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September 2014 Vol 14 No 7 www.drug-dev.com

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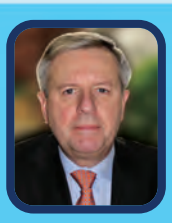

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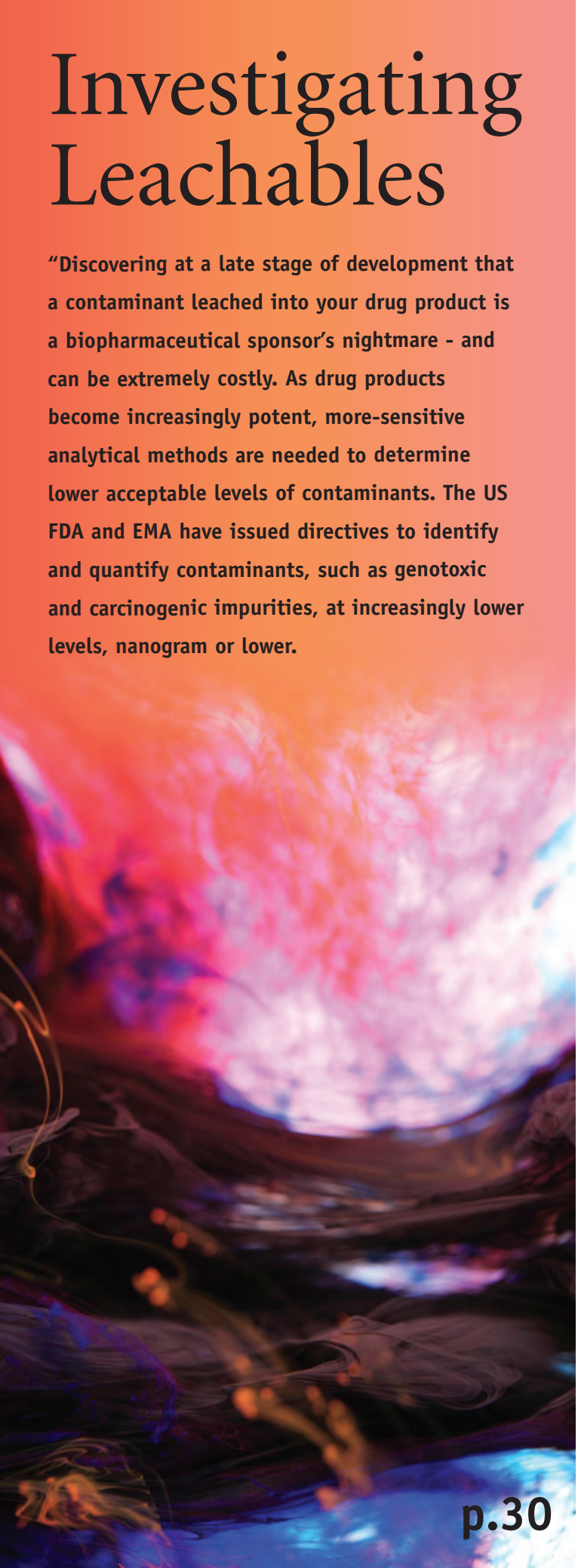
Investigating Leachables

"Discovering at a late stage of development that a contaminant leached into your drug product is a biopharmaceutical sponsor's nightmare - and can be extremely costly. As drug products become increasingly potent, more-sensitive analytical methods are needed to determine lower acceptable levels of contaminants. The US FDA and EMA have issued directives to identify and quantify contaminants, such as genotoxic and carcinogenic impurities, at increasingly lower levels, nanogram or lower.



