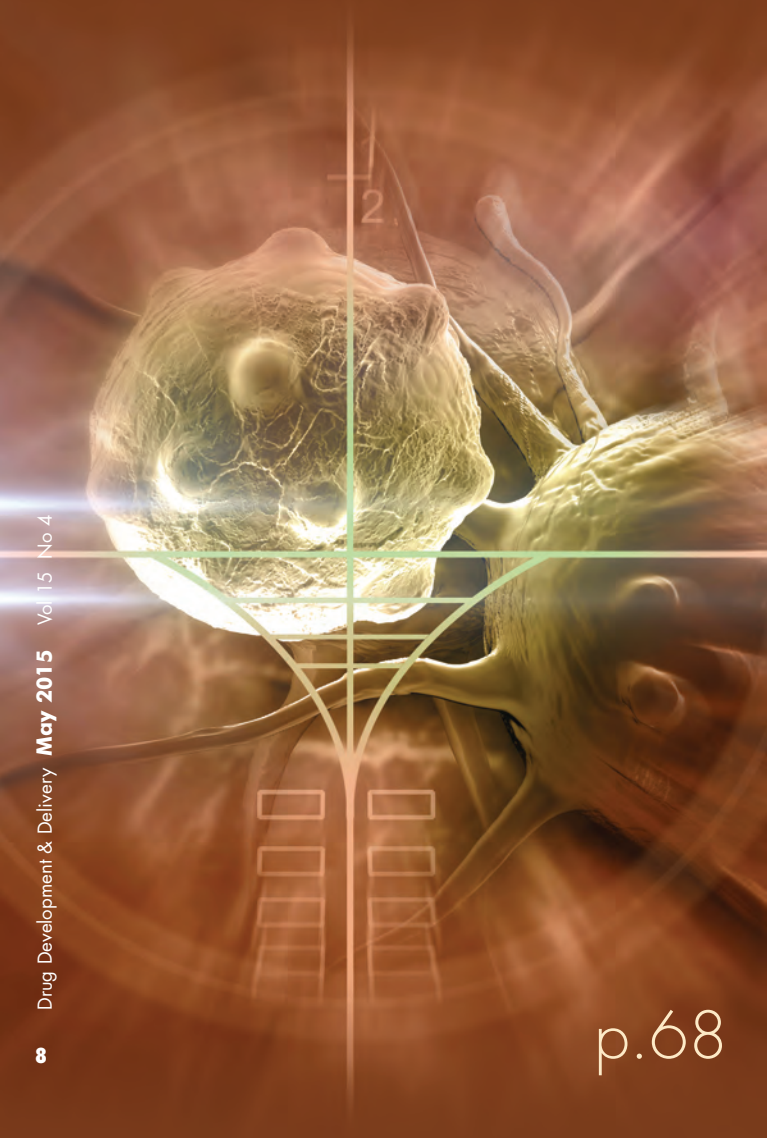
West's advanced Daikyo Crystal Zenith®
1 mL long insert needle syringe system is an
innovative solution for high-value medications.
Learn how it can help you deliver.

www.daikyocrystalzenith.com
(800) 345-9800

DAIKYO
Crystal Zenith®
THE CLEAR SOLUTION

Adenosine Receptors

"The finding that the Gi protein coupled A3 adenosinereceptor (A3AR) is highly expressed in inflammatory and cancer cells whereas low expression is found in normal body cells offers a new way to fight such diseases. Targeting the receptor with synthetic and highly selective A3AR agonists induces anti-inflammatory and anti-cancer effects."



p.68

Table of Contents

SUITE SCIENCE

Xcelience® offers a suite of services enabling clients to partner with a single CDMO for all of their clinical outsourcing needs.

- Preformulation Development
- Analytical Services
- Formulation Development
- GMP Manufacturing
- Clinical Supplies Packaging & Distribution

Xcelience takes pride in delivering the highest standards in science and service with an emphasis on quality, cost and speed.

Contact us: www.xcelience.com +1.813.286.0404

Thank You!

CMO LEADERSHIP AWARDS2015

CMO LEADERSHIP AWARDS2015 INNOVATION

CMO LEADERSHIP AWARDS2015 PRODUCTIVITY

CMO LEADERSHIP AWARDS2015 RELIABILITY

CMO LEADERSHIP AWARDS2015 REGULATORY

The Editorial Advisory Board

LET'S MAKE MIRACLES

WITH ALTHEA, YOU HAVE THE POWER TO MAKE.

You have the power to make a difference. To make new therapeutics that improve quality of life and inspire a healthier world. To do this, you need a manufacturing partner who embraces your every challenge as its own, who shares your unwavering tenacity and dedication from clinical studies through commercial success. That's The Power To Make.

CONTRACT MANUFACTURING:

- Development
- Drug Substance
- Drug Product

WHAT DO YOU WANT TO MAKE?

www.AltheaCMO.com

ALTHEA | THE POWER TO MAKE™ A MEMBER OF THE AJINOMOTO GROUP

Investigational Brain Cancer Vaccine Produces Strong Immunological Response

A first-of-its kind cancer vaccine, SurVaxM, has demonstrated safety and tolerability in patients with recurrent or progressive malignant brain tumors, according to results of a Phase I study conducted by Roswell Park Cancer Institute (RPCI) researchers. The findings were presented at the American Association for Cancer Research Annual Meeting 2015.

The study title is Phase I study of SurVaxM in patients with survivin-expressing recurrent malignant gliomas (CT301; section 24, poster board 1). This immunotherapeutic vaccine will now be evaluated in a larger Phase II clinical trial to assess its effectiveness for patients with advanced brain tumors and a new Phase I clinical trial for multiple myeloma patients.

"This recently completed clinical trial was the critical first step for the survivin vaccine, to show its safety for use in humans," said the study's senior author, Robert Fenstermaker, MD, Chair of the Department of Neurosurgery and Director of the Neuro-Oncology Program. "Through this process, we also confirmed that the vaccine produces a strong immune response and gave us a signal of potential clinical responses."

Dr. Fenstermaker and colleagues entered nine patients with survivin-positive recurrent glioblastoma (brain tumors) who received a series of up to four injections of SurVaxM at 2-week intervals. Most patients developed T cell and antibody responses to survivin, the vaccine target. The average expected survival time for recurrent glioblastoma patients is approximately only 7 months when receiving standard therapy. In this trial of SurVaxM, six of the eight patients with recurrent glioblastoma have had progressive disease, although five of these survived from 12 to 20-plus months. Two of the eight patients were still progression-free at 20 and 31-plus months.

Survivin is associated with aggressive cancers and an indicator of poor prognosis and response to conventional therapy. The SurVaxM vaccine is designed to target cancer cells that use this protein.

"SurVaxM is on the forefront of the next generation of cancer therapy. By harnessing the body's own immune system to fight cancer using immunotherapy, we believe we can give hope to patients diagnosed with malignant gliomas and other cancers," added the study's first author, Michael Ciesielski, PhD, Assistant Professor of Oncology in the Department of Neurosurgery at Roswell Park.

The mission of Roswell Park Cancer Institute (RPCI) is to understand, prevent, and cure cancer. Founded in 1898, RPCI is one of the first cancer centers in the country to be named a National Cancer Institute-designated comprehensive cancer center and remains the only facility with this designation in Upstate New York.

PhoreMost Ltd Founded to Identify New Druggable Targets for Therapeutics

PhoreMost Ltd has been founded to identify new druggable targets for cancer and other unmet diseases. Based in Cambridge, UK, PhoreMost announced it has successfully raised £2.5 million ($3.8 million) in Seed-funding from Cambridge-based Angels; Jonathan Milner, Amadeus Capital, Sunil Shah and Prashant Shah (O2H Ventures), Cambridge Enterprise, and Dr. Chris Torrance, PhoreMost's CEO. The funding will be used to build commercial operations based on a new drug discovery platform developed by the laboratory of Ashok Venkitaraman (Cambridge University) that can unmask cryptic drug sites in key disease targets and pathways currently considered undruggable by the pharmaceutical industry.

Due to advances in the speed and cost of sequencing the human genome, a diverse array of potential targets to attack cancer and other complex diseases have now been defined. However, using conventional pharmaceutical approaches, the majority of these targets are therapeutically inaccessible, or undruggable, at this time. Based on PhoreMost's proprietary Protein Interference technology, the company has developed Site-Seeker, a next-generation phenotypic screening platform that can identify the best new targets for drug development and, crucially, how to drug them. SiteSeeker can: define key disease impacting steps in cellular pathways, which cannot be predicted a priori, by using empirical live cell 'phenotypic' assays, simultaneously identify hidden druggable sites in these targets, and form a seamless assay system to de-orphan these newly identified target sites with small molecule drug candidates, thus pinpointing the best starting points for future drug development.

Using Site-Seeker, PhoreMost has identified drug candidates to a novel synthetic-lethal target for KRAS, and is soliciting collaborative partners for further development. PhoreMost is managed by a highly experienced commercial team and supported by world-renowned experts in oncology, biochemistry, and drug discovery. Dr. Chris Torrance was a founder of Horizon Discovery (LSE: HZD), which completed its IPO in March 2014, raising £37.8 million of new money. Chris has significant oncology research and development experience, including 6 years as a senior manager at pharmaceutical company Vernalis and 7 years as CSO of Horizon Discovery. Chris holds a PhD from East Carolina University and completed a Post-Doctoral position in the laboratory of Professor Bert Vogelstein (Johns Hopkins University), where he pioneered the use of genetically defined cell lines as cancer models in high-throughput screening and drug discovery.

"We are thrilled to have the backing of investors who share our passion to more efficiently translate advances in human genetics into a more effective range of new precision medicines," said Dr. Torrance. "The technical key to this goal is to focus and accelerate the development of novel drugs toward the most impacting disease targets. However, these are difficult to define upfront and invariably hard to drug using conventional drug design technologies once known. Site-Seeker will address both of these current bottlenecks in drug discovery, and thus potentially open up many new therapeutic avenues for a range of intractable diseases in the future."

"I'm delighted that an influential group of experienced investors has chosen to support PhoreMost, enabling the commercialization of research in my laboratory that has developed the Site-Seeker platform. We are well positioned to exploit our disruptive new approaches for drug discovery at a time when the pharmaceutical industry seeks to widen its pipelines," added Dr. Venkitaraman, Co-founder of PhoreMost.

Celgene & Mesoblast Enter $45-Million Agreement

Mesoblast Limited recently announced it has entered into an agreement with US-based Celgene Corporation, a global biopharmaceutical company engaged in the development and commercialization of innovative therapies for the treatment of cancer and immune-inflammatory-related diseases. Pursuant to this agreement, Celgene will purchase Mesoblast stock and has a 6-month right of first refusal to certain disease fields.

Under the terms of the agreement, Celgene will purchase 15.3 million ordinary shares in Mesoblast Limited for a consideration of A$58.5 million/US$45 million at a price of A$3.82 per share. In addition, Celgene has a 6-month right of first refusal with respect to Mesoblast's proprietary mesenchymal lineage adult stem cell product candidates for the prevention and treatment of acute graft versus host disease (GVHD), certain oncologic diseases, inflammatory bowel diseases, and organ transplant rejection.

"We are pleased that Celgene, as a global leader in development and commercialization of innovative therapies for oncologic and immune-mediated diseases, has chosen to make this investment in Mesoblast," said Chief Executive, Silviu Itescu. "We look forward to working closely together and building a strong and fruitful relationship."

"Today's agreement provides an opportunity for Celgene to add to its leading cellular and regenerative medicine pipeline. We are committed to developing important new therapies for significant medical diseases that are currently not being adequately addressed," added Celgene's President & COO, Mark Alles.

Mesoblast Limited is a global leader in regenerative medicine. The company has leveraged its proprietary technology platform, which is based on specialized cells known as mesenchymal lineage adult stem cells, to establish a broad portfolio of late-stage product candidates. Mesoblast's allogeneic or "off-the-shelf" cell product candidates target significantly advanced stages of diseases in which there are highly unmet medical needs, including cardiovascular conditions, orthopedic disorders, immunologic/inflammatory disorders, and oncology/hematology conditions.

Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global pharmaceutical company engaged primarily in the discovery, development, and commercialization of innovative therapies for the treatment of cancer and inflammatory diseases through gene and protein regulation. Its discovery and development platforms for drug and cell-based therapies allow them to both create and retain significant value within its therapeutic areas of expertise. Scientists and physicians at Celgene are the driving force behind enabling target-to-therapeutic platforms that integrate both small-molecule and cell-based therapies.

Catalent Completes $52-Million Expansion

Catalent Pharma Solutions recently announced the opening of a large-scale expansion at its Winchester, KY, manufacturing facility, which has seen the doubling of its footprint to 180,000 sq ft. The expansion features newly installed fluid bed capacity, expanded analytical laboratories, and an advanced, open facility design that provides flexibility in supporting the requirements of new customer programs. The expansion was officially opened by the Lieutenant Governor of Kentucky, the Honourable Crit Luallen, at a recent ribbon-cutting ceremony.

The expansion was completed in response to increased customer demand for the manufacture of complex, oral solid formulations. Catalent's Winchester facility has more than 20 years of experience in product development, technology transfer, and commercial manufacturing. The site has produced over 3 billion tablets and capsules annually and launched more than 100 new products into the market since its inception.

"The Winchester facility has grown through its continued investment in technical expertise and capability, and through employing a flexible business model to support tailored manufacturing solutions for its customers," said John Chiminski, Catalent's President & Chief Executive Officer. "This flexibility, along with our proven track record of success with technology transfers and product launches, has clearly driven increased demand for manufacturing services at Winchester, and our latest capacity expansion allows us to manufacture substantial marketed products for both new and existing customers."

Opened in 1992, Catalent's Winchester facility has evolved into one of the industry's premier sites for advanced oral controlled-release drug formulation and manufacturing. Construction work on the expansion began in 2013 with a $35M facility investment, followed by a subsequent investment in additional fluid bed capacity. The expansion will add as many as 140 new employees at the site, with potential to add further employees and capabilities as customer demand for Winchester's manufacturing solutions continues to grow.

Catalent is the leading global provider of advanced delivery technologies and development solutions for drugs, biologics, and consumer health products. With over 80 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance and ensuring reliable clinical and commercial product supply.

West Pharmaceutical Services Appoints New CEO

West Pharmaceutical Services, Inc. recently announced that Eric M. Green has been appointed the company's Chief Executive Officer, succeeding Donald E. Morel, Jr., PhD, current Chairman and CEO. Eric Green will join West and take on his new responsibilities on April 24, 2015. Dr. Morel will serve as West's Chairman following Eric Green's appointment, until July 1, 2015, when he plans to formally retire.

Eric Green joins West from Sigma-Aldrich Corporation, where he has served as Executive Vice President and President of the company's Research Markets business unit since 2013. In this role, Mr. Green served as a corporate officer and member of the senior executive team, with responsibility for managing a $1.4 billion business unit – the largest at the company.

"I am excited and honored to lead such a well-respected and successful company. I am impressed with West's track record for delivering both innovative packaging and integrated delivery solutions that play such a critical role in delivering injectable medicines for patients across the globe. I intend to build on the strategy the current management team has established, and partner with the Board to ensure West's continued success in the future," said Eric Green.

"Eric Green brings a wealth of leadership experience from his time with Sigma-Aldrich, a company which shares West's customer-centric approach to working with the pharmaceutical industry," said Dr. Morel. "Eric stood out among a very strong candidate list that was considered. We were particularly impressed with his track record of growing revenue and profit for the business units he has led; the diversity of his experience across different business segments, particularly in emerging markets; and his passion for leading people - all of which have prepared him well to lead West. I expect to be fully engaged in helping Eric acclimate to his new role at West and introducing him to our key stakeholders."

"West is poised for an exciting future thanks to the work of the current management team under Don Morel's leadership," said Patrick J. Zenner, Chairman of the Independent Directors. "Eric Green shares the same vision we have for West and we are confident in his ability to lead the company to realize its potential for future growth in the coming years."

West Pharmaceutical Services, Inc. is a leading manufacturer of packaging components and delivery systems for injectable drugs and healthcare products. Working by the side of its customers from concept to patient, West creates products that promote the efficiency, reliability, and safety of the world's pharmaceutical drug supply.

Firm Raises $2.8 Billion for NEA 15 Fund; $350 Million for Opportunity Fund

Global venture capital firm New Enterprise Associates, Inc. recently announced the close of its 15th fund with $2.8 billion in committed capital to its core fund, as well as an additional $350 million for its NEA 15 Opportunity Fund. With commitments totaling more than $3.1 billion, this fundraising brings the firm's cumulative committed capital since inception to nearly $17 billion.

"Like our industry, much has changed since NEA's founding nearly 40 years ago," said Peter Barris, Managing General Partner. "We have grown from a trio of founders with a $16-million fund to more than two dozen partners deploying multi-billion-dollar funds across five continents. Yet some things are constant—like the steady march of innovation, the indomitable spirit of entrepreneurs, and the unwavering support of our limited partners. I'm profoundly grateful for our limited partners' commitment to our asset class and confidence in NEA's diversified, global model. Without them, we couldn't get up and do the jobs we love every day."

In conjunction with these new funds, Scott Sandell has been appointed Managing General Partner alongside Mr. Barris. Since joining NEA in 1996, Mr. Sandell has led investments in industry-transforming companies, serving on the boards of Bloom Energy, Data Domain, Fusion-io, Spreadtrum Communications, Tableau Software, WebEx, and Workday among others. He is head of the firm's technology practice and leads NEA's investing activities in China.

"Venture capital plays an intrinsic and increasingly critical role in the innovation ecosystem," said Mr. Sandell. "It's true that it's never been cheaper to start a business - but it's also never been more important to scale quickly. To do this, companies need capital and they need partners who can meaningfully help them. As we begin to deploy capital from this new fund, we're tremendously excited to help fuel the growth of new market leaders during what we believe is a time of unprecedented innovation and opportunity."

The new core fund marks NEA's fourth consecutive $2.5-billion-plus venture fund, a reflection of the firm's scale and increasingly global focus. The Opportunity Fund is a new co-investment venture vehicle created to enhance the firm's core fund strategy. Investments will be made alongside new or follow-on venture growth equity deals, where the anticipated total check size exceeds the typical amount invested by the core investment fund.

Edge Therapeutics Raises $72.5 Million to Advance Pipeline

Edge Therapeutics recently announced it has raised approximately $72.5 million in gross proceeds from two recently completed private financing rounds. The most recent round, a $56-million Series C-2 financing, was completed in April 2015. and was led by Venrock with participation of Sofinnova Ventures, Janus Capital Management LLC, funds managed by Franklin Advisers, Inc., New Leaf Venture Partners and BioMed Ventures. The earlier round, a $16.5-million Series C-1 financing, was completed in December 2014 and included investments by a number of high net worth individuals, family offices and private foundations.

In connection with the C-2 offering, Anders Hove, MD, Partner at Venrock and James Healy, MD, PhD, Managing Partner of Sofinnova Ventures, have joined the Edge Therapeutics Board of Directors.

"This significant financing from a sophisticated syndicate of leading life sciences investors is a transformative event for Edge," said Sol J. Barer, PhD, Chairman of the Board of Directors of Edge Therapeutics. "We welcome the new members of our Board of Directors, whose deep experience in both venture capital and specifically in biotechnology will be invaluable as Edge continues to grow into a fully integrated biotechnology company."

"Edge remains committed to helping vulnerable patients who have suffered brain hemorrhages," said Brian Leuthner, President and CEO of Edge Therapeutics. "We greatly appreciate the financial investment from our shareholders which provides resources for EG-1962, earlier stage product candidates and discovery opportunities."

Edge expects to use part of the proceeds from these financings to complete its Phase I/II NEWTON study and prepare for a Phase III pivotal study for its lead product candidate, EG-1962, which is designed to improve patient outcome following an aneurysmal subarachnoid hemorrhage (aSAH), also known as a ruptured brain aneurysm.

Preliminary data from two of six patient cohorts of the NEWTON study showed that 61% (N = 11) of the 18 patients who received EG-1962, experienced a favorable outcome on the extended Glasgow Outcome Scale (eGOS). The eGOS is a validated 8 point scale (1 = death, 8 = good recovery) used to assess recovery for patients who have suffered a ruptured brain aneurysm. A favorable outcome in the NEWTON study protocol is defined as an eGOS score between 6 and 8 as measured 90 days after treatment. By contrast, only 17% (N = 1) of the six patients treated with oral nimodipine in the first two cohorts of the NEWTON study had a favorable outcome on the eGOS. Edge expects to complete enrollment of additional patient cohorts and announce top-line data from the NEWTON study in mid-2015.

Edge Therapeutics is a clinical-stage biotechnology company that discovers, develops, and seeks to commercialize novel, hospital-based therapies capable of transforming treatment paradigms in the management of acute, life-threatening neurological conditions.

EG-1962 is a novel polymeric nimodipine microparticle that utilizes Edge's proprietary Precisa development platform. EG-1962 is designed to avoid the dose-limiting side effects associated with oral nimodipine, including hypotension, by administering treatment directly to the site of the injury. Edge is also investigating a second compound, EG-1964, for prevention of recurrence of chronic subdural hematoma.

The NEWTON (Nimodipine microparticles to Enhance recovery While reducing TOxicity after subarachNoid hemorrhage) study is a multicenter, randomized, controlled, open label clinical trial evaluating the safety, tolerability and pharmacokinetics of escalating doses of EG-1962 compared to the current standard of care, oral nimodipine, in patients with aSAH.

Recipharm Makes Strategic Investment in Synthonics

Recipharm recently announced it has made an equity investment in Synthonics Inc and purchased $2 million of preferred stock in the company. A further $2 million of preferred stock will be purchased upon Synthonics' achievement of certain milestones, which could be expected during 2016.

In addition, Synthonics and Recipharm have entered into a Joint Development Agreement under which Synthonics gains access to Recipharm's expertise in drug development, marketing, and manufacturing in exchange for a royalty payment on certain of Synthonics' compounds. Synthonics has developed a unique drug delivery technology for metal coordination of pharmaceutical APIs. In connection with its investment, Recipharm's Carl-Johan Spak has joined Synthonics' board of directors.

"Synthonics is delighted to extend the partnership with Recipharm to help advance promising molecules to market," said Ken Slepicka, CEO of Synthonics. "We are very impressed with Recipharm's formulation and development teams and expect this agreement and financial support to help us further advance several of our current projects to commercialization.

"This transaction expands our footprint within the US and builds upon our existing Joint Marketing Agreement with Synthonics," added Carl-Johan Spak, Executive Vice President, Technology, and Development. "In addition, it gives us an opportunity to share in the upside of Synthonics' chemistry, which we believe offers an elegant and cost-effective means to create patentable drugs that address difficult absorption and delivery issues. We believe that this collaboration will enhance our ability to serve our customers with exciting drug delivery solutions."

Recipharm is a leading CDMO (Contract Development and Manufacturing Organization) in the pharmaceutical industry, offering manufacturing services of pharmaceuticals in various dosage forms, production of clinical trial material including API, and pharmaceutical product development. For more information, visit www.recipharm.com.

Synthonics, Inc. is a specialty pharmaceutical company focused on the discovery, development, and licensing of patent-protected drugs (metal coordinated pharmaceuticals or MCPs) that incorporate its proprietary metal coordination chemistry. Metal coordination is a platform technology with broad application that can be profitably applied both to already marketed drugs and to drugs under development. Synthonics has drug discovery and development programs underway on a handful of molecules. In addition, the company partners with large pharmaceutical companies to enhance their pipelines and marketed products. For more information, visit www.synthonicsinc.com.

Alzheon Announces $10-Million Financing to Advance Lead Drug Candidate

Alzheon, Inc. recently announced it has closed a $10-million Series A financing round. This equity financing was led by Ally Bridge Group and included investments from other new and existing investors. Proceeds of the financing will be used to advance Alzheon's lead drug candidate, ALZ-801, an oral, small molecule, first-in-class inhibitor of amyloid formation and neurotoxicity, toward completion of the clinical and regulatory studies for initiation of a potential pivotal clinical study in Alzheimer's disease in the near future.

Alzheon's upcoming clinical and regulatory programs build on the positive Phase I results with ALZ-801 reported in March 2015, which demonstrated favorable pharmacological properties of ALZ-801, a prodrug of tramiprosate. In addition, the company will leverage post-hoc efficacy analyses and safety data from an extensive Phase III program of tramiprosate in patients with Alzheimer's disease. These analyses showed sustained efficacy on cognition and function in a population of patients with Alzheimer's disease that are positive for the e4 gene variant of apolipoprotein E (ApoE4), associated with increased risk of Alzheimer's disease. Additionally, the safety dataset from the tramiprosate program, which included more than 2,000 Alzheimer's subjects treated with the small molecule tramiprosate, showed that tramiprosate was generally safe and well tolerated, and did not show brain edema, hemorrhages, or any clinical correlates of such neurological adverse events.

"With our advanced amyloid-targeting ALZ-801 clinical candidate, we are well-positioned in the dynamic field of drug candidates for Alzheimer's disease. The excitement in our company was reflected in the strong interest we have received for our Series A fundraising, which we designed to support our plans to initiate a pivotal study of ALZ-801 in Alzheimer's disease," said Martin Tolar, MD, PhD, Founder, President and Chief Executive Officer of Alzheon. "There is substantial clinical evidence that the reduction in brain amyloid translates into improvements in cognitive and functional outcomes of patients. ALZ-801 offers a unique mechanism of action that has the potential to be effective against brain amyloid as an orally administered treatment, without the limitations of the adverse side effects reported with antibody drug candidates currently being evaluated for Alzheimer's disease."

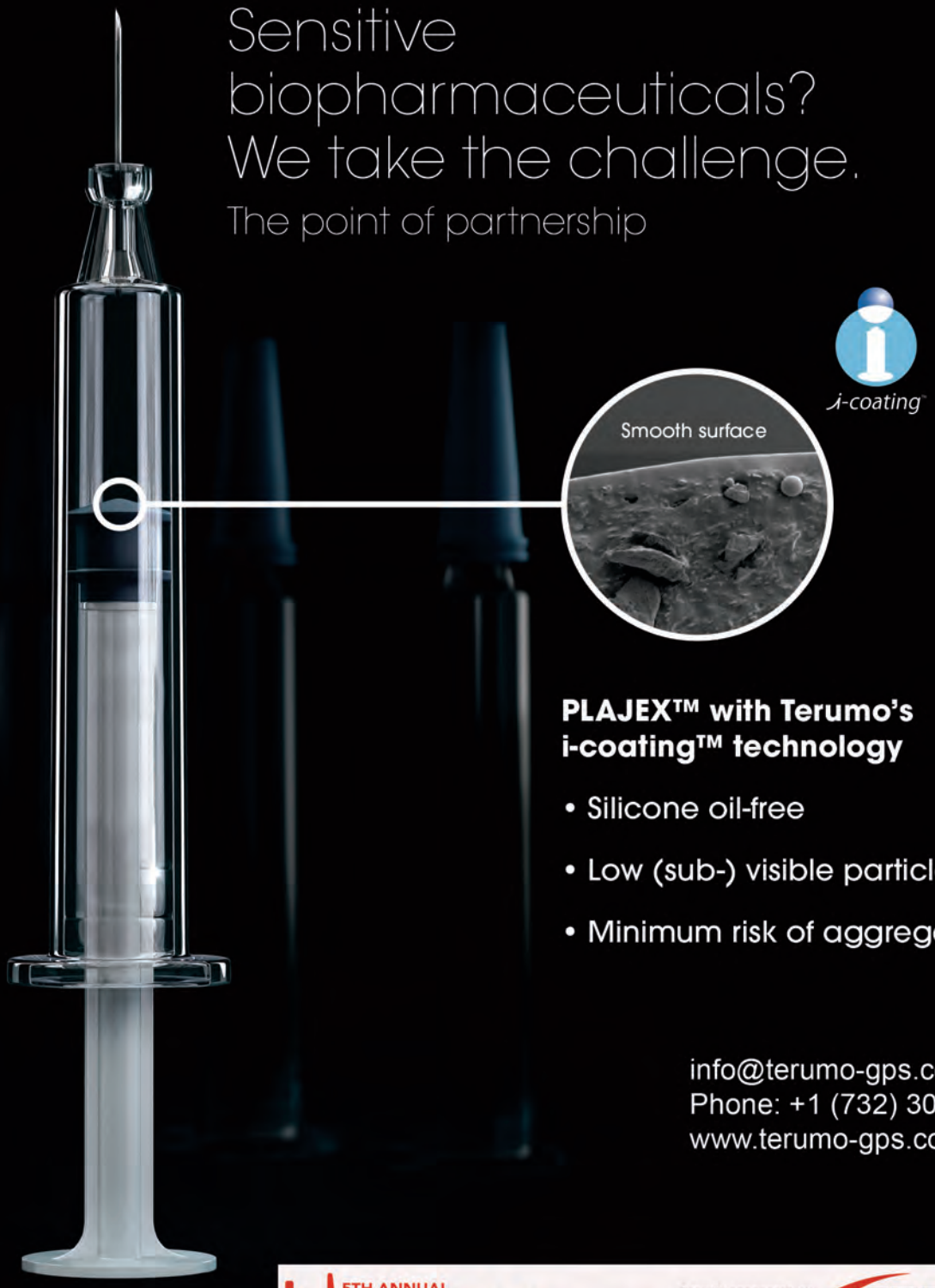
"Alzheon has an opportunity to make a truly transformational impact on the treatment of patients with Alzheimer's disease," added Jean-Pierre Sommadossi, PhD, Chairman and CEO of Atea Pharmaceuticals and a member of Alzheon's Board of Directors. "Alzheon's lead drug candidate, ALZ-801, offers a promising small molecule approach to target an important amyloid mechanism of Alzheimer's disease, and to address the unmet medical needs of millions of patients with Alzheimer's disease."

TERUMO

PLAJEX™
Terumo Ready-To-Fill Plastic Syringes

Sensitive biopharmaceuticals? We take the challenge.

The point of partnership



PLAJEX™ with Terumo's i-coating™ technology

- Silicone oil-free
- Low (sub-) visible particles
- Minimum risk of aggregation

info@terumo-gps.com
Phone: +1 (732) 302-4900
www.terumo-gps.com

5TH ANNUAL PRE-FILLED SYRINGES SUMMIT

Proudly sponsored by TERUMO

JUNE 23RD-25TH 2015 SAN DIEGO, CA
DoubleTree by Hilton San Diego

The Second Quadrant

The Birth of Physical Pharma: 1920-1960

By: Marshall Crew, PhD, VP, Global PDS Scientific Excellence, Patheon

"Evolution is a process of constant branching and expansion." – Stephen Jay Gould

Innovation can be viewed as a sort of relay race in which individuals or teams contribute to the progress of the whole. Often it's only in retrospect when we observe that those running the different legs of the race may not have been aware of where or what the finish line really was. In this column, we continue where the last one left off, observing progress that enabled spray drying for pharmaceutical applications, and other progress that has enabled the solubilization technologies and approaches we use today.

"I START WHERE THE LAST MAN LEFT OFF"[1]

In the mid-to-late 19th century, we observed the invention of methods, technologies, and chemistry for the preservation of food and prevention of infectious disease. Applications primarily for the agricultural, food, and manufacturing industries drove innovations to ensure the safety of the food supply, and to deliver methods for efficient processing and manufacturing in support an expanding and increasingly far-flung populace. And pharmaceutics were embraced to prevent and treat disease.

In the first half of the 20th century, progress accelerated in the three key components for spray drying: nozzles, pumps, and dust collection. Whereas fundamental innovations had been made in 1840, 1901, and 1906, respectively, for these components, the diffusion of knowledge and innovations in advancing these technologies progressed at a whirlwind pace from 1900-1960 (Figure 1). This progress - combined with rapid progression in the understanding of chemistry - would set the stage for the earliest applications of spray drying to pharmaceuticals.

Part of the momentum seen in the period between 1914 and continuing into the 1940s can be attributed to a national focus on advancing technologies in general in support of war efforts, and the emerging automotive and aeronautic industries. Innovations in spray drying itself soared during this same era, as the technologies on which its progress was critically dependent rapidly evolved. Figure 2 shows this progress based on the number of patents granted containing the term "spray drying" between 1900 and 1960.

Making summer plans?

Don't miss our highly anticipated

GLOBAL FORMULATION REPORT

exclusively in our

July/August Issue

Powerful Advances in Drug Development

- Drug Delivery & Formulation-Related Transactions, Approvals & Breakthrough Technologies of the past 12-18 months
- Key Opinion Leaders and their thoughts on what will have the most significant impact on the Pharmaceutical & Biotechnology industries in the next 5 to 10 years
- Fixed-Dose Combination Drug Approvals — drug/drug and drug/device
- Drug-Device Approvals of 2014
- Formulation & Drug Delivery Pipeline: Drugs in development using enhanced formulation technologies (Phases I, II, III, NDA)

Highlight your company's technologies & services by advertising in this special issue. Hurry! Closing June 26

For more information:
John Kiesewetter • 541-338-0022
jkiesewetter@drug-dev.com
Ralph Vitaro • 973-263-5476
rvitaro@drug-dev.com

Drug Development & Delivery

SPRAY DRYING FOR PHARMACEUTICAL APPLICATIONS: SIDNEY RIEGELMAN

Starting in the late 1940s, the University of Wisconsin became a hotbed for the study and development of modern spray drying. W. Robert Marshall directed comprehensive and fundamental studies that were chronicled in the publication *Atomization and Spray Drying during the period 1948-1964*".[2] Contemporaneous to this undertaking, Sidney Riegleman, now recognized as one of the fathers of modern physical pharmacy, was a graduate student in the University's School of Pharmacy.

In 1950, in the last of a four-part series of articles reporting on *Studies on Pharmaceutical Powders and the State of Subdivision*, Riegelman and three co-authors first introduced spray drying to pharmaceutical applications. Part four, *The Application of Spray-Drying Techniques to Pharmaceutical Powders,* is where Riegelman and his colleagues explore the utility of the spray dry process for the modification of "physical, pharmaceutical, and pharmacological properties of medicinal substances…"[3]

"[Spray drying techniques] have found great application in the soap and food industries in the direct processing of various products. However, the apparatus has not found large acceptance in the handling of pharmaceutical products."[2]

In this paper, the spray drying and physical properties of drug substances – sulfanilamide, colloidal and precipitated sulfur, and the excipients methyl cellulose and boric acid – were reported. It is of particular interest that the antibiotic drugs Sulfadiazine and Sulfanilamide were spray dried (Figure 3), and a sulfur/methylcellulose solid dispersion was prepared, perhaps the first precursor of a spray dried drug/excipient solid dispersion.

The inquisitive minds of these and subsequent researchers and inventors would form the foundation for today's success with spray drying to enhance bioavailability – and today's increasingly large acceptance of this technique. (Since 2005, spray drying has seen the fastest growth rate of any solubilization technology used for FDA-approved drugs.[4]) Hence, the birth of spray drying as a method to produce a solubilized form of a low solubility drug and excipients was born.

Riegelman went on to have a highly productive career as a physical pharmacist, with his work spanning three more decades until his untimely death in 1981. His accomplishments included a body of groundbreaking research in the importance of techniques to fabricate high surface area pharmaceutical powders to improve bioavailability. Riegelman also contributed pioneering work in bioanalytical chemistry, biopharmaceutics, pharmacokinetic modeling and regulatory policy.

"Spray-drying appears to be a useful tool in preparing powdered substances in a free-flowing, monodispersible, easily wetted powder. It forms a relatively homogeneous material and assures the minute amounts of additives may be uniformly distributed in a dried preparation."
– Sidney Riegelman
Photo Source: The School of Pharmacy, University of California at San Francisco

BEGINNINGS OF POLYMER SCIENCE - ADHESIVES

Another ingredient that will later enable spray drying to overcome insolubility had its roots in the 19th century. The earliest patent for rubber cement was granted in 1843. During this same period, modified cellulose

FIGURE 1

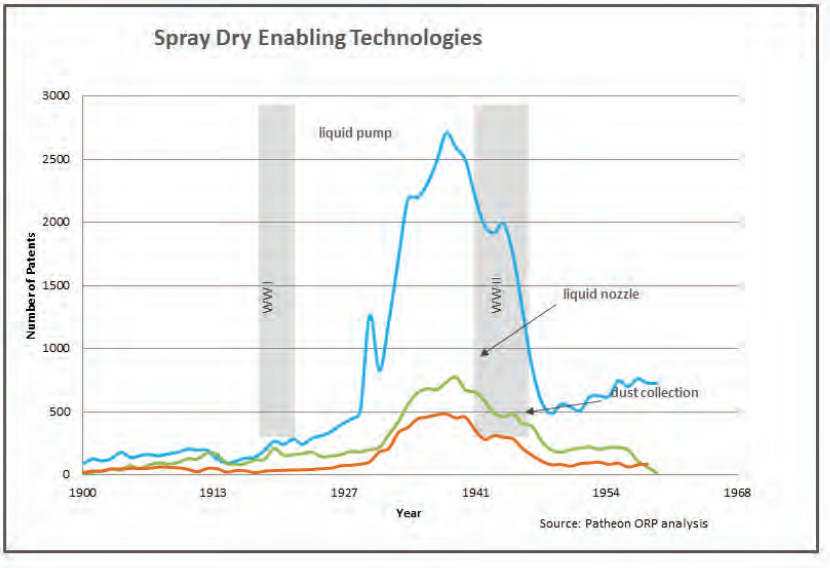
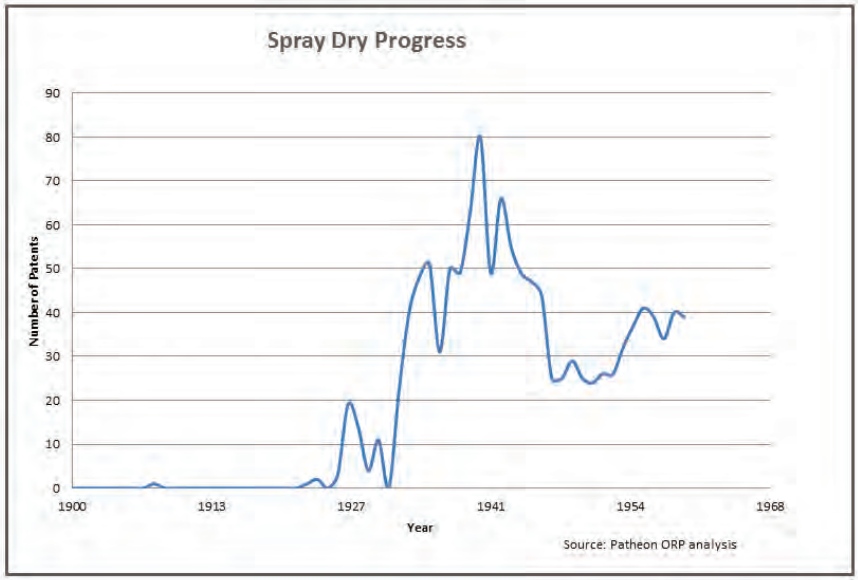


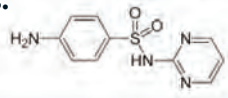
FIGURE 2



products, resins, and synthetic polymers were being developed, but it took another many decades before synthetic polymers emerged to commercial applications. Fueled by shortages of natural materials during WWI and later WWII (and the need for better adhesives for aircraft and other materiel), the birth of polymer science can be traced to 1922.[5] This is the first known use of "soybean glue," invented by scientists at the I. F. Laucks company and patented in 1927. US Patent No. 1,622,496 A, *Cellulose-fiber product treated with a size embodying soy-bean flour and process of making the same*, formed part of a body of research and innovation that sought novel ways to develop synthetics to create new, stronger and lighter materials for airplanes and other applications.[6,7] These other applications would ultimately find their way to enhancing the bioavailability of poorly soluble molecules.

FIGURE 3

Molecular structure of the Drug Sulfadiazine Spray Dried in the 1940s.



SUMMARY

Up to this point in history, we've observed the maturation of spray drying, evolving from its earliest roots in food preservation into the beginnings of the modern pharmaceutical era. During the period from 1920-1960, this technique for enhancing the bioavailabilty of insoluble molecules starts to emerge. This diffusion of innovation of this single technology over a century evidences the circuitous path to commercial success: integration of numerous and disparate technologies, "borrowing" innovations from other fields, and the creativity, tenacity, and collaboration of the individuals involved. The next column will cover the introduction of polymers for the application of spray drying for poorly soluble drugs. ◆

REFERENCES

1. Thomas A. Edison.
2. Atomization and Spray Drying, William Robert Marshall, American Institute of Chemical Engineers, 1954.
3. Riegelman S, Swintosky JV, Higuchi T, Busse LW. Studies on pharmaceutical powders and the state of subdivision. IV. The application of spray-drying techniques to pharmaceutical powders. J AAPS. 1950;39(8):444-450.
4. Crew M. BIOAVAILABILITY ENHANCEMENT - Analysis of the Historical Use of Solubilization Technologies. Drug Development & Delivery. 2014;14(2):22-25.
5. Canadian Conservation Institute, Major Developments in Adhesive Manufacture. 1750-2000.
6. US Patent and Trademark Office. US Patent No. 1,622,496 A. Cellulose-fiber product treated with a size embodying soy-bean flour and process of making the same;1927.
7. http://www.soyinfocenter.com /HSS/if_laucks_and_soybean_glue.php.

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

Marshall Crew
VP, Global PDS Scientific Excellence
Patheon
crew@agerepharma.com
LinkedIn: https://www.linkedin.com/profile/view?id=17815140

Advanced Delivery Devices

Design & Evaluation of a Polymer-Based Prefillable Syringe for Biopharmaceuticals With Improved Functionality & Performance

By:Sagarika Bose, PhD and Kevin Constable

INTRODUCTION

The use of prefilled syringes for biopharmaceutical molecules as well as small molecules continues to be an ideal standard for unit-dose medication. The development of biotechnology drug products using prefilled syringes (PFS) continues to rise rapidly with the advantages including patient self-administration, accuracy in dosing, reduction of dosing errors, patient compliance in dosing, low overfill, safety, and convenience.

Throughout the past 2 decades, biopharmaceutical drug products have made immense progress due to extensive research and discovery by academic institutions and pharmaceutical companies. The progress of genetic engineering has contributed enormously toward the success of custom-designed protein chains (large molecules) to alleviate suffering from chronic diseases. Biopharmaceutical drugs, such as Enbrel, Humira, Remicade, and Rituxan, have progressed substantially, and new drug products in prefilled syringes are coming to market every year.[1]

Important changes in patient treatment led to a shift from hospital treatment to homecare. The needs for patient self-injection for many chronic diseases and specific therapeutic areas are being enabled by the use of prefilled syringes. This shift in patient care in conjunction with the progress of biopharmaceutical drug products has fueled the growth of PFS worldwide. It is predicted that 4.5 billion prefilled syringes will be shipped in 2015, and the market is expected to grow at compound annual growth rate (CAGR) of 14% between 2015 and 2020. In terms of revenue, it is projected the use of PFS is expected to grow at a CAGR of 13% between 2015 and 2020, eventually accounting for nearly $5.8 billion.[1]

This article addresses the design of a new commercially available polymer-based prefillable syringe with enhanced performance features when combined with complex biopharmaceutical drug products. The design considerations discussed include consistent glide force, low probability for drug degradation, higher material strength, and excellent barrier properties.

OPTIMAL SYSTEM DESIGN CONSIDERATIONS FOR PREFILLABLE SYRINGES

Prefillable syringe systems need to accommodate various rigid internal and external requirements and functionalities as a container for biopharmaceutical drugs. Optimal requirements include container closure integrity, strength, consistent plunger gliding forces, and low reactivity to the drug products.

In general, two main materials for PFS are glass and polymer. Polymer-based PFS can be made from various materials, including polypropylene (PP), polycarbonate (PC),

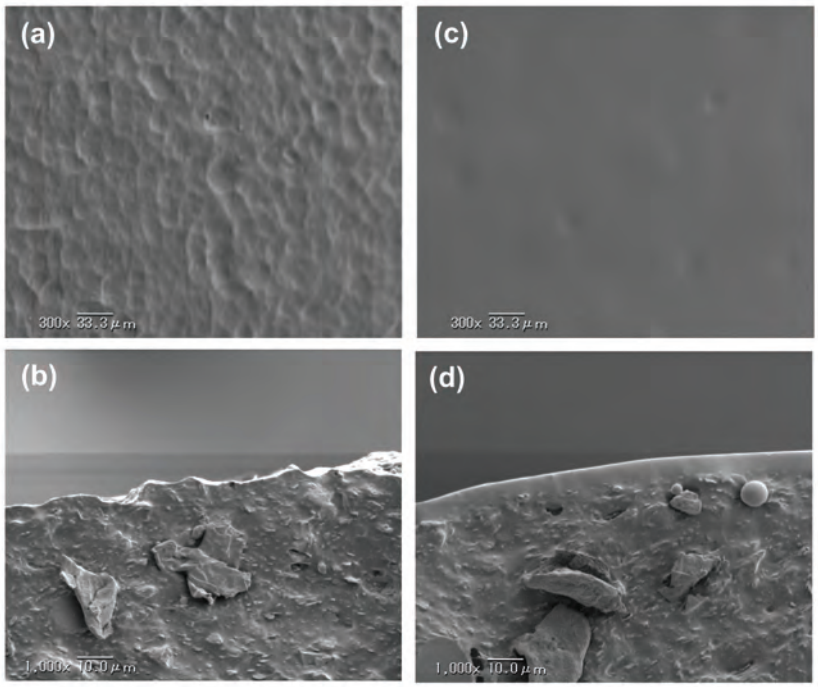
cyclic olefin copolymer (COC), or cyclo olefin polymer (COP). The choice of material is related to patient use and drug product requirements for permeability or container reactivity. In developing PFS systems, the elastomer selection and surface treatments must also be considered.

Biopharmaceutical drug products are often sensitive to aggregation and oxidation. Aggregation of therapeutic proteins is one of the most critical risk factors among all concerns as it may negatively impact the drug efficacy and safety due to the protein degradation which may trigger immune responses by patients. For example, the degradation by neutralized antibody of epoetin-alpha makes endogenous erythropoietin less active, resulting in an increased incidence of antibody-mediated pure red cell aplasia (PRCA).[2,3] In 2014, the FDA published the guidance for industry entitled Immunogenicity Assessment for Therapeutic Protein Products, recommending minimizing any aggregation risks.[4] Section V.B.8 from the guidance provides recommendations on container closure considerations.