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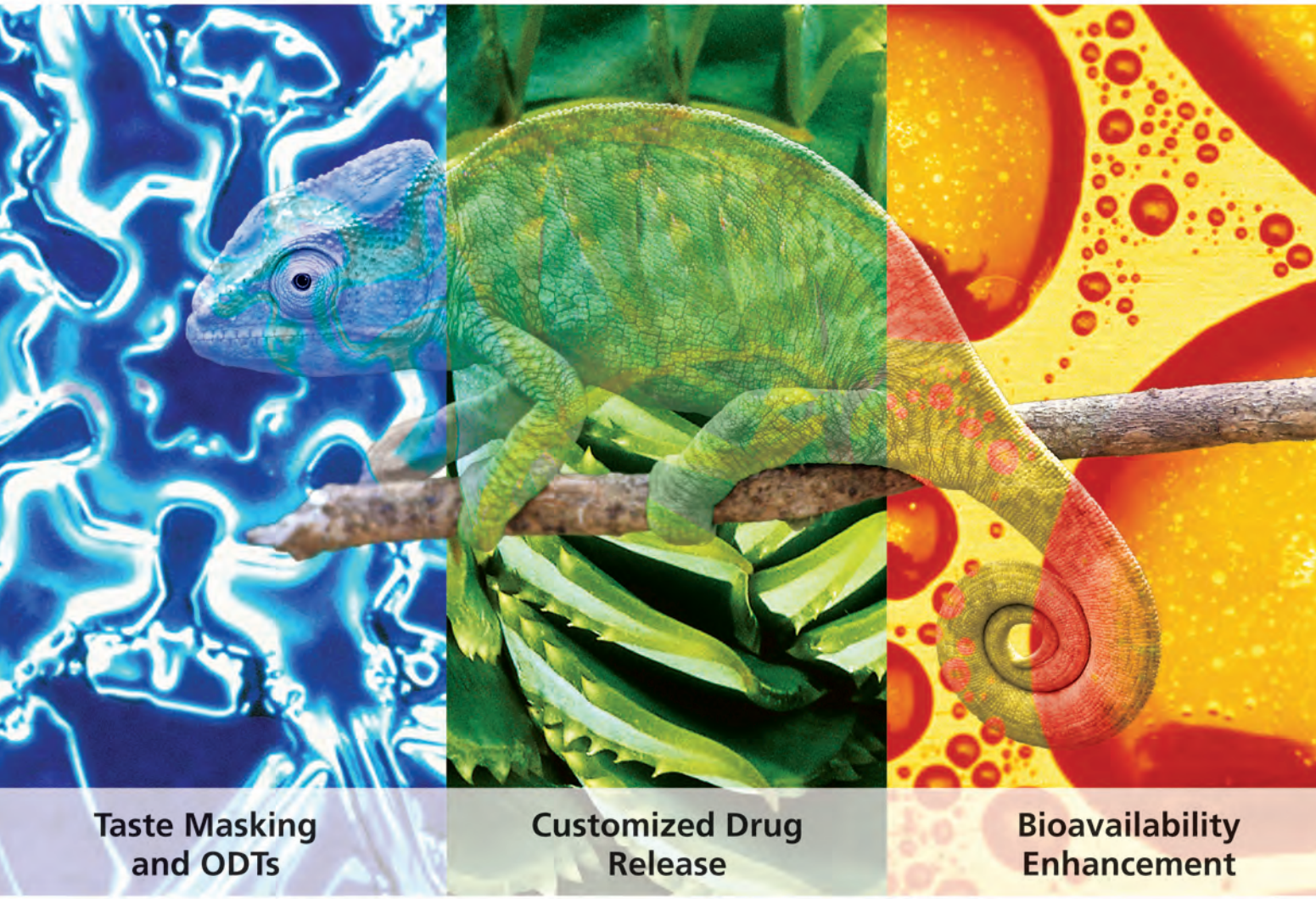

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Allergan Acquires LiRIS Program From TARIS Biomedical

Allergan Inc. and TARIS Holdings LLC recently announced that Allergan has closed a transaction to acquire worldwide rights to TARIS Biomedical's lead program, LiRIS, which is currently in Phase II trials for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS). Allergan paid $67.5 million in cash up-front, subject to certain adjustments and holdbacks. Allergan has also agreed to pay up to an aggregate of $295 million in development milestone payments and up to an aggregate of $225 million in commercial milestone payments. Prior to the closing of this transaction, TARIS spun out certain assets, including pipeline programs and intellectual property related to TARIS' platform technology, to a new company funded by TARIS shareholders.

"Allergan has a long-standing history of delivering stockholder value by developing innovative medical treatments that address unmet medical needs," said David E.I. Pyott, Chairman of the Board and Chief Executive Officer, Allergan. "Our work to develop BOTOX (onabotulinumtoxinA) as a second-line treatment for overactive bladder (OAB) has made a significant difference for patients who suffer from this chronic condition. The acquisition of LiRIS is an important addition to our growing urology pipeline and, if approved, will provide a local treatment for interstitial cystitis / bladder pain syndrome, which is a debilitating bladder condition."

"This transaction is a win for patients, for our shareholders and employees, and for the future potential of our core delivery technologies," said Purnanand Sarma, PhD, President and CEO of TARIS. "Allergan is an ideal partner for advancing LiRIS because of its team's expertise in drug delivery technologies, specialty product development, and commercialization in the urology market. We are confident that Allergan will enable LiRIS to reach patients who do not have effective options that adequately address their disease. Building on the success of LiRIS so far, we will now be able to focus our efforts on developing a rich pipeline of applications of our technology, including new treatments for bladder cancer and other areas of unmet need in urology."

LiRIS incorporates proprietary technology developed by TARIS designed to continuously deliver lidocaine over an extended period directly to the bladder of patients with interstitial cystitis/bladder pain syndrome (IC/BPS) to relieve the painful and often debilitating symptoms associated with this disease. IC/BPS is a complex bladder disease associated with significant bladder pain and disability, including in some patients lesions in the bladder, so-called Hunner's lesions. Patients also suffer from increased urinary urgency and frequency. IC/BPS may significantly impact quality of life, including loss of work and reduced personal relationships and intimacy.