Silicone oil has been used as a lubricant to obtain plunger gliding functionality. However, for biopharmaceutical drug products, silicone oil has become a serious concern as it can induce protein aggregation.[5-8] Additionally, the PFS manufacturing process for glass barrels can also pose a potential risk factor. For instance, tungsten pins are used for the glass barrel tip-forming process. It was observed in many cases that the presence of tungsten oxide can promote protein aggregation or drug degradation with potential toxic side effects.[9-12]

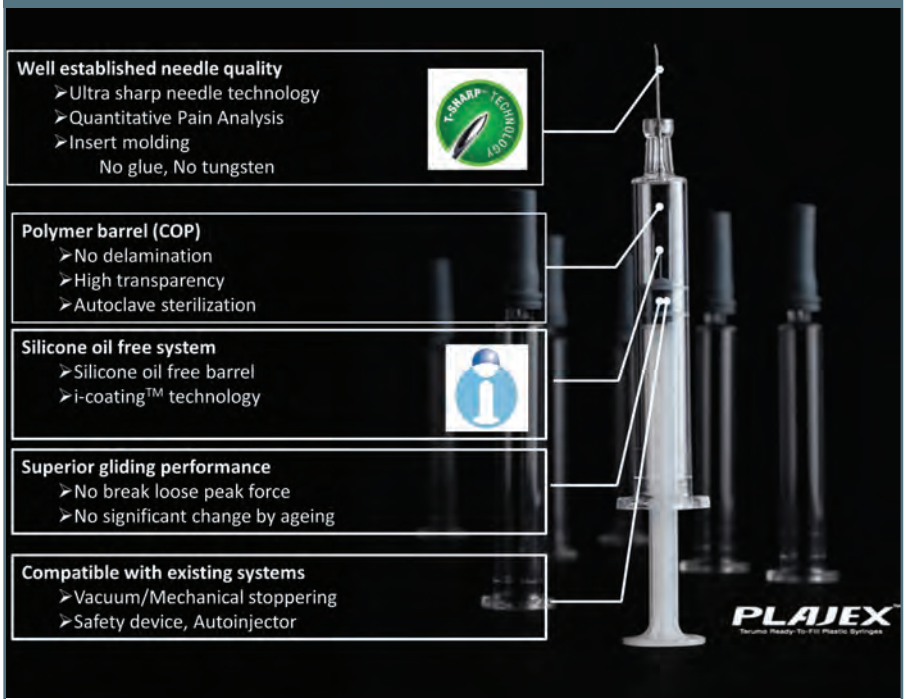
Generally, glass PFS were developed

FIGURE 1



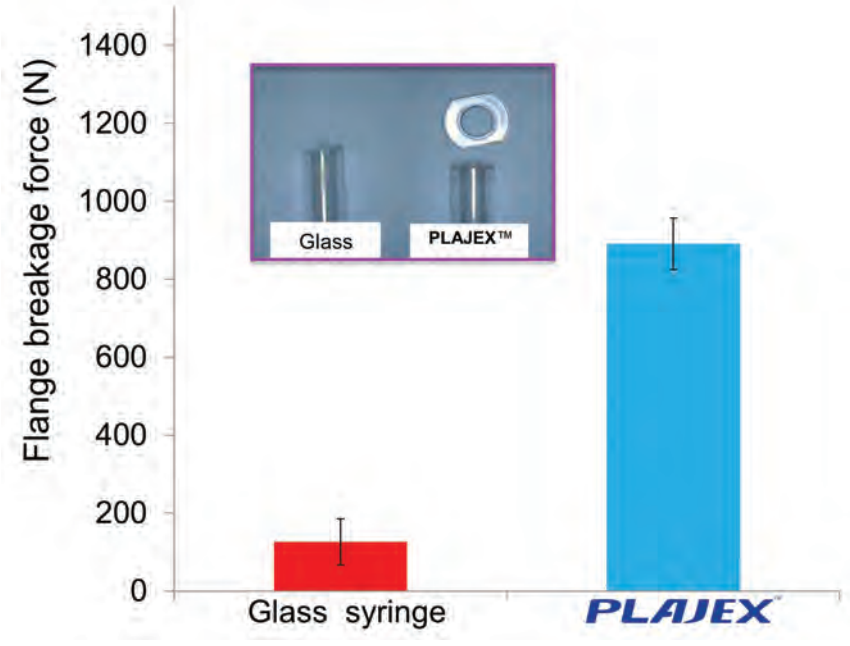
SEM micrographs of the surface and cross-section of the plunger stoppers coated by i-coating™.
(a) top surface of an uncoated plunger stopper (x300).
(b) cross-section of an uncoated plunger stopper (x1000).
(c) top surface of a coated plunger stopper (x300).
(d) cross-section of a coated plunger stopper (x1000).

FIGURE 2



The components of PLAJEX™ plastic prefillable syringe.

FIGURE 3



Flange breakage force (all flange) measured by universal tensile tester (n=10) at a stroke rate of 50 mm/min.

for small molecules. Thus, many potential quality issues appeared only when introducing therapeutic proteins into a PFS system. In general, there are three main design attributes for a PFS system for use with biopharmaceuticals: (1) Silicone oil-free system, (2) Material selection for low reactive containers, (3) Understanding the barrier properties. In the following sections, we will discuss the development of a polymer-based PFS that overcomes the challenges presented by biopharmaceutical drug product.

DEVELOPMENT OF A NEW PFS SYSTEM - PLAJEX™

Silicone Oil-Free System for Enhanced Functionality & Lower Reactivity

There are many reports for protein aggregation, as previously discussed, as well as the presence of subvisible particles and their interactions for biopharmaceutical drug products.[13-16] Increased scrutiny by regulatory agencies has also heightened the concern of the impact of aggregation and particulates on drug products. Thus, a silicone oil-free PFS system is a preferred design choice to avoid these problems.[8,16-19] To address and mitigate potential issues, a silicone oil-free PFS system was developed based on a plunger stopper combined with a specific coating technology. Terumo® launched its first silicone oil-free system (product name: MINOFIT) with a polymer-based PFS in 2005.

Following the success of the MINOFIT silicon oil-free PFS, Terumo continued to research and develop improvements to the coating method and created an improved lubricious coating. This coating is a strong, flexible, and uniform layer of silicone resin created through a chemical process including polymerization of the layer that is tightly bonded to the elastomer substrate. This coating was launched as i-coating™ technology. Additional properties have been presented in a published article, *Functional evaluation and characterization of a newly developed silicone oil-free prefillable syringe system.*[18] Scanning electron microscope (SEM) images for before and after i-coating treatment are shown in Figure 1.

Compared to an uncoated plunger stopper (Figure 1a and 1b), i-coating plunger stoppers as shown in Figure 1c and 1d provide a uniform and smooth surface layer. FTIR and XPS analysis identified the surface layer material of i-coating plunger stopper as a silicone resin with high purity. The resulting dynamic friction force from i-coating was about 10 times lower than the same uncoated rubber, with a value similar to polytetrafluoroethylene (PTFE) sheet.[18]

Polymer-Based Syringes for Low Reactivity

Glass containers have been used extensively and have been substantive for the development of parenteral drug products. However, several aspects (aggregation by tungsten, alkali elution, container breakage, and delamination) related to glass material for PFS can be problematic for biological drug products. Furthermore, the total cost of ownership of the value of biopharmaceutical drugs and the reduced yield from container breakage during manufacturing and transportation cannot be ignored.[20]

A polymer-based PFS (PLAJEX™) was developed by Terumo with a specific focus on biopharmaceuticals as a better choice when compared to glass PFS to resolve problems like protein aggregation or breakage. PLAJEX is

made of cyclo-olefin polymer (COP), which features outstanding properties, such as impact resistance, superior moisture-barrier, and excellent transparency. Moreover, the risk of protein aggregation (due to interactions with the tungsten and glue) was reduced by insert molding the cannula. The stopper of PLAJEX has i-coating technology, which provides an entirely silicone oil-free syringe system. In addition, autoclave sterilization for PLAJEX reduces the risk of protein oxidation from radicals, which are usually generated from sterilization by irradiation. Therefore, PLAJEX is an integrated approach providing an excellent combination of properties, such as high transparency, superior strength, and smooth and controllable plunger gliding properties, as well as minimal risks of protein aggregation and protein oxidation. These features are summarized in Figure 2 and discussed further hereafter.

Superior Mechanical Strength

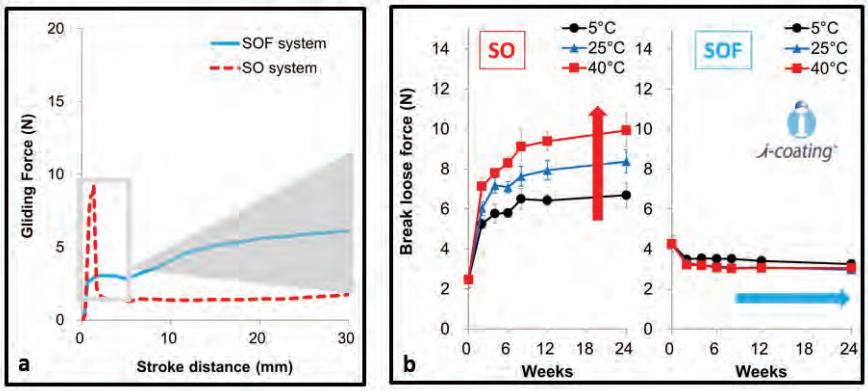
Flange breakage force (all flange) was measured by universal tensile tester at a stroke rate of 50 mm/min between glass and PLAJEX syringes. The comparison between their strength is shown in Figure 3. It was found that the flange of PLAJEX is stronger than that of a typical glass syringe by many-fold (Figure 3). This aspect is very useful when a syringe is used with autoinjectors, in terms of functionality under high forces due to viscous drug products.

Consistent Plunger-Gliding Functionality

As discussed earlier, PLAJEX with i-coating technology is a silicone oil-free system. Figure 4a shows the comparison of gliding properties between traditional silicone oil-coated syringes (SO) and PLAJEX, which is a silicone oil-free syringe (SOF). The data was collected at a stroke of 200 mm/min. Glide forces were measured with a universal tensile meter. In the case of SO syringe, the silicone oil layer between barrel and plunger stopper may vary over time, resulting in variations in initial gliding force (break loose force), which increased over time by aging.

For the SOF syringe, no change is observed by aging and at various temperature conditions as shown in Figure 4b. Break loose glide force is the maximum glide force between 0 and 5 mm of stroke distance. Data are presented as mean ± standard deviation (n=5).The surface layer of i-coating plunger stopper is a silicone resin that is bonded directly to the stopper material. The absence of break loose peaks is very beneficial for applications with autoinjectors for consistent performance and functionality for a given spring force.

FIGURE 4



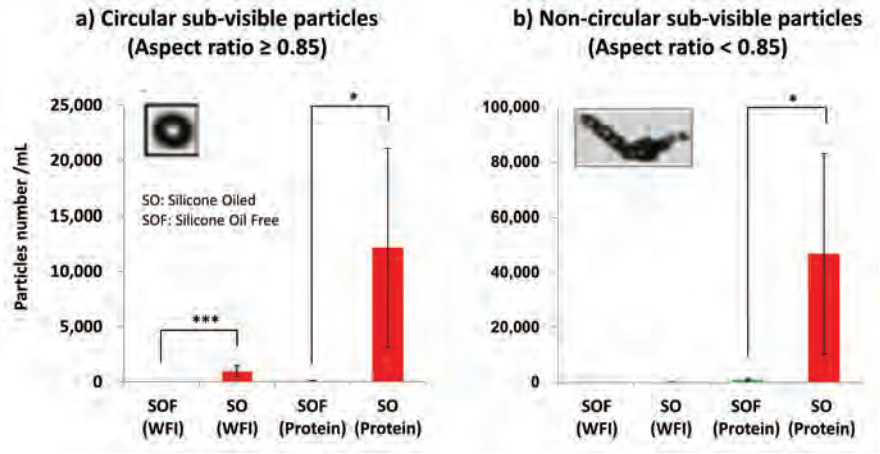
(a) Glide force profile of Silicone oil syringe (SO) and Silicone oil-free syringe (SOF) that stored 12 weeks at 40°C. (b) Break loose glide force (maximum glide force between 0 and 5 mm of stroke distance) change with aging time and temperature of SO and SOF system (n=5).

Reduced Probability of Protein Aggregation

A comparative study on protein aggregation from silicone oil interactions was conducted with L-asparaginase. L-asparaginase is highly susceptible to silicone oil and forms aggregates from its interaction with silicone oil. Thus, it was used as a model protein in this study. Protein aggregation and subvisible particles were analyzed by Micro Flow Imaging (MFI). The sample was prepared using 0.5 mL of WFI and model protein solution (protein) filled into SO and SOF systems, and the syringes were shaken for 30 min at 250 rpm. Figure 5a shows the quantification of circular subvisible particles representative for silicone oil, and Figure 5b shows the quantification of non-circular subvisible particles representative to protein aggregation. In the case of WFI, the number of circular subvisible particles increased in silicone oil-coated syringes. In contrast, this phenomenon was not observed with SOF syringes due to the lack of presence of silicone oil droplets.

Thus, it can be stated that minimal protein aggregation and subvisible

FIGURE 5



Comparison study between silicone oil system (SO) and silicone oil-free system (SOF) in terms of subvisible particles using MFI analysis. (a) ECD ≥ 5 µm, aspect ratio is more than 0.85. (b) ECD ≥ 5 µm, aspect ratio is less than 0.85 (n=10 for water, n=5 for samples). *p < 0.05, ***p< 0.001.

particles were observed with the PLAJEX SOF syringe with i-coating technology.

Concepts to Prevent Protein Oxidation

The technologies to minimize the risk of protein aggregation by minimizing subvisible particles and other quality aspects, for example, container breakage, were discussed in earlier sections. The following sections will focus on the technologies to minimize the risk of protein oxidation.

Influence of Sterilization Method

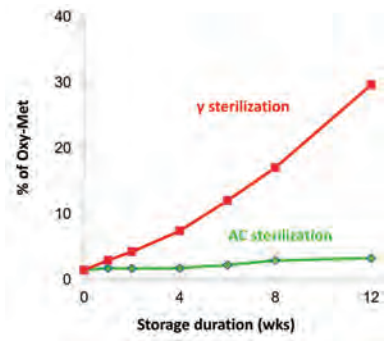
Terminal steam sterilization is frequently used for low molecular weight drug in PFS. It is known that biotherapeutic drug products are sensitive to denaturation by heat, thus aseptic filling into presterilized PFS is common. The impact of sterilization on a drug is an important aspect when choosing a method of sterilization. In this study, polymer-based PFS were filled with erythropoietin (EPO) aqueous solution and sterilized by gamma irradiation and steam sterilization, respectively. The measurement was performed by HPLC. Figure 6 shows the comparison in the percentage of oxidization of methionine during storage for gamma-sterilized polymer syringes and steam-sterilized PLAJEX products.

It was observed that polymer PFS sterilized by gamma irradiation enhanced the methionine oxidation of the biopharmaceutical drug products over time. For PLAJEX (sterilized by autoclaving), the methionine oxidation was not induced. Though more detailed mechanistic studies are underway, we assume that free radicals were generated by gamma sterilization and remained within the polymer material causing the oxidation of biopharmaceuticals, where the autoclave steam sterilization method did not generate any free radicals.[16,21,22] On the basis of these results, it is evident that steam sterilization is more appropriate for polymer-based PFS for biopharmaceutical drug products.

Preventing Oxidation

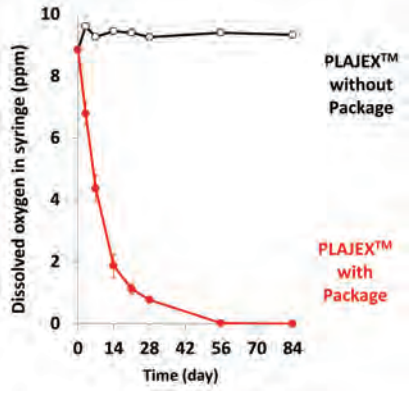
In general, biological drug products are vulnerable to oxidation. For sensitive protein applications, nitrogen control and nitrogen blanketing is necessary in all processes, such as drug solution preparation, filling, and stoppering to eliminate the risk of dissolved oxygen into the filled syringe. In the packaging of PLAJEX, the polymer permeability characteristics can be leveraged to create an advantage of a reduced oxygen environment. It is feasible to eliminate dissolved oxygen using an oxygen absorber inside the secondary sealed blister packaging along with the filled PLAJEX. This

FIGURE 6



Profile of % oxidization of model drug during storage at 25°C (n=3).

FIGURE 7



Reduction profile of dissolved oxygen in water-filled PFS (n=3).

reduction in dissolved oxygen is shown in Figure 7. Dissolved oxygen was measured by OXY-4 (PreSens).

When an oxygen-absorber material was used with PLAJEX, the concentration of dissolved oxygen decreased rapidly just after packaging and continued to decrease gradually. After 8 weeks, the concentration of dissolved oxygen became close to zero. This result shows that the combination of PLAJEX, the deoxygenated package system, and oxygen absorber can prevent protein oxidation.[21] Ideally, the oxygen absorber can be sized to reduce the package to a known concentration (25%, 50%, or 100%) as required by the stability of the drug products.

CONCLUSION

This article shows that Terumo's polymer-based PFS system, PLAJEX, offers several advantages for the delivery of biopharmaceutical drug products. This system was developed by combining specific features of a COP syringe with i-coating technology to deliver a SOF syringe system for low reactivity. This focus on system design provides a container that offers improved container closure system characteristics, including strength, low reactivity, reduced drug degradation, good barrier properties, and novel techniques to control oxidation.

The global biopharmaceutical market continues to grow at a healthy pace along with the increase in chronic diseases, an aging global population, novel drug discovery, and improvement of healthcare efficiencies worldwide. The development and adoption of PLAJEX with i-coating technology by Terumo ensures that important biopharmaceutical therapies can be safely administered, minimizing medical errors, contributing effectively to the needs of patients, healthcare workers, and the global pharmaceutical industry. ◆

Design and Evaluation of a Polymer Prefillable Syringe (PLAJEX) for Improved Functionality and Performance With Biopharmaceuticals: GPS-006-04222015

REFERENCES

1. The Prefilled Syringes Market. 2015-2030. Opportunities, challenges, strategies, and forecasts. SNS Research. 2015.
2. Casadevall N, Nataf J, Viron, B, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med. 2002;346(7):469-475.
3. Gershon SK, Lukskenburg H, Cote TR, et al. Pure red-cell aplasia and recombinant erythropoietin. N Engl J Med 2002;346(20):1584-1586.
4. US Food and Drug Administration. Immunogenicity Assessment for Therapeutic Protein Products. 2014.
5. Jones LS, Kaufmann A, Middaugh CR. Silicone oil induced aggregation of proteins. J Pharm Sci. 2005;94(4):918-927.
6. Mahler HC, Wolfgang F, Grauschopf U, et al. Protein aggregation: pathways, induction factors and analysis. J Pharm Sci. 2009;98(9):2909-2934.
7. Wang W, Nema S, Teagarden D. Protein aggregation-pathways and influencing factors. Int J Pharm. 2010;390(2):89-99.
8. Krayukhina E, Tsumoto K, Uchiyama S, Fukui K. Effects of syringe material and silicone oil lubrication on the stability of pharmaceutical proteins. J. Pharm Sci. 2015;104(2):527-535.
9. Mensch C, Davis CD. Inhibition of Tungsten-induced protein aggregation by cetyl trimethyl ammonium bromide. PDA J Pharm Sci Technol. 2012;66(1):2-11.
10. Seidl A, Hainzl O, Richter M, et al. Tungsten-induced denaturation and aggregation of Epoetin Alfa during primary packaging as a causé of immunogenicity. Pharm Res. 2012,29(6):1454-1467.
11. Liu W, Swift R, Torraca G, et al. Root cause analysis of Tungsten-induced protein aggregation in pre-filled syringes. PDA J Pharm Sci Technol. 2010;64(1):11-19.
12. Jiang Y, Nashed-Samuel Y, Li C, et al. Tungsten-induced protein aggregation: solution behavior. J Pharm Sci. 2009;98(12):4695-4710.
13. Singh SK, Afonina N, Awwad M, et al. An industry perspective on the monitoring of subvisible particles as a quality attribute for protein therapeutics. J Pharm Sci. 2010;99(8):3302-3321.
14. Ripple DC, Dimitrova MN. Protein particles: what we know and what we do not know. J Pharm Sci. 2012;101(10):3568-3579.
15. Bee JS, Goletz TJ, Ragheb JA. The future of protein particle characterization and understanding its potential to diminish the immunogenicity of biopharmaceuticals: a shared perspective. J Pharm Sci. 2012;101(10):3580-3585.
16. Forster R. Plastic container development for biological parenterals. PDA Annual Meeting 2013.
17. Majumdar S, Ford BM, Mar KD, et al. Evaluation of the effect of syringe surfaces on protein formulations. J Pharm Sci. 2011;100(7):2563-2573.
18. Yoshino K, Nakamura K, Yamashita A, et al. Functional evaluation and characterization of a newly developed silicone oil-free prefillable syringe system. J Pharm Sci. 2014;103(5):1520-1528.
19. Depaz RA, Chevolleau T, Jouffray S, et al. Cross-linked silicone coating: a novel prefilled syringe technology that reduces subvisible particles and maintains compatibility with biologics. J Pharm Sci. 2014;103(5):1384-1393.
20. Reynolds G, Paskiet D. Glass delamination and breakage. BioProcess International. 2011;9(11):52-57.
21. Nakamura K, Abe Y, Kiminami H, et al. A strategy for the prevention of protein oxidation by drug product in polymer-based syringes. PDA J Pharm Sci Technol. 2015;69:88-95.
22. Nakamura K, Kiminami H, Yamashita A, et al. Assessment of the effects of sterilization methods of protein drug stability by elucidating decomposition mechanism and material analysis. Int J Pharm. 2015;484:51-56.

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

BIOGRAPHIES

Dr. Sagarika Bose earned her PhD in Pharmaceutical Science, specializing in novel polymer coating technologies and statistical data modeling and analysis from University of Connecticut. She is the Senior Manager in Technology Development at Terumo Medical Company, responsible for the development of drug-device combinations using prefilled syringes to pharmaceutical partners by supporting their quality, manufacturing, and regulatory needs for combination devices. She started her industrial career at Wyeth Pharmaceuticals, followed by Pfizer and Endo Pharmaceuticals. She held the position as the Director, Product development and CMC in Research and Development at Amarin Pharmaceuticals prior to her career at Terumo. She has been a reviewer for several pharmaceutical journals.
E: sagarika.bose@terumomedical.com;
T: (732) 412-4122.

Kevin Constable leads the Technology Development team for Terumo's Global Pharmaceutical Solutions Division, providing drug & device solutions to the pharmaceutical industry. Prior to Terumo, Mr. Constable was employed by Pfizer working in the vaccines/biotechnology sector, supporting technology transfer, risk mitigation of supply, improved process solutions for filling and packaging, global harmonization of practices for aseptic filling, and packaging of prefilled syringes and vials. Mr. Constable has over 20 years in the pharmaceutical industry.
E: Kevin.constable@terumomedical.com;
T: (732) 412-4160.

BIOTHERAPEUTICS DEVELOPMENT

The Role of Flow Electroporation in Vaccine Development

By: James Brady, PhD, Karen Donato, PhD, and Krista Steger, PhD

INTRODUCTION

As the largest known outbreak of Ebola in human history has raced through West Africa killing thousands of people, big pharma and start-ups alike have searched for a vaccine to this deadly virus. Even if a vaccine were to be found in the near future, it could be months to years before it is commercially available because vaccine development and production is a lengthy and costly process. But, new technologies are available, and biotherapeutic development and production of vaccines can be accelerated.

Recognizing the need for rapid and reliable vaccine production, researchers have looked to recombinant technologies to develop innovative types of vaccines and new cell culture production methods that offer shorter lead times and greater production flexibility while maintaining vaccine safety.[1-3] Newer engineered vaccine modalities range from therapeutic antibodies, subunit vaccines, virus-like particles (VLPs), and virus-like replicons particles (VRPs) to virus-mediated gene therapy. Each of these engineered vaccine types - whether a simple therapeutic protein or complex modification of patient cells - requires the introduction of recombinant nucleic acids into a cell line or *ex vivo* patient-isolated cells via transfection, viral transduction, and/or creation of stable cell lines. While the downstream processing is vaccine-dependent, a single unifying platform for upstream cell transfection could significantly reduce development timelines and production costs.

For more than two decades, stable cell lines have been the standard for biotherapeutic protein production. However, their creation is a time-consuming, costly, labor-intensive process and is not feasible for all vaccine applications. As a result, researchers have turned to transient gene expression (TGE) as a means of more cost-effective protein production, particularly during early development and preclinical stages.[4,5] While TGE offers a means of rapidly expressing proteins, not all transient expression methods generate the required amount of protein or fulfill the necessary requirements for broad use throughout vaccine development and production. One transient transfection technology (flow electroporation, a proprietary technology from MaxCyte, Inc.) not only meets all the conditions but can lead to significant resource and time savings.

Flow electroporation is a universal, regulatory-compliant transient transfection technology that provides a practical solution to the time, labor, and cost challenges of developing stable cell lines and baculovirus-based expression while overcoming the flexibility and scalability limitations associated with other transient transfection methods. Flow electroporation efficiently (co)transfects cells with DNA, RNA, siRNA, and cell lysates without requiring specialized constructs, engineered cells, media additives, or chemical reagents. It transfects from 5E5 cells in seconds up to 2E11 cells in less than 30 minutes.

With more than a dozen adherent- or suspension-adapted cell lines currently in use by vaccine manufacturers, there is a

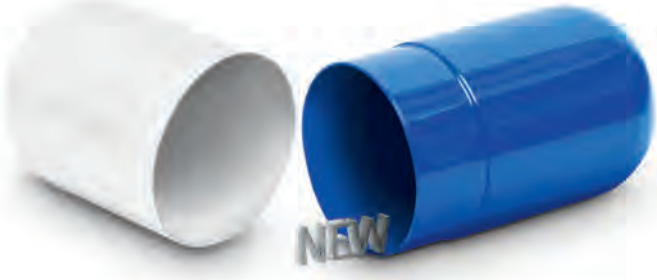
EMD MILLIPORE

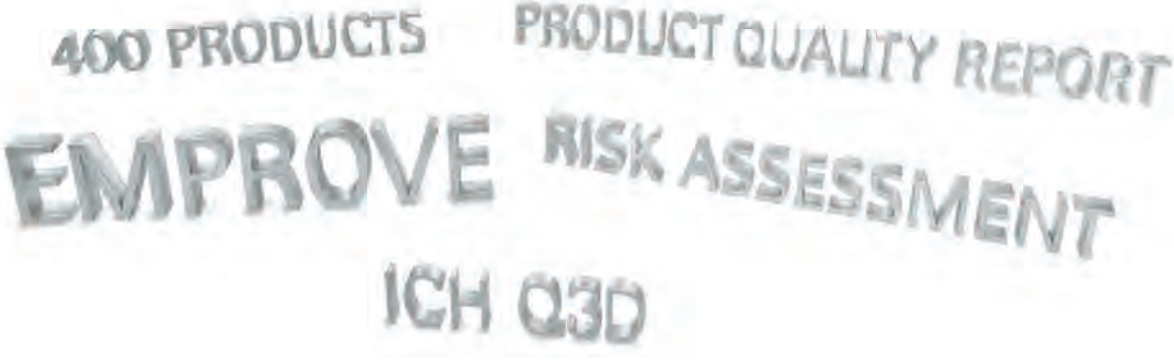
Knowledge is power.

Accelerate your risk assessment with EMPROVE® regulatory documentation.

The regulatory environment increasingly demands a thorough assessment of risks. The latest enhancement of our EMPROVE® documentation directly supports you with this challenge: Product quality reports give you detailed information about the consistency of our pharma raw materials. We are also including information on elemental impurity levels of EMPROVE® products according to ICH Q3D. These new features, in addition to the existing comprehensive EMPROVE® information package, help simplify your qualification and registration process.

For more information, visit:
www.emdmillipore.com/emprove





EMD Millipore Corp. is a subsidiary of Merck KGaA, Darmstadt, Germany

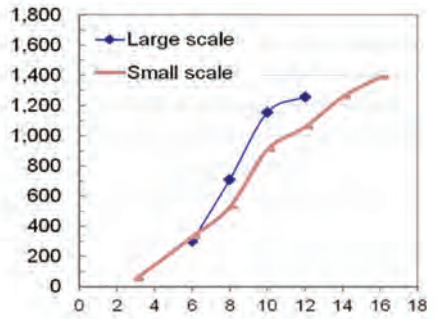
need for cell type flexibility.[1,6] MaxCyte electroporation consistently results in high levels of transfection efficiency and cell viability for a wide range of cells, including CHO, MDCK, BHK-21, Vero, NS0, insect cells, and other cell lines commonly used for bioproduction. Moreover, cell immunotherapy using modified patient-isolated primary cells requires high transfection efficiency and low cell toxicity while meeting stringent sterility and safety needs.

As well as its cell type flexibility and scalability, flow electroporation is extremely easy to use with a preloaded library of optimized electroporation protocols. The combination of features adds up to a technology that is especially attractive for rapid response vaccine generation for pandemic, biodefense, or even seasonal influenza. From antibody production to lentivirus production, flow electroporation can accelerate vaccine development and production. To exemplify this, five case studies are presented below to show the role of flow electroporation in vaccine development.

GRAM-SCALE CHO ANTIBODY PRODUCTION

Therapeutic monoclonal antibodies (mAbs) are the predominant component of biotherapeutic development pipelines for a range of clinical indications, including inflammatory disorders, cancers, and infectious diseases. mAbs can be used as prophylactic or therapeutic interventions via a variety of means ranging from targeted radioimmunotherapy to anti-idiotype immunization.

FIGURE 1



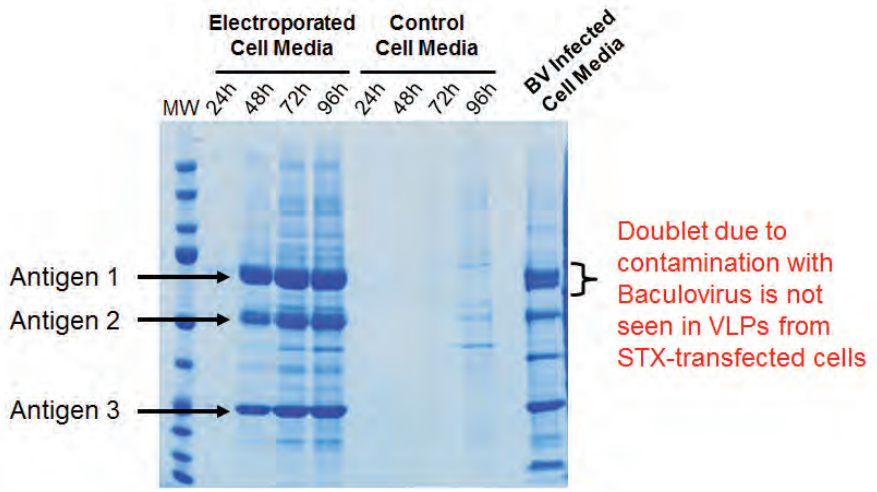
	Culture Volume	EP Volume	# of Cells	[IgG]	Total IgG Produced
Small Scale	20mL	0.4mL	8E7	**1.40 g/L**	28mg
Large Scale	2.8L	50mL	1E10	**1.22 g/L**	3.42 g

High-Titer Antibody Production With Seamless Scalability
CHO-S cells were transfected with an antibody expression plasmid via small-scale or large-scale MaxCyte electroporation. Cells were seeded at 6E6 cells/mL post electroporation. 1 mM sodium butyrate was added to cultures and the temperature lowered to 32°C 24 hours post electroporation. Cultures were fed daily with a media optimized for antibody production. Secreted IgG titers were measured via ELISA on various days post transfection and total IgG production calculated.

The amount of protein required throughout mAb development varies from low milligram to multi-gram quantities. Despite advances in transfection methods and culture optimization, the majority of CHO cell-based TGE methods have reported antibody titers ranging from 2 to 250 mg/L upon full optimization.[7-11] More recently, there have been reports of 2 g/L after extensive work engineering a CHO cell line and optimizing culture conditions, something that is not feasible when a rapid response is needed.

Large-scale flow electroporation studies have demonstrated the ability to rapidly produce secreted antibody titers >400 mg/L, which can exceed >1 g/L with optimization of post transfection culture conditions, such as cell density, feeding conditions, media additives, and culture temperature.[12] This translates into the production of multi-gram quantities of antibodies within days of transfection. With a moderate amount of post transfection process development, flow electroporation has resulted in antibody titers greater than 1.2 g/L, producing greater than 3 g of antibody from a non-engineered CHO culture of less than 3 L in 12 days (Figure 1). Further scale-up to biomanufacturing using the MaxCyte VLX® Large Scale Transfection System allows for transfection of up to 2E11 cells, which would equate to the production of more than 50 g of antibody within 2 weeks of a single transient transfection. The speed and simplicity of the process allows for rapid generation of quantities of antibody to meet rapid response needs.

FIGURE 2



Sf9 VLP Production Using MaxCyte Electroporation: Plasmid to Protein in 2-4 Days
Sf9 cells were transfected via small-scale electroporation with a single plasmid encoding three antigens that co-assemble into VLPs. Culture media was collected at various times from cells post electroporation or following baculovirus infection and analyzed using SDS-PAGE.

HIGH-LEVEL SUBUNIT VACCINE EXPRESSION

Similar to inactivated virus vaccines, subunit vaccines are generally easy to administer, do not contain infectious material, nor require a cold chain for distribution. Unlike inactivated viruses, subunit vaccines contain only the antigen(s) that best stimulate a protective immune response. Subunit vaccine antigen(s) can be isolated directly from the pathogen, as is the case with the Haemophilus influenzae type b vaccine (parenteral form), or expressed recombinantly, like the current hepatitis B vaccine composed of the hepatitis B virus surface antigen (HBsAg). One advantage of recombinant expression is that the antigen(s) can be manipulated to increase immunogenicity, to elicit a more protective immune response, or to be expressed as peptides or fusion proteins.

Tests between flow electroporation and conventional methods have shown electroporation to be a rapid means of expressing recombinant antigens with superior performance. In CHO-S cells that were transfected with an HIV-1 gp145 expression plasmid via electroporation and PEI, the viability of PEI-transfected cells dropped off substantially by day 3, while >95% viability is maintained for 10 days after electroporation. Higher cell viability was reflected as 25-fold higher expression of the HIV-1 gp145 envelope protein based on volumetric titers.

RAPID RESPONSE VACCINES USING INSECT CELL VLP PRODUCTION

VLPs are a promising avenue of vaccination with an inherently higher level of safety compared to inactivated or live attenuated viral vaccines. These particles consist of one or more recombinantly expressed viral structural proteins that self-assemble into complexes that closely mimic the three-dimensional structure of native virus but lack the viral genome. VLPs have been produced for a variety of viruses, including influenza, and are an FDA-approved vaccine against human papillomavirus.[3,13,14]

VLPs are manufactured using an assortment of cells, including mammalian and insect cells. Insect cells are used because they are easy to culture with simplified cell growth that is readily adapted to high-density suspension and they post-translationally modify proteins in a manner similar to that of mammalian cells. While both transient transfection and recombinant baculovirus platforms are commonly used methods for insect cell protein expression, there are advantages to using electroporation.[15,16]

Baculovirus-mediated protein production is an extended, multi-stage process, despite development of specialized media and baculovirus vectors aimed at simplifying gene cloning and virus stock production. This 6- to 8-week process requires construction of expression plasmid(s), transfection of insect cells, viral stock preparation, and subsequent infection of insect cells, all prior to final production and purification of the recombinant protein(s) of interest.

In comparison to baculovirus, the MaxCyte STX® Scalable Transfection System, which directly transfects Sf9, Sf21, and SL3 cells with >90% cell viability and transfection efficiency levels, allows for rapid, high-level protein production within 3 days. In one

experiment, Sf9 cells were transfected via electroporation with an expression construct encoding three VLP antigens that resulted in significant secretion of the VLP within 48 hours post transfection. In tandem, a baculovirus expression system was used to produce VLPs containing the identical three antigens. Analysis of VLPs following sedimentation through a sucrose cushion shows the presence of the three VLP antigens in all electroporation and baculovirus samples; however, baculovirus protein contaminants were also present in preparations of VLPs from baculovirus-infected cultures. This is consistent with the literature, which documents the propensity for baculovirus protein contamination, creating purification challenges, and yield loss.[17,18] VLP production is streamlined with flow electroporation because there is no need to create a viral stock, go through several rounds of virus amplification, or remove contaminating baculovirus proteins during purification.

INCREASED EFFICIENCY OF ALPHAVIRUS VRP PRODUCTION

Alphaviruses have a broad cellular tropism, but preferentially infect dendritic cells, thereby acting as a delivery vehicle to professional antigen-presenting cells (APCs), which in turn stimulate both humoral and cellular immune responses. Alphavirus-derived particles, called virus-like replicon particles, represent a viable next-generation vaccine option, particularly against NIH Risk Group 3 viruses (such as H5N1, HIV, Ebola, etc) as low biocontainment facilities can be used to produce the non-pathogenic VRPs.

VRPs are produced by (co)transfecting cells with an alphavirus replicon RNA and helper RNAs or DNA plasmids expressing the alphavirus structural proteins, followed by harvesting of VRP-containing culture media. Many different cell lines are permissive to alphavirus infection, allowing a variety of cells to be used for VRP production. Vero and BHK are most common, but others including CHO and HEK have been used. Several VRPs produced via electroporation of Vero cells have entered into clinical studies.[17]

Alphavirus VRP experiments have been conducted in which the current "best practice" of transfection was compared to electroporation. Production of two VRPs was assessed: one expressing GFP and the second expressing the HIV gag protein. Electroporation led to 9X higher relative titers of both the GFP and HIV gag-expressing VRPs over the current best practice method.

STREAMLINED SCALE-UP OF LENTIVIRUS PRODUCTION

Lentiviruses, a subclass of retroviruses, are popular *in vivo* gene delivery vectors due to their unique ability to integrate into the host genome of non-dividing cells, the minimal immune response they induce, their reduced risk of insertional mutagenesis, and the long-term nature of their expression. Lentiviral vectors are developed by removing all the viral genes except those required *in cis* in order to complete a single round of replication. All other viral components are provided *in trans* during lentivirus stock production, and for biosafety considerations, the components are generally encoded by three to five separate plasmids

Due to the toxicity of vector components to the host cell, stable lentivector production cell lines are difficult to generate. Thus, lentivirus stocks are historically produced by transiently co-transfecting a host cell line with the multiple plasmids encoding the various lentivector components.[18] Inefficiencies associated with chemical-based transfection methods, particularly when they are used for multi-plasmid co-transfection, typically restrict lentivector production to adherent cells, which are easier to transfect but are challenging to culture at large scale. Flow electroporation offers a rapid, fully scalable and cGMP-compliant alternative to chemical-based transfection methods that efficiently co-transfects suspension-adapted cells.

Flow electroporation has proven reliable performance. In large-scale production studies using a 4-plasmid lentiviral system, titers of approximately 38 ± 3.21 transducing units of virus per cell were achieved in three pilot qualification lots manufactured at a cGMP facility.[19] These studies demonstrated the consistent, highly reproducible nature of flow electroporation.

SUMMARY

Two factors should be foremost when facing a rapid response situation: the need to accelerate development of vaccines and the need for a large quantity of protein. Flow electroporation can provide large quantities of protein

using commercially available cell lines and standard processes. Furthermore, flow electroporation can accelerate development of antibodies, recombinant antigens, VLPs, VRPs, viral vectors, and cell immunotherapies, thereby reducing cost and shortening timelines. With unmatched quality, flexibility, and scalability, flow electroporation is a universal, cost-effective platform that supports the full range of biotherapeutic and vaccine development activities. ◆

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

REFERENCES

1. Whitford W. Using Disposables in Cell-Culture-based Vaccine Production. Bioprocess Int. 2010; 8(S4): S20-S27.
2. Reisinger KS, Block SL, Izu A, et al. Subunit Influenza Vaccines Produced from Cell Culture or in Embryonated Chicken Eggs: Comparison of Safety, Reactogenicity, and Immunogenicity. J Infect Dis. 2009; 200(6): 849-857.
3. Lambert L, Fauci, A. Influenza Vaccines for the Future. N Engl J Med. 2010; 363(21): 2036-2044.
4. Agrawal V, Bal M. Strategies for Rapid Production of Therapeutic Proteins in Mammalian Cells. Bioprocess Int. 2012; 10(4): p32-48.
5. Baldi L, Hacker DL, Adam M, Wurm FM. Recombinant Protein Production by Large-scale Transient Gene Expression in Mammalian Cells: State of the Art and Future Perspectives. Biotechnol Lett. 2007; 29(5): 677-684.
6. Whitford W, Fairbank A. Considerations in Scale-up of Viral Vaccine Production. BioProcess Int. 2011; 9(S8): S16-28.
7. Bollin F, Dechavanne V, Chevalet L. Design of Experiment in CHO and HEK Transient Transfection Condition Optimization. Prot Expr Purif. 2011; 78(1): 61-68.
8. Galbraith DJ, Tait A, Racher AJ, et al. Control of Culture Environment for Improved Polyethylenimine-Mediated Transient Production of Recombinant Monoclonal Antibodies by CHO Cells. Biotechnol Progr. 2006; 22(3): 753-762.
9. Liu C, Dalby B, Chen W, et al. Transient Transfection Factors for High-Level Recombinant Protein Production in Suspension Cultured Mammalian Cells. Mol Biotechnol. 2008; 39(2): 141-153.
10. Ye J, Kober V, Tellers M, et al. High-level Protein Expression in Scalable CHO Transient Transfection. Biotechnol Bioeng. 2009; 103(3): 542–551.
11. Rajendra Y, Kiseljak D, Baldi L, et al. A Simple High-yielding Process for Transient Gene Expression in CHO cells. J Biotechnol. 2011; 153(1-2): 22-26.
12. Steger K, Brady J, Wang W, et al. CHO-S Antibody Titers >1 Gram/Liter Using Flow Electroporation-Mediated Transient Gene Expression Followed By Rapid Migration to High-Yield Stable Cell Lines. J Biomol Screen. Accepted for publication.
13. Landry N, Ward BJ, Trépanier S, et al. Preclinical and Clinical Development of Plant-Made Virus-Like Particle Vaccine against Avian H5N1 Influenza. PLoS ONE. 2010; 5(12): e15559.
14. US Food and Drug Administration. Complete List of Vaccines Licensed for Immunization and Distribution in the US. 2014. http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm. Updated September 29, 2014. Accessed May 1, 2014.
15. Liu F, Wu X, Li L, et al. Use of Baculovirus Expression System for Generation of Virus-like Particles: Successes and Challenges. Prot Expr Purif. 2013; 90(2): 104-116.
16. Kushnir N, Streatfield SJ, Yusibov V. Virus-like Particles as a Highly Efficient Vaccine Platform: Diversity of Targets and Production Systems and Advances in Clinical Development. Vaccine. 2012; 31(1): 58-83.
17. Vander Veen RL, Harris DJH, Kamrud KI. Alphavirus Replicon Vaccines. Anim Health Res Rev. 2012; 13(1): 1-9.
18. Howarth JL, Lee YB, Uney JB. Using Viral Vectors as Gene Transfer Tools. Cell Biol Toxicol. 2010; 26(1): 1-10.
19. Witting SR, Li L-H, Jasti A, et al. Efficient Large Volume Lentiviral Vector Production Using Flow Electroporation. Hum Gene Ther. 2012; 23: 243-249.

BIOGRAPHIES

Dr. James Brady is Director of Technical Applications at MaxCyte, Inc, where he has worked since 2004. Dr. Brady earned his BS in Biology from the College of William and Mary and his PhD in Genetics from Indiana University. He also completed postdoctoral training at the National Eye Institute of the National Institutes of Health.

Dr. Karen Donato is Executive Vice President, Global Business Development and Marketing at MaxCyte, Inc. She earned her PhD in Chemical Engineering from Ohio University with broad experience in new business development, R&D, and operations in multinational, mid-size, and start-up companies.

Dr. Krista Steger is President and Founder of Forge 4ward and a consultant to MaxCyte, Inc. She has more than 15 years of experience in global scientific marketing at leading biotechnology companies and start-ups. Dr. Steger earned her PhD in Cell and Molecular Biology at the University of Wisconsin-Madison.

Special Feature

Prefilled Syringes & Parenteral Contract Manufacturing: Anticipating the Needs of the Future

By: Cindy H. Dubin, Contributor

Safety and shielding systems (BD Medical-Pharmaceutical Systems)

Overall world revenue for pre-filled syringes will reach $4.3bn in 2015[1], and is expected to grow at a CAGR of 13% through 2020 when the market will account for nearly $6 billion[2] thanks to increasing demand for chronic disease treatment, market entry of biologics and biosimilars, and innovative prefilled injection devices. Prefilled pen systems and auto-injectors will grow at a CAGR of more than 20% over the next five years.

And while glass continues to remain the gold standard for prefilled syringes, the proportion of plastic-based prefilled syringes is expected to increase by 5% between 2015 and 2020, due to concerns of glass breakage and plunger failure.

A Smithers Rapra report estimates that there are approximately 3.5 billion prefilled syringe units produced a year and this will grow to 6.7 billion units by 2020.[3] The rapid update of prefilled syringes is driven by several key factors:

- Prefilled syringes are simple compared with a traditional syringe and vial. The products reduce the number of steps required for drug administration while improving safety by reducing the potential for drug contamination, needlestick injuries and dosing errors.
- An increasing incidence of chronic disease means patients are requiring injectable drugs to self-dose at home, which is much easier and safer with pre-fills.
- Pharmaceutical companies can offer a premium and differentiate their brands with drugs sold in prefilled syringes. They can also reduce overfill of drug containers.

- Improvements in technology and manufacturing to lower levels of extractables and leachables and to cater to biologics and more sensitive drugs will encourage drug companies to switch to pre-fills.
- A number of prefilled syringe manufacturers have developed dual- and multi-chambered syringes, to cater to drugs that must be reconstituted at the point of delivery.

This exclusive annual *Drug Development & Delivery* magazine report highlights several of the players in the prefilled syringe and parenteral manufacturing market. These companies are offering a range of services and systems that cater to today's issues addressed above as well as anticipating the needs of the future.

Althea—A Range of Batch Sizes, Capacity, and Services

Prefilled syringes offer many advantages as a unit-dose medication drug delivery system and are continually employed for clinical testing and commercial products. The benefits compared to vial-disposable syringes are convenience and ease of handling as well as advantages in safety and reducing drug overfill, says Jennifer Cannon, PhD, Marketing Director, Althea. "Precise dosing is met by using pre-filled syringes compared to vials where there is an additional manipulation step during administration as well as an additional cost."

Althea is a leader in executing drug formulation and aseptic fill/finish for prefilled syringes and vials. Producing more than 2,000 lots of finished cGMP product in its facility, Althea provides clients with the capacity to advance projects through all stages of clinical and commercial development.

Althea's prefilled syringe contract manufacturing services include parenteral manufacturing on a high-speed prefilled syringe line that utilizes Restricted Access Barrier (RAB) technology to ensure the required sterility for fill/finish, explains Dr. Cannon.

Althea also offers a range of batch sizes for prefilled syringe projects with media fill formats covering most configurations. The clinical manufacturing facility at Althea fills batch sizes of up to 20,000 prefilled syringes and batch sizes of up to 100,000 units for commercial-scale programs. Althea's INOVA H3-5V supports glass or polymer syringes ranging in sizes from 0.5mL to 20mL syringes. The syringe line runs at a rate of 13,000 syringes per hour and performs non-destructive weight checks, all within cGMP standards and FDA guidelines.

In addition to aseptically filling of prefilled syringes, Althea has the capacity to fill liquid and lyophilized vials. Althea's vial capacity for clinical programs include batches as small as 100 units up to batch sizes reaching more than 70,000 vial units. Vial volume sizes range from 0.5mL to 100mL depending on the client-specific needs of the drug product.

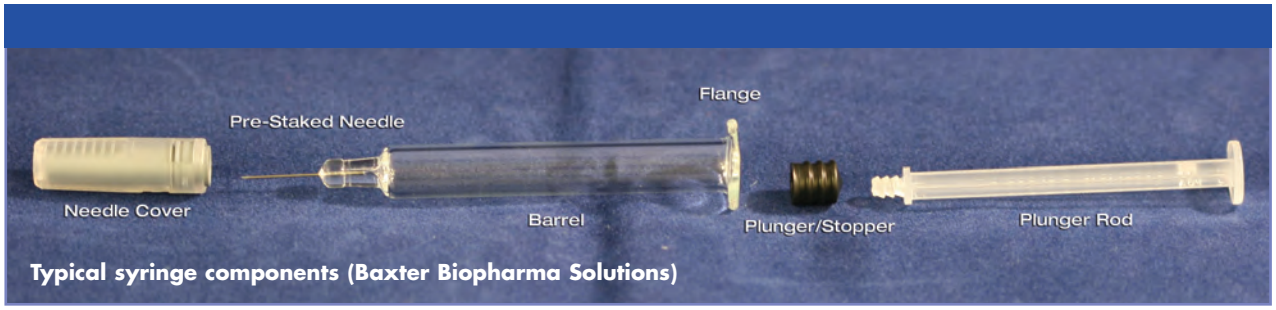
Althea also offers cGMP lyophilization services in conjunction with fill/finish capabilities. "If there is an existing lyophilization process in place, Althea will transfer and adapt the lyophilization cycles to its equipment," says Dr. Cannon. Althea's VIRTIS Ultra 35EL lyophilizer has a maximum lot size of 6,100 x 2mL vials and can fill a range of vial volumes from 2mL to 50mL.

Baxter Biopharma Solutions—Parenteral Experience and R&D/Manufacturing Collaboration

BioPharma Solutions (BPS), the contract manufacturing business unit of Baxter, partners with pharmaceutical companies globally to support commercialization objectives by providing formulation development, lyophilization development/optimization, sterile contract manufacturing solutions, parenteral delivery systems, and customized support services.

As a global contract manufacturer in prefilled syringe fill/finish, BioPharma Solutions offers clinical through high-volume commercial sterile manufacturing. Redundant like-in-kind filling lines can help increase production potential, mitigate supply risk, and ensure on-time delivery.

Baxter Scientist Greg Sacha cites advances in the industry with respect to syringe design, which include new types of components, changes to the



Typical syringe components (Baxter Biopharma Solutions)

manufacturing process to reduce the quantity of silicone used to coat the syringe, changes to the process to decrease tungsten and adhesive residuals, dual-chamber devices, and needle-free devices. Advances in types of components include changes in the materials of construction such as the polymeric syringes changes in tip cap and plunger formulations as well as changes in the design of plungers.

Plungers are seated by one of two mechanisms. BioPharma Solutions uses a mechanism that collects the plunger in stainless steel tubes that compress the plungers and a plunger insertion rod pushes the plunger into the syringe barrel. Compressing the plunger before placement allows air to escape around the plunger so that it will remain in place when it expands to fit into the barrel.

BPS has expertise in filling glass and polymeric syringes using filling mechanisms that include time/pressure filling machines, rotary piston pumps, and peristaltic pumps. Syringe filling and stopper placement can be challenging considering the need to closely control the fill volume and the headspace between the liquid in the syringe and the bottom of the plunger. Additional challenges include interactions between the syringe components and the drug solution, especially for biologics. For example, a coating of silicone is needed on stoppers to improve their machinability

Baxter's contract manufacturing site in Bloomington, IN, has an onsite research and development department that is experienced with the challenges of interactions of drug solutions with container closure components and has analytical equipment to aid in identifying and preventing potential problems.

Along with BioPharma Solutions' contract manufacturing services for pharmaceuticals in prefilled syringes, clients may leverage BPS' expanded Drug Master File (DMF) for diluent syringes. Established DMFs have been successfully incorporated into client submissions for drug and biologic products. "By choosing a custom fill volume and labeling, while streamlining development work and process validation batches, and eliminating capital equipment costs, clients can considerably reduce time to market. Additionally, if a customer with a product currently in a vial decides to move their product from a vial to a prefilled syringe, BioPharma Solutions offers services to aid clients in making a seamless transition," says Dr. Sacha.

BD Medical—Pharmaceutical Systems—Advancements in Prefillable Syringe Technologies Enhance Patient Outcomes and Performance

BD Medical–Pharmaceutical Systems offers a portfolio of drug delivery systems, including prefillable syringes, self-injection systems, and safety and shielding solutions, to meet the current and evolving needs of the pharmaceutical industry.

In the past, global needlestick safety legislation has driven the requirement for prefillable syringes with staked needles to be equipped with needlestick safety to protect healthcare workers. However, as more drugs are being self-injected, it is important for safety and shielding systems to also incorporate a patient-centered design to support end-user needs. Improved ergonomic features, such as larger finger flanges and plunger rod heads can help provide additional support to users performing injections. "Improved patient outcomes have been documented in a recent article in the *British Journal of Dermatology*, where 100% of test

Baxter

ViE
Vaccine Industry Excellence
AWARDS
• Winner 2015, 2012-2010

- Small Molecules
- Biologics
- Cytotoxics
- ADCs
- Highly Potent

- Prefilled Syringe Filling
- Liquid and Lyo Vial Filling
- Cartridge Filling
- Diluents for Reconstitution
- Proprietary Flexible Bags
- And more...

Parenteral Contract Manufacturing

is the *only* thing we do at Baxter BioPharma Solutions

Whether you face formulation challenges, clinical supply hurdles, surges in demand due to market fluctuations, risk mitigation concerns, or patent expiry challenges, we offer tailored, versatile solutions–and over 80 years of parenteral experience–to help you achieve your commercialization objectives.

Ultimately, our goal is to make you feel confident and secure in choosing BioPharma Solutions as your CMO–assisting you to avoid the unexpected and guiding you through marketplace complexities to help you achieve the full potential for your molecule.

Visit our website today:
baxterbiopharmasolutions.com

Your Parenterals CMO

BioPharma Solutions

subjects successfully self-administered treatment using a prefilled syringe equipped with the BD UltraSafe™ Passive Needle Guard," says Sarah Baer, Strategic Marketing Leader, BD Medical–Pharmaceutical Systems.

Additionally, pharmaceutical companies are developing more advanced injectable therapies that require expertise and innovation on the part of solution providers like BD. Many of these drugs must be delivered in higher volumes and at higher viscosities than has traditionally been the case. Furthermore, as the trend is to reduce overall healthcare costs by moving patient care out of the hospital/clinic and into the home setting, a focus on patient-centered design, acceptance, and adherence to these innovative drugs is critical.

While traditional injection volumes are typically up to 1mL, the latest formulations are pushing the boundaries, and a need exists for injection volumes up to 5mL and larger. The market is demanding novel primary containers to support these drugs and delivery devices to enable self injection, whether large volume autoinjectors or wearable patch injectors. "As a result, BD is leveraging its Neopak™ glass prefillable syringe technology to offer 2.25mL prefillable staked syringes, as well as solutions to deliver up to 10mL in a wearable patch injector," says Paul A. Upham, Worldwide Director, Strategic Marketing, Self-Administration Injection Systems, BD Medical–Pharmaceutical Systems.

The Credence Staked Companion reduces development and supply chain risk for the manufacturer while providing the end user improved safety and usability.

For primary containers, issues such as breakage are a serious concern. Glass breakage or weakening can occur throughout the supply chain of the syringe: from processing to handling to use at the time of injection. This has resulted in increased costs and longer time to market for pharmaceutical companies. "BD DuraShield™ syringes use proprietary technology to improve glass performance, reducing the total cost of ownership and enhancing the risk mitigation profile for the pharmaceutical company," explains Maggie Tsai, Product Marketing Manager, BD Medical–Pharmaceutical Systems "Performance can be improved by making the glass stronger and more durable, that is, the ability to maintain strength and resist cosmetic defects during any handling or processing. This is achieved by increasing the level of compressive stress at the glass surface. Surface stress is induced by treating glass in molten salt (KNO_3) causing ion-exchange of smaller sodium (Na) ions from the glass with larger potassium (K) ions from the salt. The treated syringes, when compared to controls, are stronger and more durable leading to improved and more consistent performance."

Finally, the macro trends of an

aging society, a rise in chronic conditions and healthcare reform are driving healthcare demand and costs. As a result, the healthcare industry is now increasingly focused on improving outcomes. A key way to achieve this is by addressing unmet needs related to self care and treatment adherence. "BD recognizes the important role that interconnected and informatics-enabled ("smart") medical devices can play in delivering targeted solutions that simplify and improve the quality of patient self care while enabling providers to better treat and monitor their patients," says Justin M. Wright, PhD, Senior Director, Strategic Innovation, BD Medical-Pharmaceutical Systems.

Credence MedSystems—*Innovation Without Change* Redefines the "Staked" Needle

When Credence MedSystems introduced its Companion Safety Syringe System last year, the paradigm shifted for a pharmaceutical company looking to launch an injectable drug in a differentiated delivery system. Credence's *Innovation Without Change* design philosophy builds an integrated needlestick retraction safety device off of existing, commercially available primary package components. "By offering the *innovation* of the final device without the traditional *changes* to the primary package and supply chain that drive substantial development effort and risk, the Credence Companion addresses the critical needs of both the end user performing the injection and the pharmaceutical manufacturer commercializing the drug," describes John A. Merhige, Chief Commercial Officer, Credence MedSystems.

With its recently introduced Staked Needle version of the Companion, Credence has redefined 'staked,' keeping the desired and beneficial elements while eliminating many areas of concern with the conventional staked needle syringe, he continues. "As with any pre-attached needle, the user's preparation process is simplified and the risk of attachment error is eliminated; the user must only remove the needle shield and then perform the injection." Additionally with the Staked Companion, the needlestick safety is integrated into the syringe, allowing conventional syringe operations. Upon completion of the injection, audible, visual, and tactile cues signal that the injection is complete and then the needle automatically retracts into the barrel of the syringe and the syringe is permanently disabled.

"Born from the *Innovation Without Change* philosophy, the Staked Companion allows the pharma company the flexibility to source from its preferred vendors and choose from existing syringe barrel, plunger, and needle shield primary package components. This capitalizes on the efficiencies of using existing components with a performance history, permits the components to be matched with the requirements of the drug product and application, and minimizes supply chain risk," says Mr. Merhige. The Companion is compatible with ready-to-fill or bulk syringe processing and the filling process is unchanged. The Companion plunger rod and finger flange (if desired) are assembled after filling using conventional secondary packaging processes.

Building the Companion off of a platform of existing primary package components simplifies the commercialization path for the pharmaceutical manufacturer, but additionally, the Staked Companion offers solutions to other challenges faced during combination drug-device development. For instance, the challenges and risks stemming from the presence of adhesives (conventionally used to mount needles), residual tungsten (an artifact from the syringe manufacturing process), and silicone (for lubrication) are well known within the industry. Adhesive, tungsten residue, and excessive silicone have been shown to lead to protein aggregation with sensitive biologics, and the adhesive application also carries risk of needle occlusion. The Staked Companion is glue-free and allows for a tungsten-free delivery device.

The elimination of glue from the needle-mounting process carries with it other important benefits; the Staked Companion is compatible with baked-on silicone, silicone-free and silicone-immobilizing lubrication techniques,

which allow greater control of the silicone content, and the pre-attached needle can be virtually any length or gauge.

"With the Staked Companion Syringe, pharmaceutical manufacturers can launch their drugs in a device that provides a safe and improved user experience, drives compliance with needlestick safety regulations, eliminates many challenges in the development and regulatory process, and achieves a differentiated market position, providing a simplified path to a next-generation differentiated device," says Mr. Merhige.

Elcam Medical—Auto-Injectors for Biopharma Drug Delivery

Elcam Medical, a provider of disposable medical devices to the U.S. and European OEM markets, has developed a line of drug delivery devices designed for administration of biopharmaceutical drugs. In recent years, Elcam Medical, and its E3D (Injectable Drug Delivery Devices) Division, has been focusing on developing and manufacturing high quality and patient compliant auto-injectors for biologic drugs and other self-injectable drugs.

The Flexi-Q Drug Delivery line includes a range of disposable auto-injectors and multi-use auto-injectors designed to maximize user compliance. This product line provides a range of customization options such as low-high viscosity, liquid or lyophilized, prefilled syringes and vials for safe and simple injection, says Dr. Zucker, Vice President, Head, of Elcam Drug Delivery Devices.

Elcam's newest auto-injector under development is the Flexi-Q eMU, an electronic multi-use auto-injector. The Flexi-Q eMU-P comprises a reusable driving unit and a disposable cassette and is compatible with standard PFSs containing biologics or cartridges suitable for variable dosing. The Flexi-Q eMU-C is comprised of a reusable driving unit for use with standard 1.5-3mL cartridges suitable for variable dosing. The Flexi-Q eMU is intended for use with chronic diseases that require frequent injections. The reusable design lowers the cost per injection and reduces the volume for storage and disposal. Features include a reusable driving unit with a disposable cassette utilizing standard prefilled syringes, USB communication port, RFID drug detail recognition, and wireless communication to remote database.

Gerresheimer—Prefilled Syringes Support Ophthalmic Applications

Developments in prefilled syringes add to the tools an ophthalmologist can rely on to successfully treated diseases. "Recent developments in prefilled syringe treatment has caused a shift from surgery to injection, and brings therapy options to patients who could not be cured previously," says Bernd Zeiss, Manager Technical Support Medical Systems, Business Development, Gerresheimer.

The two largest eye therapy areas are the anterior segment of the eye where cataract surgery is performed, and the inner eye, which can be affected by diseases such as wet macular degeneration, diabetic macular edema (DME), and retinal vein occlusion.

In cataract surgery, the opaque lens is basically removed and replaced by an intra-ocular lens (IOL). In order to protect the delicate cornea cells during surgery, a prefilled syringe is used to administer hyaluronic acid into the cavities of the anterior chamber and lens.

The other field of applications comprises treatment of the inner eye by intravitreal injections of monoclonal antibodies to prevent the growth of veins, corticosteroids to fight bacterial infections, and silicone

Elcam Medical's Flexi-Q eMU is an electronic, multi-use auto-injector with disposable cassette and wireless communication.

Gerresheimer 's RTF® syringes allow for ophthalmic high-end application.

oil to fix the retina to the eye after retinal detachment.

In addition to patients, eye surgeons benefit from these prefilled syringe developments. "A prefilled syringe is handy and ready to be administered. New application systems substitute the classic vial filled with liquid or lyophilisate. Compared to a vial in combination with a disposable syringe, many preparation steps can be skipped by using a prefilled syringe. Dose errors are minimized, as the syringe already comes with the filled volume in the right concentration," says Mr. Zeiss.

Nevertheless, there are challenges with prefilled syringes. In contrast to vials, prefilled syringes are siliconized for lubrication and even if silicone oil is absolutely harmless to the human body, it may have an impact on vision. Gerresheimer's Baked-on® siliconization offers a solution, as this lubrication method reduces the amount of freely floating silicone oil droplets by more than 90%. Performance of baked-on staked-needle syringes have been tested with a variety of different plunger stoppers.

"Breakage of a syringe is an extremely rare event, but with glass syringes, in combination with highly viscous liquids administered by high pressure, surgeons and patients are afraid of this kind of failure," says Mr. Zeiss.

In addition, eye surgeons need a good grip of the syringe. RTF® syringes by Gerresheimer address these problems by the TELC® closure. Aside from offering a tamper-evidence feature, this Luer lock closure is fixed tight to the cone so loosening is hardly possible. As an alternative, ClearJect™ COP-syringes can be used. This syringe is unbreakable, and the Luer lock adapter and syringe are one piece that cannot be loosened.

Oval Medical Technologies Ltd.—Auto-Injector Technology Resolves Issues Associated With Other Devices

Oval's auto-injector technology was developed to satisfy unmet needs in the market to provide a novel primary drug container that resolves many of the fundamental limitations of glass syringes in existing auto-injectors, especially suited for biologics; a patent protected PDC closure/seal technology (cup seal and foil); improved reliability and safety; and patient-intuitive use, with no visible needle that is virtually error free.

"Oval's technology effectively eliminates key causes of unreliability and inconsistency that have led to well-documented product recalls and quality issues with marketed auto-injectors," says Bastiaan Deleeuw, Head of Business Development, Oval Medical. "It allows for smaller and more flexible auto-injector designs and is cost-competitive with the existing alternatives."

Oval's PDC technology uses advanced plastics, cyclic olefin (COC), to replace the glass syringes used in auto-injectors and the unique cup seal and foil PDC closure technology forms the basis of a smooth operation of the injection system, explains Mr. Deleeuw.

The Oval design eliminates many

of the issues that arise from glass syringes, including contamination by silicone/tungsten that cause degradation with biological drugs, drug adsorption to the glass, delamination of glass resulting in particles that can be injected, inconsistent injection times arising from sticking rubber plungers that result in the patient removing the auto-injector before the dose has been completely delivered, and unsuitable-for-delivery of formulations with viscosities greater than 15cP.

Key features of the Oval auto-injector that confer improved patient acceptability include small size, ease of self administration, concealed needle, and reduced needle-stick injuries thanks to a lock-out mechanism.

Devices can be designed for different users by modifying only the outer shell while still using the same auto-injector mechanism and primary drug container, Mr. Deleeuw points out.

Oval Medical's 1mL auto-injector

REVOX Sterilization—Meeting New Sterilization Needs For Latest Innovations

It's been more than two decades since the FDA approved a new industrial sterilization method. That long streak came to an end in May 2014 with the FDA 510(k) clearance of the OsteoSymbionics® pre-sterilized CLEARSHIELD®, a Class II cranial implant, using the REVOX® sterilization technology. The device had previously been 510(k) cleared using Ethylene Oxide (EO), a sterilization process performed in-hospital prior to surgery.

The REVOX™ technology was developed as an extended application for a Cantel Medical Peracetic Acid (PA) liquid sterilant, a market leader in the endoscope reprocessing field. The ability to achieving full sterilization via room temperature vaporization opens new opportunities to expand the range of materials suitable for use in advanced medical devices, biologics, and pharmaceuticals, and offers operational flexibility and efficiencies that were previously constrained by traditional sterilization methods.

REVOX sterilization started with an idea. Mason Schwartz, co-inventor and Lead Technical Advisor for REVOX Sterilization Solutions says the invention sprung from the knowledge that the PA chemistry was unparalleled in terms of efficacy and materials compatibility for liquid disinfection. "It consistently proved to be the most stable, gentle, fast, and effective solution in the world of endoscopy reprocessing," he says. "We knew we had a special formulation, but liquid disinfection has obvious limitations in terms of the types of things that can be sterilized using it." Nevertheless, Mr. Schwartz had the basic chemical formulation and he went to work to find a new and more effective sterilization process with PA in vapor form.

The room temperature REVOX process offers potential for removing challenges associated with other sterilization methods such as material

The PharmaCircle Drug Delivery and Formulation Newsletter and Blog

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

For over a decade, PharmaCircle has been the premier database for connecting product and pipeline information for drugs and biologics with formulation and component details, and providing due diligence level data on nearly 6,000 drug delivery technologies and delivery devices.

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

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

The PharmaCircle Drug Delivery and Formulation Newsletter - redesigned and featuring:

Kurt's Drug Delivery & Formulation News: A wrap up of the past week's top news items as selected by Kurt Sedo, Senior Vice President of PharmaCircle.

Tips and Tricks: Ideas for getting better search results more quickly and easily when using PharmaCircle, plus a periodic look at new information resources in the public domain.

Perspective & Insight: Detailed stories spotlighting and examining companies, pipelines, technologies and the numbers that impact the drug delivery business from the PharmaCircle Team and industry thought leaders.

Sign up today for the newsletter at http://www.pharmacircle.com/rc/ or email your subscription request to newsletter@pharmacircle.com.

PharmaCircle™

Providing best-in-class online information for pharmaceutics professionals and the whole team

PHARMACIRCLE™

T: 1-800-439-5130 (USA & Canada)
T: 1-760-436-1199 (International)
E: contact@pharmacircle.com
www.pharmacircle.com

compatibility issues resulting from elevated temperatures and chemical residuals, while achieving sterility assurance levels of 6 log or greater. "We're still exploring our limitations in terms of material compatibility but we're having success with the most advanced innovations that incorporate sensors, batteries, large molecule formulations, and other new innovations," says Mr. Schwartz.

He adds, "With no special ventilation or other expensive installation requirements, the REVOX sterilization method also offers manufacturers the opportunity to maintain full on-site control of manufacturing and sterilization processes to maximize cost and quality efficiencies."

REVOX room temperature sterilization offering both contract and on-site capabilities.

SHL Group—A User-Centric Approach to Advanced Drug Delivery Systems

SHL designs, develops, and manufactures a range of drug delivery devices such as auto-injectors, pen injectors, and inhalers that address existing and upcoming needs of injectable medicines. This includes the ability to accommodate various primary containers, higher drug viscosities and larger delivery volumes. With the goal of improving patient compliance, SHL's portfolio includes devices with simple operations, ultra-compact designs, ergonomic exteriors, and innovative feedback systems.

As self-administered injections become available in more therapies, device designs have to be adapted for different patient populations. "The application of human factors/usability engineering is essential to minimize user-related risks, enhance ease-of-use, and ultimately allow end users to handle the device safely and effectively," says Nicholas Heaton, Executive Director of Business Development, SHL.

Involving targeted patient groups in user studies early during research and development can help engineers better understand patient dynamics and ensure their needs are integrated into the device design. For example, patients with Rheumatoid Arthritis (RA) can have certain dexterity issues that affect their ability to uncap or grip a device properly while administering an injection. A device with more tailored uncapping and grip designs can aid users with such conditions.

SHL's Amber™ Auto Injector features an ergonomic design that embodies various grip options during cap removal and when performing an injection.

Unique identification on each container (SiO2 Medical Products)

SHL's Amber™ Auto Injector features an ergonomic design that embodies various grip options during cap removal and when performing an injection. In addition, unique surface extrusions around the cap and the viewing window create an additional friction area for better handling. Utilizing SHL's Pushclick™ technology, the Amber Auto Injector can be operated in just 2 steps – uncap and inject – and integrates essential safety features such as a permanently hidden needle and a range of audible, visual, and tactile feedback mechanisms, explains SHL Chief Industrial Designer Jochen Ratjen.

While design considerations of a patient-centric device is paramount to the success of combination products like auto-injectors and pen injectors, designing for manufacturability is just as vital to ensure that the product is producible at high volumes.

SiO2 Medical Products—Bringing the Best Features of Glass and Plastic in Parenteral Fill/Finish Containers

SiO2 Medical Products (SIO) is a vertically integrated manufacturer of primary containers. Building on its plastic technology knowledge, SiO has brought new solutions to the traditional challenges with plastic and glass containers. Using patented advanced materials science, SiO has developed a line of parenteral drug containers that offer improved performance and consistency over existing plastic and glass containers, says Peter Sagona, Vice President, SiO2.

SiOPlas™ containers are precision molded from medical-grade polymers with a thin, transparent, silicon oxide-based coating applied to the interior surface of the container. "This allows our parenteral containers to provide customers the durability of plastic with the high purity and barrier properties of glass, while eliminating the shortcomings of existing glass and plastic containers," says Brian Fitzpatrick, Program Manager, SiO2.

More complex drug formulations and an ever-increasing focus on the quality and safety of injectables requires a new approach in parenteral packaging. Mr. Sagona says SiOPlas containers provide a number of improvements over existing plastic or glass containers, such as track-and trace compability. During the manufacturing process, a SIO laser etches a unique 2D bar code and/or serial number onto each individual SiOPlas container. This is a GS1-compliant tracking ID.

Additionally, during the manufacturing process from bead to finished container, SiO performs more than 6 in-process, non-destructive quality checks on each SiOPlas container, such as scanning the interior surface to assure a particle-free container down to 50 microns.

Another improvement is there are no leachables/extractables. The silicon-oxide barrier coating system applied to each container provides a barrier to any leachables. In addition, SiOPlas containers use no silicone oil, so aggregation will not be seen. Additionally, SiO's containers are stable across a wide pH range, minimizing the need for reformulation. And, the pure silicon-oxide plasma coating applied to the container interior provides an oxygen barrier similar to containers constructed of glass, and because it is pure SiO2 there are no heavy metals or trace impurities typically found in borosilicate glass, eliminating the mechanism of delamination. "With these advances, the drug product will see improved shelf life and reliability," says Larry Thomas, Head of Business Development, SiO2.

Terumo's Plajex™ ready-to-use prefillable syringe platform features i-coating™ technology on plunger stops to create a silicone oil-free system.

Terumo Global Pharmaceutical Solutions—Addressing Regulatory and Viscosity Challenges

The pharmaceutical industry is challenged by new regulations and complex drug products that require new and innovative delivery techniques for patient care. Regulators are requesting that the industry seek improvements in drug administration, quality and safety, and risk mitigation of drug degradation. In addition there is a renewed focus on improving the therapeutic outcome and patients' quality of life.

Terumo Corporation has more than 15 years of experience in plastic prefilled syringes and offers technology that addresses regulatory requirements. Rutger Vandiest, Marketing Director Terumo, explains that therapeutic protein products are at the forefront of pharmaceutical development and are driving the market for parenteral administered drug products. "These biopharmaceuticals show great prospects for therapeutic treatment for various diseases; many of those are chronic diseases, requiring frequent self-medication by the patients. Protein and monoclonal antibody drug products and their administration by injection are posing several issues and risks, in particular immune responses to therapeutic proteins that adversely affect their efficacy and safety."

Several issues related to traditional primary drug containers and prefilled syringes may add to these challenges and/or generate other problems, such as silicone oil interaction, tungsten, aggregation, (sub-) visible particles, and glass delamination/breakage. Furthermore, proteins and monoclonal antibodies are complex large molecules often requiring high concentrations to obtain the immunogenic response. This can create injectability challenges due to viscous effects of high concentrations of drug products.

The introduction of advanced technologies and application of specific know-how for parenteral drug delivery, such as polymer-based prefillable syringes and the application of a novel silicone oil-free system (i-coating™ technology), can address many of these issues and challenges effectively.

Mr. Vandiest explains how Terumo introduced its Plajex™, COP ready-to-use prefillable syringe platform with i-coating technology on plunger stoppers to create a silicon oil-free system. "At the same time, by using steam sterilization, we are excluding protein degradation through oxidation as a result of free radicals generated from sterilization by irradiation."

Mr. Vandiest further emphasizes that innovations in needle technology bring solutions towards improving injectability for manually given injections as well as for applications with auto-injectors. Terumo created a double-tapered needle technology for use with high viscous drug products.

"We aim to ensure that medication is delivered safely and reliably, ensuring the efficacy of treatment and patient outcome, while minimizing patient trauma, pain, and discomfort."

Vetter—Tackling Issues of Traceability and Customization

The industry trend toward self-administration continues to drive to an ever-increasing demand for easy-to-use delivery systems such as prefilled syringes, pens, and auto-injectors with the goal of patient safety, compliance, and convenience. In addition, regulatory guidelines with regards to combination products and safety features have an impact on the prefilled syringe design and the requirements for medical devices. And along with new innovative materials, there is also a strong development in the primary and secondary packaging for syringe systems that enable more product-specific handling.

Vetter is a contract development and manufacturing organization (CDMO) specializing in the aseptic filling and packaging of syringes,

"The number of counterfeit drugs on the market is growing and has quickly become a serious global challenge. Lawmakers and regulatory agencies around the world have responded by creating guidelines to increase drug safety. "The key is serialization and track-and-trace, meaning the distinct identification of the smallest packaging unit with a unique identification number."

cartridges, and vials. As a full-service provider and strategic partner, Vetter supports pharmaceutical and biotech clients with liquid or lyophilized substances, from preclinical development through global market supply and life cycle management, explains Bernd Stauss, Senior Vice President Pharmaceutical Production/Engineering, Vetter. "We help to find the most suitable delivery system for our customer's drug product, including manufacturing processes as well as customized packaging."

"Our responsibility is to keep abreast of the challenges of a changing business and regulatory environment, and investing in new technologies and solutions that best meet our customer's needs," he continues. This involves reliable and flexible processes that allow for the highest possible product quality: the number of counterfeit drugs on the market is growing and has quickly become a serious global challenge. Lawmakers and regulatory agencies around the world have responded by creating guidelines to increase drug safety. "The key is serialization and track-and-trace, meaning the distinct identification of the smallest packaging unit with a unique identification number."

In response, Vetter offers several options for the drug serialization. These include the availability of different serial number and code formats, interfaces and reports, and various aggregation depths.

West Pharmaceutical Services, Inc.—Packaging and Delivery Systems Combine to Prevent Needlestick Injury

West Pharmaceutical Services, Inc., has made several advances in drug packaging and delivery systems

The West NovaGuard™ SA safety system helps protect healthcare workers and patients against accidental needlestick injuries when using a prefilled syringe. (Copyright 2013 West Pharmaceutical Services, Inc.)

and materials in recent years. The company's NovaPure® components, which include FluroTec®-coated closures provide quality for sensitive biologic drugs and combination products, and have been incorporated into West's primary containers and prefillable solutions. West also offers Daikyo Crystal Zenith® (CZ) prefilled syringes for biopharmaceutical and pH-sensitive drug products that have unique packaging requirements.

"West has combined its packaging knowledge with innovative delivery systems in order to better meet the needs of patients and healthcare providers," explains Graham Reynolds, Vice President, Marketing and Communications, West Pharmaceutical Services, Inc. The ConfiDose® auto-injector system technology platform can be used with a CZ 1mL insert needle syringe or traditional prefillable syringe. The SmartDose® electronic wearable injector and features a CZ-prefilled cartridge. "These platforms offer a range of options for dose volume and injection time and are designed to help improve patient compliance and outcomes, while meeting the challenges of today's innovative drug products," he says.

To help ensure safety of patients when using its drug containment and delivery solutions, West also offers solutions to guard against needle-stick injuries. West has developed an portfolio of offerings that enable safe and effective drug administration, including a range of active and passive safety systems. The NovaGuard™ SA (staked-needle automatic) safety system is a user-controlled safety system that shields the exposed needle of a prefilled syringe before and after injection, which helps reduce the risk of accidental needlestick and the transmission of bloodborne pathogens.

West's NovaGuard™ LP passive safety system for Luer lock syringes features a plastic shield surrounding the needle before injection. Once the needle is pressed to the skin, the protective shield is activated and covers the needle as it is withdrawn.

Additionally, West's éris™ passive safety system is used for staked needle prefillable syringes outside of North America to reduce the risk of needle-stick injuries. ◆

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

References

1. Pre-Filled Syringes Market Forecast 2015-2025: Prospects for Leading Companies in Plastic Pre-Filled Syringes, Pen Injectors & Autoinjectors, and Glass Pre-Filled Syringes, Visiongain, (https://www.visiongain.com/Report/1397/Pre-Filled-Syringes-Market-Forecast-2015-2025), February 2015, accessed April 14, 2015.
2. Pre-Filled Syringes Market: 2015 – 2030 – Opportunities, Challenges, Strategies & Forecasts, Reportlinker, Nov. 13, 2014, http://www.prnewswire.com/news-releases/the-pre-filled-syringes-market-2015--2030--opportunities-challenges-strategies--forecasts-282630371.html, accessed April 14, 2015.
3. The Future of Alliances and Partnerships in the Pre-Filled Syringes Market to 2020, Smithers Rapra, February 2015, http://www.eandl-conference.com/news/2015/february/global-market-for-pre-filled-syringes-forecast-to, accessed April 14, 2015.

A strategic level partnering event with a wide range of drug delivery technologies

PODD

5TH ANNUAL

PARTNERSHIPS OPPORTUNITIES IN DRUG DELIVERY

OCTOBER 5 - 6, 2015 **INTERCONTINENTAL BOSTON, BOSTON, MA**

KEYNOTE
Robert Langer, PhD
David H. Koch Institute Professor
MIT

INDUSTRY KEYNOTE
Bahija Jallal, PhD
EVP
MedImmune

CEO KEYNOTE
Stéphane Bancel
CEO
Moderna Therapeutics

CHAIR
Barbara Lueckel, PhD
Global Business Development Director
Roche

DDS TECHNOLOGY
Julia Rashba-Step, PhD
Senior Director, Novel Delivery Technologies
Pfizer BioTherapeutics

RNA THERAPEUTICS
Jessica Ballinger
Senior Director, Protein Pharmaceutical Development
Biogen Idec

SANOFI CASE STUDY
Paul Jansen
VP, Medical Device Development
Sanofi

LARGE VOLUME DELIVERY
Anand Subramony, PhD
VP, Drug Delivery & Device Development
MedImmune

DRUG DELIVERY TECHNOLOGY PRESENTATIONS IN THREE TRACKS

Injectable Formulation Technologies • Non-Injectable Formulation Technologies
Drug Delivery Device Technologies

Organized by

THEconferenceFORUM

15% discount with code DDD

Media Partner

Drug Development & Delivery

Follow us on Twitter @ConferenceForum #PODD2015

REGISTER AT WWW.THECONFERENCEFORUM.ORG OR CALL 646-350-2580

Drug Development
EXECUTIVE

Yoshiki Matsuda
Director
SOLIZE Corporation

SOLIZE: 3D Data-Based Engineering & Manufacturing to Accelerate Delivery Device Development

SOLIZE, established in 1990, is a technically focused group with more than 1,300 engineers fluent in product design, analysis, prototyping, tooling, and manufacturing technologies. We provide support for the complete product development cycle to our global clients from branches located in Japan, China, India, and the UK. With 3D CAD expertise and engineering technology developed across a variety of industries throughout the past 25 years, SOLIZE is now proactively participating and driving the success of product development in the drug delivery device market. We have been deeply involved in product development of the automotive industry. Our high-speed prototype manufacturing technology, which effectively combines our advanced 3D design and simulation expertise with optimal use of 3D printing technique, has made the development smarter and shorter. Our Design for Manufacture (DFM) and 3D-based standardized tool manufacturing techniques revolutionized the mobile phone industry by slashing the lead time on prototype tooling to 1/24th of the standard duration. This enabled us to capture more than 70% of the global market share of the prototype development in the mobile phone industry. *Drug Development & Delivery* recently spoke with Yoshiki Matsuda, Director of SOLIZE, to discuss how the company can create new and innovative solutions to accelerate the development of devices and combination products built thereon.

"The key for development has always been SPEED. We learned this from our long-term experience in the automotive and mobile phone industries. SOLIZE leverages the power of 3D data and engineering expertise in prototypes and tooling. Our DFM enables clients to have a seamless product development environment and to realize product validation/verification at an early stage of development. We continue to innovate device development in terms of SPEED and contribute to the realization and value of drug delivery devices."

Q: What is the value SOLIZE offers to the development of drug delivery devices?

A: The market uptake of biotechnology drug products is growing rapidly and thus is driving increased demands on the functionality, mechanical complexity, and variety of materials of delivery devices. In the process of developing these devices more time and effort is required to complete studies such as User Requirements Specification (URS), Functional Requirements Specification (FRS), and Proof-of-Concept (PoC).

The value SOLIZE provides is in quickly designing and manufacturing prototypes with the high-quality tolerances, finishes, and functionality required to complete the tests and evaluations required by these advanced delivery devices. Just like we have demonstrated in the automotive and mobile phone industries, we deliver speed and quality from the early stage of delivery device development.

We believe our prototypes not only directly accelerate the development of devices, but also enable the front-loading of clinical trials of combination products built thereon. In the constantly changing regulatory environment, quicker development results in quicker entry into the market. This speed means you have a better chance of finishing the development in the same world in which you started, securing competitive advantages and growth opportunities.

Q: How does SOLIZE work with its clients, and what have you achieved?

A: SOLIZE has worked with clients ranging from the earliest of new ventures to the world's leading medical device manufacturers, design consultancies, and pharmaceutical companies. We cover a wide variety of high-end delivery devices, including syringe pens, autoinjectors, infusion systems, dry powder inhalers, nasal pump systems, and eye droppers. With our proprietary 3D design, engineering, and manufacturing technology, we provide comprehensive support from product design and analysis through prototyping, and support of mass production.

Because we can provide fully functional and well-toleranced components in just 3 to 4 weeks, our clients are able to accelerate technical studies, user acceptance tests, and market studies that are now considered a major part of human factors engineering. For example, during an autoinjector project for our client in the UK, we were involved early and in-depth during the product development phase, leveraging our DFM to finalize the product design fast. We engineered and manufactured 11 tools in 4 weeks, and supplied more than 5,000 sets of fully functional devices without a single malfunction. Our client was able to run their development loop of PoC and market studies in half of the time they expected.

For the market studies in particular, a high-profile finish and fully functional prototypes add persuasiveness to support the adoption of their innovative devices. We are currently in the middle of preparation for molding 10,000 sets of prototype parts under cleanroom ISO8 conditions, providing support for the regulatory approval process. This is a typical example of our development support usage; providing a seamless development experience from early development through clinical studies and contributing to the reduction of total development lead time.

As an another example, we had a client request to modify an existing off-patent DPI inhaler device. Because there was not a single manufacturing reference available for the existing device, we proposed a comprehensive product development support strategy using our reverse-engineering expertise. We first CT scan the existing device and then carefully

analyzed how each plastic component functions within the device. This allowed us to determine the correct product contours, including each component's assembly mechanism, raw material usage, as well as the tolerance setting of each critical dimension. With the product design reverse-engineered, we immediately applied our DFM and turned the product data into manufacturable data. We then modified the design of the blister cover to meet the new regulatory requirement, and manufactured 12 sets of injecting molding tools, each with a capacity to produce 100,000 sets of plastic components to fulfill needs from the early development through clinical studies to the early industrialization phase. We finished all of these activities within 2 months and enabled our clients to have the working devices ready for their clinical Phase III study in plenty of time.

SOLIZE does not simply provide parts. We always seek to clearly understand our clients' needs and provide the optimal engineering support and flexible short- and long-run manufacturing capability to fit their budgets and applications.

Q: How are you able to be so much faster than the competition?

A: SOLIZE's 3D data design and analysis skills combined with the tool manufacturing know-how is the key. When manufacturing prototype tooling, we leverage these assets digitally to optimize the tool design, tool structure, material selection, and its cutting methods. With these best practices, we are able to propose the optimized product and tool design in half of the time compared to the existing manufacturers, minimizing the manufacturing effort.

Our DFM also contributes greatly in reducing the product design lead time. We begin in-depth DFM exercises very early in our clients' product design phase. By providing these DFM iterations, we make the lives of our clients' design engineers easier, allowing them to focus on the maturation of functionality and aesthetics of the device, leaving all of the design validation of manufacturability to SOLIZE.

Because our engineers have access to 10,000 tools worth of DFM data and tooling knowledge, our experts can directly apply the tool engineering know-how earned across a wide range of industry and products to provide accurate DFM within 24 hours. We provide support for a broad range of products, from large-scale diagnostic devices and hand-held medical devices to tiny pieces of a needle shield.

This new style of DFM-based design and prototyping service provides much quicker and efficient product development with smoother and more flexible production ramps to meet all our clients' development needs.

Q: I understand that SOLIZE is fast, but how can you also maintain high quality?

A: Our DFM also contributes greatly to ensure the quality of prototypes built during the development phase. Because our DFM optimizes the product design considering its manufacturability, our prototype tools are always made with minimal risk of quality defects. In addition, we manufacture prototypes with our ISO9001- and ISO13485-certified process of quality control.

We exceed the speed, quality, and validation requirements of the ordinary prototypes. As our clients will attest, we have succeeded in revolutionizing prototype development.

Q: How were you able to revolutionize the current prototype development process ?

A: Normally, prototype manufacturing is known to produce one-off, unrepeatable parts made under gray room. But we are different. Not only do we provide quality and delivery speed, we also offer choice in supply quantity as well as the availability of cleanroom molding.

By supplying fully automatically made, sustainable prototype devices ensured by our DFM concept, we meet the validation requirement equivalent to that of pilot- or small-scale production tooling, allowing us to produce over 100,000 sets of devices under cleanroom conditions. So essentially, we offer pilot tool quality service and experience with the cost and lead time of prototype tooling. This allows our clients to have a lot of flexibility in choosing when to start realizing the prototypes, from initial functional testing through clinical studies, as well as marketing samples. This unified proto-pilot tooling service, including early cleanroom molding capability, contributes to the reduction of development lead time for both the device and the combination product. ◆

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

PATIENT SAFETY NARRATIVES

Clinical Trials: Medical Writing & Patient Safety Narratives

By: Yvonne Moores

INTRODUCTION

Patient safety narratives are a key element in clinical study reporting. We will look at current regulatory requirements regarding safety narratives, a proposed process for their development, and review and examine ways to simplify the reporting process. These procedures are aimed at reducing the burden of time and cost.

Patient safety narratives should be prepared for all phases of clinical studies, whether conducted in healthy volunteers or in patients with the disease/condition under study. For ease of reporting, we shall refer to patient safety narratives throughout this discussion (although narratives for healthy volunteers/subjects in Phase I studies should be included).

ICH GUIDANCE ON CLINICAL STUDY REPORTS

According to the International Conference on Harmonisation (ICH) tripartite guideline on the Structure and Content of Clinical Study Reports (CSRs) E3 (Section 12.3.2), a CSR should contain brief narratives describing each death, each other serious adverse event, and other significant adverse events that are judged to be of special interest because of clinical importance.[1]

The guidance document indicates that events clearly unrelated to the test drug/investigational product may be omitted or described very briefly. In the interests of transparent reporting, it is suggested herein that patient safety narratives be prepared for all criteria detailed above.

A patient safety narrative provides a full and clinically relevant, chronological account of the progression of an event experienced during or immediately following a clinical study.

As Per ICH E3 guidelines, a patient safety narrative should describe the following:

- the nature, intensity, and outcome of the event
- the clinical course leading to the event
- an indication of timing relevant to study drug administration
- relevant laboratory measures
- action taken with the study drug (and timing) in relation to the event
- treatment or intervention
- post-mortem findings (if applicable)
- Investigator's and Sponsor's (if appropriate) opinion on causality

Specifically, narratives should include the following:

- patient identifier
- age and sex of patient; general clinical condition of patient, if appropriate
- disease being treated (if this is the same for all patients, this information is not required) with duration (of current episode) of illness
- relevant concomitant/previous illnesses with details of occurrence/duration
- relevant concomitant/previous medication with details of dosage
- test drug administered, including dose, if this varied among patients, and length of time administered

FORMAT & LOCATION FOR NARRATIVES

The guidance is less specific with regard to the format and location of patient safety narratives, stating [they] can be placed either in the text of the CSR or in Section 14.3.3 (Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events), depending on their number. Although no cut-off is specified, this author suggests that five or fewer narratives may logically and clearly be reported in text, although this is dependent on several factors, including therapeutic area, complexity of reporting, relevant course of events, and flow of information in the CSR. If in doubt, it is recommended that narratives should be prepared as separate documents and compiled in Section 14.3.3 during CSR publishing.

FIGURE 1

ADDITIONAL CONSIDERATIONS

It is important to identify the approximate number of patient safety narratives to be prepared early in the planning process. This determines the narrative format and impacts the timing of production (that is, whether prior to or following database lock).

If patient safety narratives are written from draft (unclean) data prior to database lock, updates are required based on the final (clean) data. This approach can consume more time than preparing all narratives after database lock, but is more feasible for projects where a large number of narratives are required to be drafted in a short span (eg, for a regulatory submission).

Good communication is essential for the success of any project, but is particularly important for projects including the preparation of a large number of patient safety narratives. There should be a good understanding of requirements by all parties, and agreement of the scope and main principles prior to project start.

SOURCE DATA

A Medical Writer will use various sources of information when preparing patient safety narratives. These include Council for International Organizations of Medical Sciences (CIOMS) forms, Case Report Forms (CRFs), MedWatch

forms, Data Clarification Forms (DCFs), and clinical database listings.

Because source data are captured during study conduct and narratives are often prepared prior to database reconciliation and lock, a Medical Writer is often able to identify data discrepancies between the clinical study database and other sources. The situation is complicated further as CIOMS forms are updated on an ongoing basis during a clinical study. A Medical Writer is well placed to assess the impact of any discrepancies and provide feedback to a Sponsor, thereby assisting with the data cleaning process.

PROCESS

The narrative production process differs across companies and is dependent to a small degree on whether reporting is performed internally or by a Clinical Research Organization (CRO). The emphasis of this discussion will be reporting by the CRO, and specifically Quanticate.

When significant numbers of narratives are required, it is useful to develop a template to define overall structure and content, and obtain approval from all stakeholders prior to initiation of work. In the template, consideration should be given to a number of factors, including order of information, sentence structure, date format, relevance of specific medical history and concomitant medications, use of trade or generic names for medications, and whether normal ranges should be included for some/all laboratory test results.

A comprehensive template that is flexible enough to suit Sponsor requirements whilst maintaining internal consistency is a very effective tool. However, care should be taken to ensure all writers involved in the preparation of the narratives understand the limitations of the template, and feel empowered to deviate from it as data require for transparent reporting.

It is recommended that patient safety narratives be produced as follows:

- Preparation of first draft narrative from patient/subject data by the Medical Writer
- Scientific and editorial peer review by the CRO project lead to check the document is accurate, complete, and consistent with requirements and across documents
- Clinical review of draft narrative: It is recommended that this be performed by the Sponsor or designate, although the CRO can provide this service as necessary
- Medical Writer revision based on clinical review: If the writer does not agree with clinical review comments, for example, when requested amendments conflict with the evidence or when changes would introduce inconsistencies between narratives, or when review comments are unclear, these should be discussed with the Sponsor or designate, as appropriate, and responses retained on file
- Quality control (QC) review based on final patient/subject data. Given the often large number of narratives required for individual studies and small size of each document relative to the CSR, it is recommended that a single QC review be performed toward the end of the process, rather than QC review of the first draft and final deliverable

FIGURE 2

- Medical Writer revision based on QC review findings. Note: when significant findings are identified during QC review, these should be discussed with the Sponsor and clinical reviewer, as appropriate, and further updates should be checked for consistency and accuracy
- Approval by the Sponsor after a final review

The process can be scaled according to number of narratives required. In scenarios in which there are few subjects/patients with events that require safety narratives, a Sponsor may prefer to review the narratives as part of the draft CSR, which would normally undergo QC review prior to release, and a final QC review prior to finalization.

CONSISTENCY

When preparing a large number of documents for a single purpose, including patient safety narratives, it is essential that consistency is maintained. A large project will require the involvement of several Medical Writers. A CRO project lead should be assigned to act as a single point of contact to work closely with the Sponsor and other stakeholders. In addition to managing communication and delivery, he/she should act as a peer reviewer, ensuring consistency of reporting across all narratives, reviewing as if he/she was part of the Sponsor study team.

During a large project, it is not unusual for the scope of work and content of narratives to evolve over time, particularly when narratives are prepared on an ongoing basis. For example, it may become apparent from events reported during an ongoing study that specific endpoints (eg, liver function test results) are more important than considered originally. An effective single point of contact will be able to work with the Sponsor to ensure the process specifications are adapted quickly, and will disseminate the relevant information to the writing team in a timely manner, through meetings and the use of study specific documents. When it is necessary to update narratives already prepared and possibly reviewed, this person will again work with the Sponsor to identify a solution that integrates updates into the overall narrative development process in the most effective and expeditious way.

TRACKING

The majority of Phase II IV studies have a large number of patients meeting pre agreed patient safety narrative criteria. Excellent project management skills are essential for tracking such projects in which a large number of narratives are written by several writers, particularly later in a project when the delivery of newly drafted narratives overlaps with the return of clinical review comments and QC checking, and finalization of narratives at the end of the process. The importance of careful management should not be underestimated; ensuring accuracy and consistency across a large number of narratives is a challenging and time consuming task.

Tracking is critical in projects involving a large number of patient safety narratives. Microsoft Excel spreadsheets can be used as an excellent tracking tool for managing high volumes of narratives, and it is particularly useful if all stakeholders are able to adapt their processes, if necessary, to share the same documents. In practice, this may not be possible, particularly when a CRO, for example, records confidential information, such as time spent per narrative for budgetary purposes.

DELIVERY

Whatever the size of the project, it is beneficial to deliver patient safety narratives in batches with pre-agreed units/numbers for Sponsor review. The batch size will be dependent on total number of narratives to be prepared, data availability, completion timelines, number of writers working on the project, and reviewer availability, and should take into account any ramp up time required.

Experience shows that it is preferable to deliver a small number of patient safety narratives (eg, five to 10 depending on complexity) prepared by one writer (usually the project lead) for Sponsor review in the first instance. This allows for fine tuning of the content, presentation, and process prior to implementing preparation on a larger scale. Restricting the number of people involved early in the process allows for faster resolution of any issues such that a streamlined process can be agreed quickly and minimizes confusion when rolled out to the larger team. By working in this way, duplication of efforts can be kept to a minimum, which is beneficial to

all parties. The in house team can subsequently be trained on the agreed Sponsor requirements.

When sending the narratives for review, it is advisable for the CRO project lead to clearly state the timeframe within which all review comments should be returned, thereby minimizing unnecessary delays, and to request that comments from all reviewers be provided in a consolidated manner.

FUTURE DIRECTIONS

CIOMS Forms

It is becoming more common for Sponsors to consider including direct links to CIOMS forms from CSR appendices instead of including individual patient safety narratives. This approach should be used with caution. CIOMS forms are completed by an Investigator in the country in which the study is being conducted; sometimes, with English not his/her fist language. These forms are updated frequently as key information becomes available, which makes data repetitive and unwieldy. One patient may have several CIOMS forms for separate events, which cross reference one another. A Medical Writer can spend several hours distilling the most relevant and up-to-date information from such forms in order to prepare a narrative that is succinct, accurate, and readable for a single patient. Because the purpose of a patient safety narrative is to present a full and clinically relevant, chronological account of the progression of an event or events, a regulatory reviewer may not take kindly to having to derive a clear account from one or more lengthy CIOMS report(s).

Furthermore, the Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorization Applications, specifies that in Appendix 16.3 of the CSR, CIOMS reports (or equivalent) and CRFs should be available on request.[2] Because CIOMS forms should be made available as required and are not mandated, it may be considered less acceptable for them to be linked routinely to the CSR in place of patient safety narratives.

Automation of Patient Safety Narrative Preparation

Another development in clinical study reporting is the automation of patient safety narrative preparation using programming and statistical support to prepare output directly from SAS datasets. Several case studies and papers are publicly available that document the benefits of such an approach (which include increased standardization, reduced preparation time, and reduced cost). With time invested at the start of an individual project or program of work to define the fields to be presented, the benefits are real, particularly for patient safety narratives for significant non serious adverse events that are judged to be of special interest.

There are some limitations to this approach that should be considered at the outset:

- Serious Adverse Events - Because data relating to serious adverse events are obtained directly from other sources, such as CIOMS forms, routine automation of reporting is generally not practicable. However, such narratives can be partially automated with information such as demographics, study treatments, event details (onset and resolution dates, severity, relationship to study drug, etc), prior medications, ongoing medications at event onset, and medications started during an event, output as routine. Such information is useful to the Medical Writer and can save a significant amount of time when drafting a narrative.

- Timing - As detailed above, the timing of narrative preparation is a key decision at the start of the reporting process. When following an automated process, there is little benefit to starting prior to database lock as any changes made during Medical Writer review will be lost when the narratives are re-run from clean data. If timings are such that increased efficiencies are required, this approach may be followed as long as the programmed outputs based on clean and draft data are compared, preferably via an automated process, with changes flagged to the Medical Writer for inclusion late in the narrative writing process, but ideally prior to Sponsor review.

Working with Sponsors, a low-cost solution is available by providing defined output when SAS datasets are provided in a specific format. If SAS

datasets are not available, but other data formats such as Microsoft Excel spreadsheets are used, the same information may be extracted through additional programming techniques. It is recommended that Medical Writer review be included to ensure complete, coherent, and consistent reporting.

INDIVIDUAL CASE SAFETY REPORTS

It is important to avoid confusion between patient safety narratives and Individual Case Safety Reports (ICSRs). ICSRs are a core component of pharmacovigilance (PV) services and drug safety, and differ from patient safety narratives in a number of respects.

A patient safety narrative in, or appended to, a CSR describes all relevant events for a single patient, with relevant background information as detailed above. An ICSR concerns one patient, one or more identifiable reporter(s), one or more suspected adverse reaction(s) that are clinically and temporally associated, and one or more suspected medicinal product(s).[3] In the context of a clinical trial, an individual case is the information provided by a primary source to describe a serious adverse event related or unrelated to the administration of one or more investigational medicinal products to an individual patient at a particular point of time.[4] The event reported should be the diagnosis. If a diagnosis has not been made at that time, the case may contain several signs and symptoms instead, and therefore, more than one reported event. ICSRs prepared post-marketing can differ from this in that several event terms may be reported in a single case; these events should be temporally or clinically associated, and they will be ordered according to clinical relevance for the product, ie, a serious unexpected event would be designated the "primary event" for reporting purposes, whereas non-serious or expected events would be ranked lower within the case. Furthermore, in post-marketing ICSRs, all spontaneous reported events are considered related to the medicinal product unless specified otherwise by the reporter, whereas in a clinical setting, the Investigator makes his/her interpretation as to causality.

The regulations pertaining to ICSRs are both complex and precise and dictate that reports be presented in a standardised format. This can prove to be challenging, particularly for smaller companies involved in drug development, and they often outsource this work to CROs who can provide an end-to-end PV service on their behalf. ◆

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

REFERENCES

1. International Conference on Harmonisation. July 1996. Topic E3 Structure and Content of Clinical Study Reports.
2. EMEA (now EMA; European Medicines Agency). December 2004. Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorisation Applications.
3. Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. 2011. Part II [ONLINE] Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. [Accessed 29 January 2014].
4. Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. 2011. Annex 1.2. [ONLINE] Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. [Accessed 29 January 2014].

BIOGRAPHY

Yvonne Moores is Head of Operations at Quanticate (www.quanticate.com). She joined the company in 2008 after working as a Programming Group Manager at AstraZeneca for eight years. In collaboration with Quanticate's Medical Writing and Pharmavogilance specialists, Yvonne and her team have authored this and several other articles around industry topics related to medical writing and PV. Quanticate Medical Writers are experts in medical narrative preparation, having worked closely with several customers preparing narratives in recent years. For further information, Email: enquiries@quanticate.com.

Technology & Services
SHOWCASE

ANALYTICAL SUPPORT SERVICES

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

CDMO SERVICES

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

STERILE PARENTERAL CONTRACT MANUFACTURING

As a parenterals specialist with over 80 years of expertise, **Baxter's BioPharma Solutions** business offers unique drug delivery systems and a variety of sterile contract manufacturing form/fill/finish services and solutions for injectables, designed to meet complex and traditional sterile manufacturing challenges. A leader in pharmaceutical contract manufacturing for more than 30 years, BioPharma Solutions' esteemed scientists provide a wealth of industry experience in biologics, small molecules, vaccines, and cytotoxics (including ADCs). Offering resources to help you solve the high-stakes challenges you face in today's complex parenteral marketplace, we know that the work we do is ultimately vital to the patients you serve. For more information, visit **www.baxterbiopharmasolutions.com** or contact Baxter BioPharma Solutions at (800) 4-BAXTER.

HPMC CAPSULES

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

Technology & Services
SHOWCASE

ODT TECHNOLOGY

Catalent's Zydis® ODT fast-dissolve formulation is a unique, freeze-dried oral dosage form that disperses instantly in the mouth, requiring no water. This may enhance the molecule's performance and may also contribute toward better patient compliance. With more than 20 products launched in 50 countries, Zydis is the world's best-in- class, orally disintegrating tablet (ODT) technology. Whether to advance pharmacokinetics through pre-gastric absorption, improve patient compliance, or add marketing advantage to a valued brand, Catalent's customers draw on Zydis fast- dissolve technology to potentially enhance investment value and accelerate a product's potential. Catalent has now expanded the Zydis technology platform to include Zydis Bio, to deliver fast-dissolve formulations of large molecule proteins and peptides, overcoming the traditional oral delivery challenges of such therapies. For more information, contact Catalent at (888) SOLUTION or visit **www.catalent.com**.

FULL-SERVICE CDMO

CordenPharma is your full-service CDMO partner in the Contract Development & Manufacturing of APIs, Drug Products, and associated Packaging Services for 6 technology platforms: Peptides/Lipids/Carbohydrates, Injectables, Highly Potent, Small Molecules, Antibiotics, and Oncology. With multiple cGMP manufacturing facilities across Europe and the US, CordenPharma experts translate your complex ideas into high-value products at any stage of development. CordenPharma provides proprietary peptide, lipid, and carbohydrate technologies for cGMP-compliant products and services. We additionally specialize in the manufacturing and containment of highly potent peptide APIs (with exposure limits as low as 1 ng/m3), highly potent formulations (solid forms), cephalosporins & penicillins (oral & sterile), oncology drug products (oral & sterile), and packaging. Visit CordenPharma at Tides 2015 - Booth 203 & Bio 2015 - Booth 3326 or visit **www.cordenpharma.com**.

REGULATORY DOCUMENTATION

With the ever-increasing regulatory challenges drug manufacturers are facing, creating documentation for your pharmaceutical products on your own can be costly and time-consuming. That's why we developed the EMPROVE® concept. With a portfolio of 400 raw materials, EMD Millipore helps you obtain the documentation and approvals you need to bring your products to market faster than ever. Backed by our proven expertise and reputation for uncompromising reliability, you can avoid potential error sources of manual documentation. Benefits include speed approval preparation for faster time to market, time and money savings, and creating formulations with full regulatory compliance. Our EMPROVE dossiers comprise detailed, usage-specific documentation that includes information on manufacturing, test methods, purity, and stability data, helping you to successfully navigate regulatory challenges. For more information, visit EMD Millipore at **www.emdmillipore.com/emprov**e.

DRUG DELIVERY SYSTEMS

Founded in 2000, **Insulet Corporation** is an innovative medical device company based in Billerica, MA. The revolutionary OmniPod Insulin Management System has been used to treat thousands of patients worldwide. Since its launch ten years ago, the wearable patch pump platform has expanded into multiple other drug delivery applications. The OmniPod is a discreet and easy-to-use system with no tubing; automated, virtually pain-free insertion; and a simple, intuitive user interface. For more information, contact Insulet at **drugdelivery@insulet.com** or (866) 941-4576.

Technology & Services Showcase

Airless Bottle

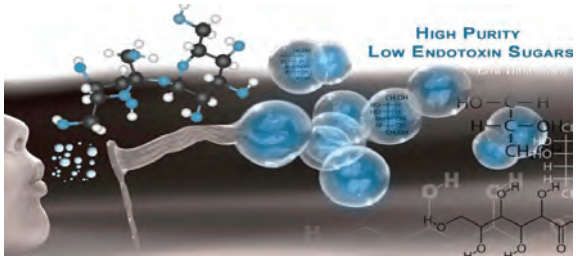
LABLABO's new EasyFoil bottle is fitted with a pouch consisting of an aluminum multilayer film rolled up and welded around a superior ring and an inferior cup, both produced in a thick plastic material. The film is composed of an exterior PET layer and an interior PP or PE layer wrapping a central aluminum layer of 12 microns in thickness. Depending on the nature of the product used, the internal layer choice will be PP or PE, the ring and cup being produced in the same material with a sufficient thickness to provide a perfect barrier, especially against oxygen or UV. EasyFoil accepts the most viscous products (> 100.000 cps) and the most fluid (alcohol) and offers excellent restitution, the bottle could be used upside-down, precise dosage delivery, or containment of the pouch at a stand still position, an ideal packaging for transdermal applications. For more information, visit Lablabo at **www.lablabo.com**, or e-mail l.khoury@lablabo.fr

Development & Manufacturing

Patheon®
Performance the World Over®

Patheon, a business unit of DPx Holdings B.V., is a leading provider of contract development and commercial manufacturing (CDMO) services to the pharmaceutical and biotechnology sectors. The company offers one of the broadest sets of solutions to customers, including commercial manufacturing, drug product services, biologics, pharmaceutical product development services, and active pharmaceutical ingredients (APIs). With a reputation for quality, scientific technical excellence, the company has more than 20 locations and 8,000 employees across North America, Europe, Latin America, and Australia. For more information, see Patheon at BIO International, Philadelphia, Booth No. 3613 or visit **www.patheon.com**.

Specialized Products & Services



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

Knowledge Management

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

Technology & Services
Showcase

Advanced Medical Technology

Terumo Corporation, founded in 1921, is a global and innovative medical technology company of Japanese origin. Today - with almost 100 years of experience - Terumo offers you advanced technology that covers product design, development, quality management, manufacturing, logistics, customer service, and regulatory expertise. Our PLAJEX™ Ready-to-Fill polymer syringes have specific features that address several current issues with protein/peptide biopharmaceuticals, such as aggregation, viscous injection, and reduction of (sub-) visible particles. Among these features, PLAJEX syringes are steam sterilized and utilize proprietary i-coating™ technology to provide a silicone oil-free platform for applications requiring low reactive containers. For more information, visit Terumo Corporation "Innovating at the Speed of Life" at **www.terumo-gps.com/US/**.

Wearable Injectors Platform

Unilife's wearable injector platform is prefilled, preassembled, and fully customizable to specific drug, patient, and user needs. Designed for use with standard materials and filling processes, they require no terminal sterilization. Only three simple steps are required for patients to peel, stick, and click. Suitable for doses between 1 mL and 15 mL, with bolus, basal, and variable rate systems available. Customization options include removable electronics and Bluetooth LE. For more information, contact Unilife at (717) 384-3400, info@unilife.com, or **www.unilife.com**.

Electronic Wearable Injector

Intuitive and easy to use, the SmartDose® injector is designed to take patients out of the clinical setting and lets them get on with their lives. Designed for use with a Daikyo Crystal Zenith® polymer cartridge, the SmartDose injector is an ideal solution for high-viscosity formulations and for delivery volumes greater than 1 mL. Designed and manufactured by West, this single-dose disposable unit with integrated needle safety has audible and visual cues, and a pre-programmable injection rate. West works side-by-side with healthcare partners from concept to the patient, designing and manufacturing packaging, diagnostic, and delivery systems that promote efficiency, reliability, and safety. West leads the way with cutting-edge technologies, a thorough understanding of global regulatory compliance, and quality systems. West also has an unmatched knowledge of relevant pharmaceutical product testing, development, and packaging. For more information, visit West at **www.westpharma.com**.

CDMO Services

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

Drug Development
EXECUTIVE

Niels Düring
Head
Gerresheimer Plastic Packaging

GERRESHEIMER

Gerresheimer: Plastic Perfection

Niels Düring could probably turn a tablet container upside down in many places around the world and read the word DUMA on it. This brand has been a very important part of his career because he's been involved with it right up to the present day. The name DUMA is derived from the surname of Peter Dudek, the man who established a plastics factory in Værløse by the name of Dudek Plast in 1964 and a Swedish company called Mavello. Today, the Duma product family sets the global standard for plastic pharmaceutical containers. Mr. Düring, who has a background of accounting being a CPA, started working with Dudek Plast A/S in 1991. He went on to become a Partner and Managing Director of the company in 1996. He and Peter Dudek sold the company in 1999 to Superfos A/S and, and from then on, he was in charge of the Pharmaceutical Packaging Division of Superfos. Throughout the following years, Superfos focused exclusively on the production of pharmaceutical packaging. At the end of 2005, the Gerresheimer Group acquired the Superfos Pharma Packaging division and offered Mr. Düring the position Head of Gerresheimer Plastic Packaging. *Drug Development & Delivery* recently spoke with Mr. Düring to discuss Gerresheimer's Plastic Packaging division and the complementary synergies working for a company that also manufactures glass provides.

Q: What are your favorite principles?

A: Never expect more from others than you expect from yourself; treat others as you would like to be treated; and integrity, honesty, hard work, and willingness to learn are the key to success.

Q: Gerresheimer manufactures both plastic and glass containers? Is it difficult to work in a company that has competing products?

A: Not at all! As I see it, the products complement each other rather than competing with each other. Glass has obvious strengths and advantages that create the value in the customer products, where

plastics – the newer material – offers different features, advantages, and benefits, so it is the basis for the next generation of many products.

Q: Do you derive any synergies from the know-how transfer between your glass and plastics experts?

A: The market and customers are, to a certain extent, the same, so we have advantages through our sales set-up and through knowledge-sharing between our glass and plastics colleagues. We are also able to offer our customers an even more comprehensive range of products. We give them the value they need to continue developing and optimizing their business. From a technological perspective, however, the glass and plastics processes are quite different, so the KPIs are also very different. That having been said, we both need to stay committed to improving our competitiveness. The key drivers are people, processes, constant technological development, and ensuring value for money.

Q: Gerresheimer has worldwide locations for the production of plastic packaging? How do they work together?

A: Our organization is currently structured into three main regions of Europe, South America, and India. Within these regions, we try to have a single management set-up supporting the sharing of the capability, know-how, and knowledge available in the organization between each production site. In addition, one of my goals in major projects is for the management teams from different regions to make annual visits to other regions so they can learn from and be inspired by their colleagues and challenge the status quo. Looking back over the past 8 years, I'm very proud to see how all sites have developed strongly, and this development is based on reciprocal learning and the commitment to improvement.

Q: How has Gerresheimer become such a leader in the plastic packaging business?

A: Gerresheimer Plastic Packaging is made up of a number of acquired companies. Each of the companies was formerly a leader in its niche market/specialist field within our industry. By combining their expertise and promoting continuous learning and knowledge sharing, we have been able to take them to an even higher level. In Europe, we have our very well-known brand Duma, which was developed in 1967 – as a world-wide innovation – bringing solid packaging to the market in the form of HDPE bottles. The bottle itself, and the unique closure, made it the tightest container and closure concept available in the world. Our set-up in South America is also founded on some very strong brands for ophthalmic and solid applications, closures, and PET products by the name of Allplas and Védat. These strong brands are still part of the product portfolio.

Q: Which products are the drivers of your business today?

A: Gerresheimer Plastic Packaging provides a very comprehensive product portfolio for solid, ophthalmic, liquid, and parenteral applications. The sizes range from 3-mL to 3-L bottles, plus a comprehensive assortment of excellent closures with tamper-evident or child-resistant features, or senior friendliness functions, dispenser systems, desiccants, and so on.

Q: Which products will be your drivers in the near future?

A: In addition to participating in a number of large-scale customer projects, the main drivers will be our MultiShell vials for parenteral drugs, our improved barrier solid containers, as well as devices and aids to help in the use of medications. With our Gx MultiShell, we have been able to develop a very stable homogeneous multilayer vial with a much-improved barrier and characteristics, which have also been used in improving the barrier for our solid products.

Q: In 2011, Gerresheimer acquired Védat in Brazil, followed by Triveni in India in 2012. How successful were these acquisitions?

A: Both acquisitions have successfully supported our development, but for completely different reasons. With the Védat acquisition in 2011, we were able to combine the company with our existing platform – Allplas – to create a

"Our strength is our people. Gerresheimer has a good reputation and a strong name in the market as supplier for the pharmaceutical industry. Our very broad and deep product offering both in glass and in plastics provides the customers with the product they need in the market. Our willingness to constantly innovate and improve our quality are main drivers sustaining our success."

strong, market-leading player in the Brazilian market. Even though we have a very dominant position, we have decided to act modestly by underlining to the market and to our customers that we are here to support them now and in the future. Since the acquisition, we have seen the constant strong growth and development of our platform in Brazil. The acquisition of Triveni allowed Gerresheimer Plastic Packaging to enter the Indian market. We took the opportunity to expand the current bottle operations and develop an all-inclusive offering by adding closures to the portfolio and providing full documentation of the complete packaging. We also introduced ophthalmic and parenteral products.

Q: In Brazil, Gerresheimer is one of the market leaders. Can you explain how this was accomplished?

A: As previously mentioned, Gerresheimer Plastic Packaging in South America is based on the acquisitions of Allplas and Védat. Both companies were already strong players in their fields and, as a result of their combination and our continuous development of them, we were able to become the real market leader. I'm very proud to say we have by far the most comprehensive portfolio of products supplied in very high quality. This, plus our production set-up and continuous development, have set the standard in the market.

Q: Can you explain more about Triveni and its business?

A: Triveni was the first company to start manufacturing the US-type bottles for solids in India back in the 1990s. In fact, they were the first to get a DMF on their products manufactured in India. In this position, the company has undergone more than 15 years of continuous development in the very strong and fast-moving Indian market. Gerresheimer acquired 75% of the shares with the objective of facilitating further growth and expanding its business in different ways. First, we want to extend our product portfolio in India – initially by complementing the bottle business with closures, and we expect to be ready to market child-resistant closures in 2015. We will also be offering ophthalmic and parenteral products in this market. Second, we have extended our global presence and are now able to bring the US-type solid bottles into both the US and the European markets.

Q: How do you develop new ideas? How do you get from initial idea to finished product?

A: That depends. Developing a breakthrough type of innovative product, plus the time our customers need to get the product tested, registered, and validated, we're easily talking about 3 to 7 years. That being said, we sometimes take a more incremental approach to developing innovative products, so these projects can be implemented faster and more easily. Sometimes this can be less than a year – and in some cases, we can deliver a new range of bottles to the customer in less than a month. When you're developing any new product or system, it's always important to understand the requirements and the impact on the customers' registrations and operations.◆

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

THERAPEUTIC FOCUS

Adenosine Receptors – The Promise of A3AR Research

By: Pnina Fishman, PhD

INTRODUCTION

Adenosine is a neuromodulator that suppresses synaptic transmission. Adenosine receptors, part of the superfamily of G-protein-coupled receptors (GPCRs), come in four sub-varieties: A1, A1A, A2B, and A3. A separate gene encodes each of these four, and each has different physiological roles. The A3AR is less widely distributed than the A1, A1A, and A2B adenosine receptors, and in humans, the A3AR is expressed in the lungs, liver, brain, aorta, testis, and heart. Recent research has demonstrated that the A3AR holds promise as both a therapeutic target and as a biological predictive marker.

THE PROMISE OF A3AR RESEARCH

The reasons for such optimism are twofold. First, researchers have shown that the A3AR is overexpressed in cancer and inflammatory cells, while low expression is found in normal cells. They have also demonstrated that peripheral blood mononuclear cells (PBMCs) of patients with cancer or inflammatory disease show high receptor expression.

Specifically, A3AR is overexpressed in various neoplastic cells, including leukemia, lymphoma, astrocytoma, melanoma, and pineal tumor cells. Research captured similar data in other studies that showed the receptor expression levels in tumor tissues derived from patients with breast, colon, hepatocellular, pancreatic, small cell lung carcinomas, and melanoma in direct comparison with adjacent normal tissues. Furthermore, studies have described a direct correlation between A3AR tissue expression levels and disease progression in breast and colon cancer.

A similar pattern of receptor overexpression was described in inflammatory cells both in experimental animal models and humans. Rat studies of rheumatoid arthritis (RA) detected A3AR overexpression in paw tissue. When mice inhaled lipopolysaccharides findings showed similar data in colon tissues, as well as in colon tissues derived from rats with colitis.

Similarly, over-expression of A3AR has been described in PBMCs of patients with psoriasis and patients with Crohn's Disease, suggesting that this is a general phenomenon in immuno-inflammatory diseases.

The A3AR is also highly expressed in anterior segment tissues derived from eyes with pseudoexfoliation syndrome when compared to the eyes of healthy subjects.

Second, scientists have synthesized highly selective A3AR agonists that clearly induce specific anti-inflammatory and anticancer effects.

Additionally, experiments have illustrated a protective effect of the agonists on normal cells. This has caused many to believe that this unique differential effect of the agonists will contribute to a safety profile of these drug candidates in both preclinical and clinical studies.

At present, A3AR agonists are being developed for the

treatment of inflammatory, ophthalmic, and liver diseases and demonstrate excellent safety and efficacy in Phase II clinical studies.

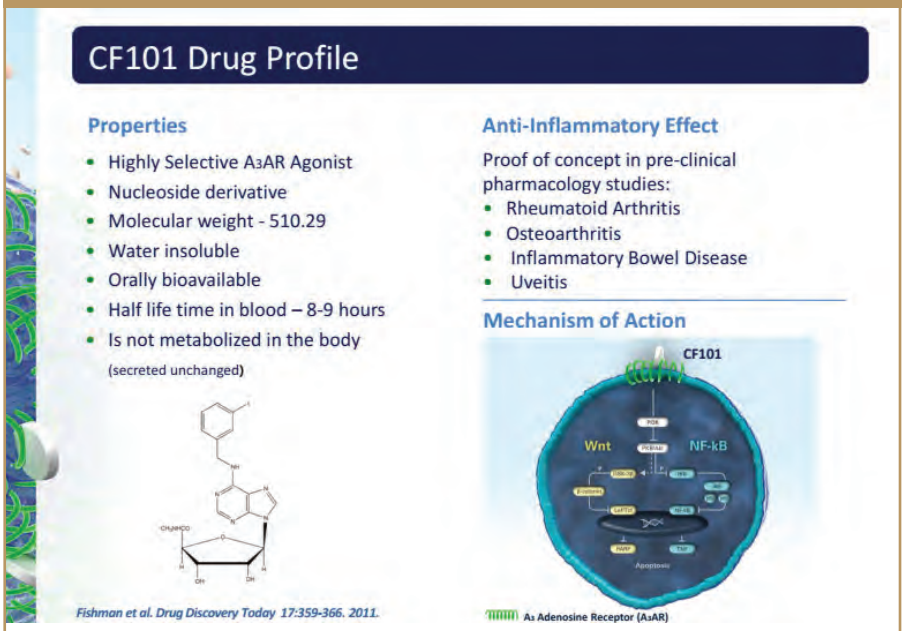
THE EXAMPLE OF PLAQUE PSORIASIS

Plaque psoriasis affects 2% to 3% of the population, and it is the most common of the five varieties of psoriasis (guttate, inverse, pustular, and erythrodemic being the others). The plaque variety appears in itchy red patches covered in dead skin or scale that looks like a white, silvery build up. Often, these patches will bleed.

Traditional dermatology has focused on topical treatments, such as corticosteroids or salicylic acid and coal tar-based substances, although Hippocrates himself recommended arsenic. In general, these topical treatments have enjoyed enough success that they remain the first line of defense in dealing with plaque psoriasis.

Alternatively or in addition, phototherapy has shown some positive effect on the condition as well. There are two types of UVB treatment, broad band and narrow band. The major difference between them is that narrow band UVB light bulbs release a smaller range of ultraviolet light. Narrow-band UVB is similar to broad-band UVB in many ways. Several studies indicate that narrow-band UVB clears psoriasis faster and produces longer remissions than broad-band UVB. It also may be effective with fewer treatments per week than broad-band UVB. However, during UVB treatment, psoriasis may worsen temporarily before improving. The skin

FIGURE 1



Canfiteconcept1 - Can-Fite BioPharma's lead compound, CF101, is an oral anti-inflammatory agent that binds with high affinity and selectivity to the A3AR.

may redden and itch from exposure to the UVB light which can discourage the patient from further treatment, and consistency in phototherapy is vital to success.

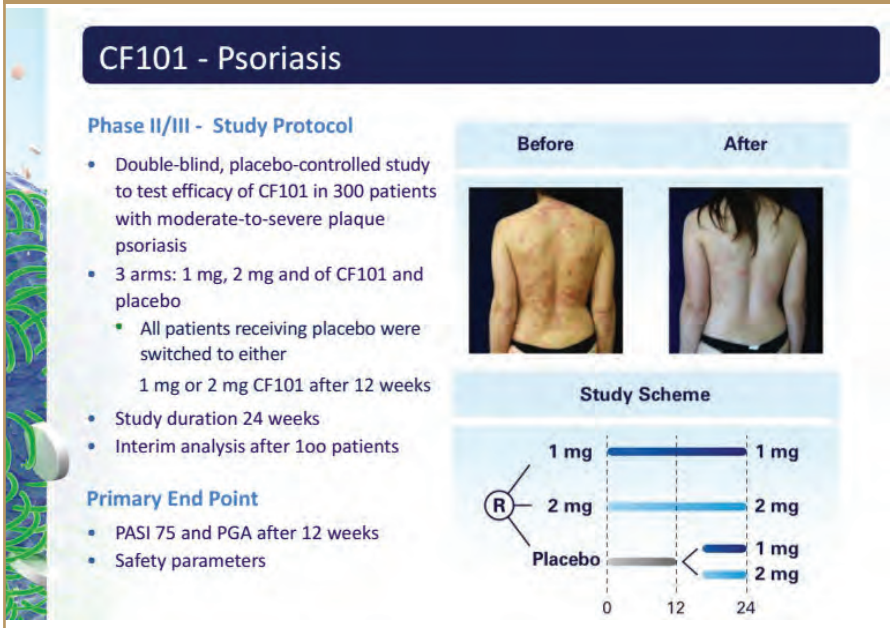
In the past decade or so, however, data have demonstrated that the disease is much more systemic than previously known. Therefore, systemic treatments show great promise in treating plaque psoriasis – this is all the more the case when topical treatment and phototherapies have failed. Such systemic treatments include Acitretin (Soriatane), Cyclosporine, and Methotrexate, as well as off-label systemic treatments. Each has shown some efficacy, but each also has side effects and may not be tolerated well by certain individuals.

Can-Fite BioPharma's lead compound, CF101, is an oral anti-inflammatory agent that binds with high affinity and selectivity to the A3AR. CF101 has been successfully tested in animal models and is currently in advanced stages of clinical development for rheumatoid arthritis (RA) and psoriasis. All human clinical studies have demonstrated this drug to have an excellent safety profile.

In two Phase II studies in which CF101 has been given as a stand-alone drug, data indicated that it acted as a disease-modifying anti-inflammatory drug in RA patients. The Phase II and the interim analysis of the Phase II/III clinical studies in psoriasis were successfully concluded showing efficacy and safety of CF101. Can-Fite has conducted a Phase II clinical study of the safety and efficacy of CF101 for the treatment of patients with moderate-to-severe plaque psoriasis. In previous Phase II studies conducted in patients with rheumatoid arthritis, CF101 demonstrated a marked anti-inflammatory effect.

As our study sample for CF101 as a treatment for plaque psoriasis, we enrolled males and females, aged 18 to 70 years with moderate-to-severe chronic plaque psoriasis of at least 6 months duration and a Psoriasis Area Sensitivity

FIGURE 2



CF101Psoraisislide - The Phase II and the interim analysis of the Phase II/III clinical studies in Psoriasis were successfully concluded showing efficacy and safety of CF101.Brains

Index (PASI) score ≥10. The exclusion list was fairly comprehensive, disqualifying patients of: a diagnosed with erythro dermic, guttate, or pustular psoriasis; history of treatment with systemic retinoids, corticosteroids, or immuno-suppressants within 6 weeks of the baseline visit; treatment with moderate-high potency topical corticosteroids (Class I–III), calcification within 2 weeks of the baseline visit; treatment with phototherapy or Dead Sea climato-therapy within 4 weeks of the baseline visit; treatment with a biological agent within a period of time equal to five times its circulating half-life, or 30 days, whichever is longer, prior to the baseline visit; history of poor clinical response to methotrexate after an adequate regimen and duration of treatment; pregnancy, planned pregnancy, lactation, or inadequate contraception as judged by the investigator or other conditions that would confound the study evaluations or endanger patient safety.

This was a Phase II, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study. Eligible patients were assigned to one of three sequential dosing cohorts with planned sample sizes of approximately 15 patients each. A total of 84 patients with moderate-to-severe plaque psoriasis were screened. Patients who met the inclusion criteria (n=75) were randomized to placebo (n=19), CF101 1 mg q12 hours (n=25), CF101 2 mg q12 hours (n=17) or CF101 4 mg q 12 hours (n=15). Patients were permitted to use emollients along the study period. Most of the patients completed the study (n=64, 84.2%).

We set as our exploratory efficacy endpoints: Change from Baseline (CFB) in PASI Scores; proportion of patients achieving 50% and 75% improvement in PASI scores (PASI 50 and PASI 75, respectively); and static Physicians' Global Assessment (PGA), which measures the physician's impression of the disease at a single point (graded on a 0-5 scale as follows: 0=absent, 1=slight, 2=mild, 3=moderate, 4=marked, 5=severe). These parameters were calculated at weeks 2, 4, 8, 12, and 14. Safety assessments included recording of treatment-emergent adverse events, and changes in vital signs, physical examinations, clinical laboratory tests and electrocardiography findings.

In general, the study showed CF101 to be safe and well tolerated. There were 20 adverse events reported, and 15 of the 20 were adverse events that were possibly related to the study drug; all were mild or moderately severe except for one exacerbation of psoriasis judged to be severe. Within the CF101 1-mg group, the incidence of adverse events was 58.3%, and it is in this group that the severe incident was reported. The adverse event rate was 17.6% in the CF101 2-mg group and 13.3% in the CF101 4-mg group. Within the placebo group, the rate was 21.1%. Within the placebo group, we had a single serious adverse event - moderately severe arrhythmia/atrial fibrillation occurred during this study and was not attributed to study medication.

No clear patterns of difference between the CF101 treatment groups and the placebo group were evident for any body system/organ classes. Only four patients were withdrawn from the study due to adverse events, including arrhythmia patient from the placebo group.

Turning to the efficacy of CF101 shown in the study, there was no therapeutic effect in the 1-mg q12 hour group. However, looking at the mean change in the baseline PASI score at week 12 revealed a statistically significant difference between the 2-mg

CF101-treated group and the placebo group (P<0.001 vs. baseline and P=0.031 vs. placebo). The 4-mg CF101 dose treatment resulted in lesser improvement than that of the 2-mg dose treatment.

Within the 2-mg CF101-treated group, we saw a progressive improvement in the mean change from baseline in the PASI score throughout the study period was observed (week 2: 1.64±0.9; week 4: 3.76±1.9; week 8: 6.22±1.9; week 12: 8.77±2.1), with a statistically significant difference from placebo at weeks 8 and 12 (P=0.047 and P=0.031, respectively).

In the 2-mg CF101-treated group, 35.3% (6 out of 17) of the patients achieved PASI ≥50 response. Among this group, 11.8% (2 out of 17) of the patients achieved a response that was very close to PASI 50 (47.7% and 49.9%) at week 12. Furthermore, of those patients achieving PASI 50, one showed PASI improvement of 73%, and one reached PASI 90%. Because there was no entry requirement for a minimum PGA score, analysis of PGA data was performed on patients who entered the trial with a PGA score >1 to avoid confounding by low baseline scores.

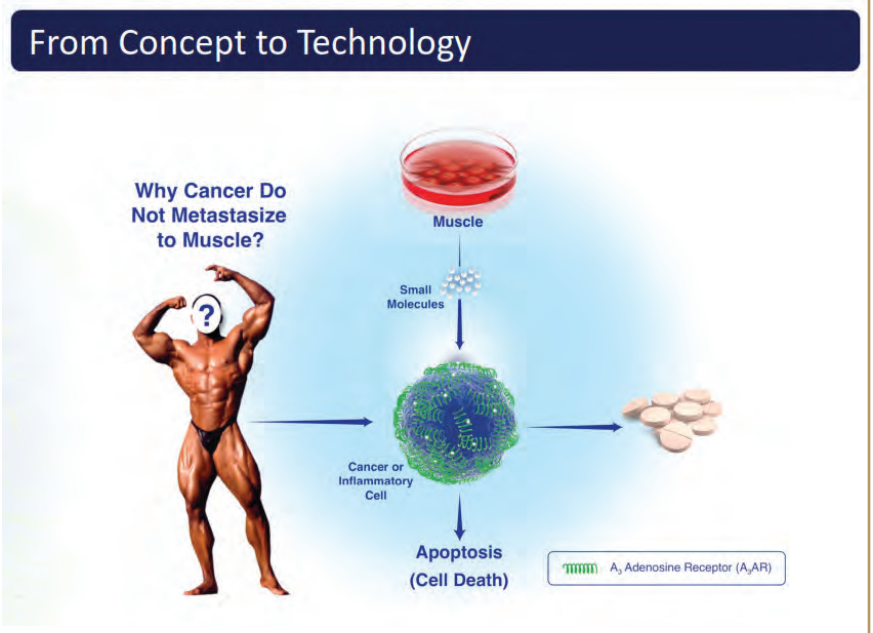
At week 12, 23.5% of the patients treated with the 2-mg CF101 dose achieved a score of 0 or 1, in comparison with 0% in the placebo group (P<0.05).The percentage of patients presenting only slight or no clinical signs (PGA score 0-1) increased throughout the study period in the 2-mg CF101-treated group.

Based on these largely successful results, Can-Fite has finalized enrollment in its Phase II/III trial of CF101 for the treatment of psoriasis with over 300 patients through 17 clinical centers in the US, Israel, and Europe. Top line results from the trial are expected in the first quarter of 2015.

The Phase II/III double-blind, placebo-controlled study is designed to test the efficacy of CF101 in 300 patients with moderate-to-severe plaque psoriasis. The first study cohort was composed of three arms with patients receiving: 1 mg of CF101; 2 mg of CF101; and placebo. All patients receiving placebo were switched to either 1 mg or 2 mg of CF101 after 12 weeks. The primary efficacy endpoints are a statistically significant improvement in standard measures used by dermatologists to assess psoriasis, including the PASI score and the PGA score as well as various safety parameters.

Not long ago, we released our interim safety and efficacy results from the first 103 patients who completed 24 weeks of treatment in the trial. The positive clinical effects of CF101 at the 2-mg dose relative to placebo were observed through PASI and PGA scores, with the responses accumulating steadily over the 24-week treatment period. To allow the trial to meet its full objectives, the study protocol has been amended to enroll patients for the 2-mg dose and placebo administration for an extended study period of 32 weeks.

FIGURE 3



Mechofactionslide3 - Targeting the receptor with synthetic and highly selective A3AR agonists induces anti-inflammatory and anti-cancer effects.

BEYOND PLAQUE PSORIASIS

Can Fite's scientists believe that CF101 offers a great deal of hope for those with plaque psoriasis because of its anti-inflammatory effect, its well-defined mechanism of action, and the excellent safety profile. Moreover, because CF101 has shown utility in other treatments, further investigation of its uses for other indications makes sound scientific sense. CF101 is also currently developed for the treatment of rheumatoid arthritis (PhaseIIb glaucoma (Phase II).

Can-Fite is also developing a commercial biomarker blood test kit for the A3AR predictive biomarker. The kit is designed for use at any molecular biology lab prior to treatment to help identify an individual patient's responsiveness to the company's drugs, thus providing personalized medicine. The US Patent and Trademark Office had previously issued Can-Fite a patent for A3AR as a biomarker to predict patient response to CF101 in autoimmune inflammatory indications.

OTHER A3AR AGONISTS

In addition to CF101, Can-Fite is working to develop a different A3AR agonist called CF102, an oral small molecule drug generically known as Cl-IB-MECA (2-chloro-N6-(3-iodobenzyl)-adenosine-5′- N-methyl-uronamide). CF102 has potent anti-cancer effect, particularly against hepatocellular carcinoma, and anti-inflammatory activity demonstrated in preclinical animal models of liver inflammation.

CF102's mechanism of action is mediated via de-regulation of the NF-κB and the Wnt signal transduction pathways, resulting in apoptosis of tumor cells. The protective effect of CF102 is mediated via down-regulation of the NF-κB signal transduction pathway and preventing apoptosis. The safety of CF102 has been demonstrated in preclinical studies, a Phase I clinical study, and in Phase I/II clinical studies demonstrating a favorable safety profile.

Recently, Can-Fite submitted to the US FDA the protocol for its global Phase II trial for the treatment of advanced hepatocellular carcinoma (HCC) with Child-Pugh Class B cirrhosis. The planned Phase II study will be conducted in Israel, Europe, and the US with 78 subjects and will investigate the efficacy and safety of CF102 as compared to placebo. Following Can-Fite's submission, the FDA agreed with the protocol design. The FDA had also previously granted Can-Fite Orphan Drug designation for CF102 in this indication.

Moreover, Israel's Ministry of Health has just approved CF102 for Compassionate Use for a liver cancer patient who has already benefited from the drug during clinical trials.

In addition, the European Union granted Can-Fite a patent for its invention titled, Method for Inducing Hepatocyte Proliferation and Uses Thereof. The patent covers CF102 in the treatment of liver function following liver resection (surgery) by helping the liver to regenerate and repair itself. Preclinical studies have found CF102 offers potential efficacy not only for cancer patients after a tumor has been surgically removed from the liver, it may also offer important benefits for patients with other kinds of liver diseases.

Another drug coming from this technology platform is CF602, a novel A3AR allosteric modulator that enhances the receptor activity in the presence of the native ligand. The molecule is characterized by high selectivity at the A3AR and is capable to avoid receptor desensitization, thus magnifying the agonist activity at low doses. The activity of CF602 was examined in experimental animal models of arthritic diseases. Oral administration of CF602 induced an impressive anti-inflammatory effect, manifested by a decrease in the disease signs and symptoms. CF602 induces down-regulation of the PI3K-PKB/Akt-NF-kB signaling pathway in the inflammatory cells.

CONCLUSION

The finding that the Gi protein coupled A3 adenosinereceptor (A3AR) is highly expressed in inflammatory and cancer cells whereas low expression is found in normal body cells offers a new way to fight such diseases. Targeting the receptor with synthetic and highly selective A3AR agonists induces anti-inflammatory and anti-cancer effects. In addition, the receptor is suggested as a biological marker based on human clinical data showing that high receptor expression at baseline predicts good patient's response to drug treatment. ◆

BIOGRAPHY

Dr. Pnina Fishman is the scientific founder of Can-Fite BioPharma and was previously a professor of Life Sciences and headed the Laboratory of Clinical and Tumor Immunology at the Felsenstein Medical Research Institute, Rabin Medical Center. Prof. Fishman is a very accomplished scientist and has authored or co-authored over 150 publications and presented the findings of her research at many major scientific meetings. Her scientific work was the foundation on which Can-Fite was built. This scientific work has gained recognition as one of the leading approaches for new- generation therapies for cancer and other diseases. Her past managerial experience included 7 years as CEO of Mor Research Application (MRA), a company that was in charge of the commercialization of intellectual property from all hospitals and research centers of Clalit Health Services, the largest healthcare provider in Israel, and was also the first clinical CRO in Israel. She was also involved in the establishment and served on the Board of Directors of several life sciences technology start-ups.

May 2015 Advertiser Index

COMPANY	PAGE	PHONE	WEBSITE
ABC Labs	Cover		www.abclabs.com
Althea	11		www.altheacmo.com
Baxter Biopharma Solutions	39		www.baxterbiopharmasolutions.com
Capsugel	15	888-783-6361	www.capsugel.com
Carbon Leads	12	973-227-6003	www.carbonleads.com
Catalent Pharma Solutions	17,76	1-888-SOLUTION	www.catalent.com
Corden Pharma	5	800-868-8208	www.cordenpharma.com
Drug Development & Delivery	4,21	973-299-1200	www.drug-dev.com
EMD Millipore	31		www.emdmillipore.com/emprove
Insulet	3		www.insulet.com
Lablabo	13		www.lablabo.com
Patheon	2		www.patheon.com
Pfanstiehl	14		www.pfanstielhl.com
PharmaCircle	45	1-800-439-5130	www.pharmacircle.com
PODD	51	646-350-2580	www.theconferenceforum.org
Terumo Medical Corp.	19		www.terumogps.com
Unilife	75		www.unilife.com
West Pharmaceuticals	7	1-800-345-9800	www.daikyocrystalzenith.com
Xcelience	9	813-286-0404	www.xcelience.com

June Issue Highlights

Biotechnology Drug Development

Management Insight

Lyophilization Manufacturing

Injection Devices

Formulation Development

Excipients

Market News

For More Information About Advertising Contact:
John Kiesewetter - T: 541-338-0022 Email: jkiesewetter@drug-dev.com
Ralph Vitaro – T: 973-299-1200 Email: rvitaro@drug-dev.com

External Delivery

Fight the Good Fight

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.

The expression "never bring a knife to a gunfight" often holds true in a business environment. All of us have experienced situations in which we feel strongly about an issue or project and are prepared to "fight" for what we so strongly believe in. Courage is mandatory in these circumstances; however, courage alone is not the only necessity. I believe placing yourself in a position of strength is what will lead you to success. Remember, not everyone is going to be on your side or agree with you.

The first thing you must do is work out the balance of information and understanding. This means you have to make your presentation understandable to the people who have the least ability to comprehend the information without insulting the intelligence or boring the most capable people in the meeting. You cannot afford to lose either group.

Second, you must triple check your information to make certain every bit of it is accurate and defensible. People are going to challenge what you say, some for information reasons, and others for political reasons. But either way, if you say something that is inaccurate or indefensible, then you are in grave danger of losing the "fight." Facts are facts, and they are often your best ammunition. People can and will challenge facts, but if you have done your homework, then your facts are always defensible and will stand up to any challenge.

Third, you must do is what is referred to in Japanese management style as Nemawashi. This is what is most often referred to as Japanese consensus management. However, Japanese consensus management does not mean everyone agrees as most non-Japanese believe. It means that everyone has been consulted and had their opinion heard prior to the decision on the issue or project being debated. I find Nemawasi to be of great benefit to me for situations in which I have to convince multiple people to approve and support the issue or project I am looking to take forward.

The Nemawashi process states you must meet with each individual personally prior to the group meeting to hear his/her concerns and objections. This affords you the opportunity to hear what everyone has to say and to discuss solutions or compromises to his/her concerns and objections. You do not want this type of conversation to take place in the group meeting. In this case, your audience may develop mob mentality very quickly. The other benefit is that you will know ahead of time what the push back will be and who it will come from, and you can make your defense preparations ahead of the meeting. Most likely the push back will be minor and be raised so that others at the meeting will know the information is not being accepted carte blanche.

The ultimate benefit to Nemawashi is that, if done correctly, when the decision is made, people as a group will support the decision, even if they do not necessarily agree with the decision. The non-agreement people will most likely support the decision because they realize their opinion was heard during the one-on-one process and considered in the decision. So Japanese consensus management does not mean everyone agrees. It simply means everyone's opinion has been heard and considered, and the decision will be supported even by those who are not in agreement.

All of this is to say that thorough preparation and communication is essential for success in these situations. Fighting the good fight is commendable as long as you bring the right tools to the fight! ◆

UNILIFE®

Deliver Brilliance

Wearable Injectors

Pre-filled,

Pre-assembled,

Ready-to-Inject.

Simple to customize

Ready to address the therapy, patient and branding needs of a portfolio of therapies.

Simple to Integrate

Standard filling processes.
Standard materials.
No terminal sterilization.

Simple to Use

The most intuitive user experience with just three steps to Peel, Stick & Click.

Enquire about Bluetooth connectivity

E: info@unilife.com W: www.unilife.com

This product has not yet been evaluated by the FDA

Catalent®

best technologies.
broadest expertise.
faster development.

NEW
Catalent Acquires Micron Technologies
LEADER IN PARTICLE SIZE ENGINEERING

RP SCHERER SOFTGEL TECHNOLOGIES
CONTROLLED RELEASE TECHNOLOGIES
OPTIMELT™ HME TECHNOLOGY
OSDrC® OPTIDOSE™ TECHNOLOGY

Our 18 R&D teams in 10 countries are now working on 500+ projects, applying multiple proven and innovative drug delivery technologies to help you deliver optimal release profiles, enhanced bioavailability and better dose forms—preferred by patients and payers.

TECHNOLOGY SPOTLIGHT

ZYDIS® FAST-DISSOLVE TECHNOLOGIES

World's best orally dissolvable tablet – about 3 seconds. Uniquely delivers small or large molecules. 20 Rx and OTC products in 50 markets. NEW taste-masking and higher dose options.

DEVELOPMENT DELIVERY SUPPLY

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

US + 1 888 SOLUTION (765 8846) **EU** 00800 8855 6178
solutions@catalent.com catalent.com

CTLT LISTED NYSE

TECHNOLOGY SELECTION & APPLICATION ▸ FORMULATION & ANALYTICAL SERVICES ▸ CLINICAL & COMMERCIAL SUPPLY ▸ TAILORED OR END-TO-END SOLUTIONS