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Ashland Commits to Major Capacity Expansion to Meet Customer Demand

Ashland Specialty Ingredients, a commercial unit of Ashland Inc. recently announced plans to significantly expand production capacity of its Klucel hydroxypropylcellulose (HPC) product line in Hopewell, VA. The expansion is expected to begin production in the second half of calendar 2016. Klucel HPC is a tablet binder and coating ingredient used in pharmaceutical applications and dietary supplements worldwide.

"Ashland is committed to the overall pharmaceutical market and has made a number of sizeable investments over the past 2 years to strengthen our position," said David Neuberger, Vice President, Pharmaceutical Specialties, Ashland Specialty Ingredients.

Those investments include the opening of Ashland's pharmaceutical center of excellence in Hyderabad, India, earlier this year; the pending expansion of Ashland's technical capabilities in Wilmington, DE, and the Polyplasdone crospovidone expansion in Texas City, TX.

Ashland Specialty Ingredients is the No. 1 global producer of cellulose ethers and a global leader in vinyl pyrrolidones. It offers industry-leading products, technologies, and resources for solving formulation and product-performance challenges. Using natural, synthetic, and semi-synthetic polymers derived from plant and seed extract, cellulose ethers, and vinyl pyrrolidones, as well as acrylic and polyurethane-based adhesives, Specialty Ingredients offers comprehensive and innovative solutions for today's demanding consumer and industrial applications.

Boehringer Ingelheim Announces US Filing for Fixed-Dose Combination Drug

Boehringer Ingelheim recently announced that the US FDA accepted for review the NDA for the fixed-dose combination (FDC) of tiotropium and olodaterol delivered via the Respimat inhaler for the proposed indication of long-term, once-daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. Tiotropium + olodaterol FDC will not be indicated to treat acute deteriorations of COPD or to treat asthma.

Tiotropium + olodaterol FDC is an investigational treatment consisting of the long-acting muscarinic antagonist (LAMA) tiotropium and the long-acting beta agonist (LABA) olodaterol, and is being evaluated for once-daily use via the Respimat inhaler. The Respimat inhaler is a propellant-free inhaler that generates a slow-moving mist.

"The FDA's acceptance of our application for the FDC of tiotropium and olodaterol is an important milestone for our company, and it reinforces Boehringer Ingelheim's steadfast commitment to COPD," said Sabine Luik, MD, Senior Vice President, Medicine & Regulatory Affairs, Boehringer Ingelheim Pharmaceuticals, Inc.

The NDA submission for tiotropium + olodaterol FDC is based on results from three global Phase III trials - the 52-week replicate TONADO 1&2 studies (NCT01431274/NCT01431287) and the 6-week cross-over VIVACITO study (NCT01559116). The TONADO 1&2 studies evaluated the long-term effect of tiotropium + olodaterol FDC on lung function, while VIVACITO investigated the 24-hour bronchodilator profile of two tiotropium + olodaterol dose combinations. These studies are part of a large Phase III clinical trial program (TOviTO) for tiotropium + olodaterol FDC, which includes more than 7,000 people living with varying severities of COPD worldwide.

Tiotropium monotherapy, which is marketed as Spiriva HandiHaler (tiotropium bromide inhalation powder) in the US, is a once-daily LAMA indicated for both the maintenance treatment of bronchospasm associated with COPD and to reduce COPD exacerbations. Olodaterol monotherapy - marketed as Striverdi Respimat (olodaterol) Inhalation Spray - is a once-daily LABA indicated for the long-term maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

Capsugel & Cardax to Collaborate on Development of Proprietary Products

Capsugel and Cardax, Inc. recently announced a collaboration to develop unique astaxanthin products for the consumer health market. The goal of the collaboration is to commercialize proprietary formulations of nature-identical synthetic astaxanthin products with pharmaceutical-grade purity that will provide improved oral bioavailability compared with other astaxanthin products on the market. Astaxanthin is currently used as a specialized antioxidant.

The astaxanthin products will be jointly developed using Capsugel's proprietary lipid multi-particulate (LMP) technology, which encapsulates dissolved or suspended active ingredients into spherical lipid matrix particles for oral dosage in capsules, sachets, suspensions, or tablets. LMP technology utilizes a range of approved lipids to deliver the benefits of lipid-based formulations in multi-particulate format, including improved bioavailability, controlled release, and effective taste-masking. The companies will seek a strategic partner for retail commercialization in the mass market. Specific business terms were not disclosed.

"Our strategic partnership with Cardax provides an opportunity to be at the forefront of developing unique astaxanthin products for consumer health applications," said Amit Patel, Capsugel SVP and Dosage Form Solutions President. "Our premier bioavailability enhancement technology suite and lipid-based formulation expertise, coupled with our encapsulation know-how and infrastructure, will be leveraged to meet our partners' product profile and commercial goals of a high-quality final dosage form."

"Our collaboration with Capsugel provides the formulation expertise and infrastructure necessary for the advancement of proprietary astaxanthin products for consumer health applications," added David G. Watumull, Cardax President and CEO. "Participation in more of the consumer health value chain as a true partner with Capsugel could add substantially to our revenues, and the new intellectual property anticipated from this collaboration may provide a meaningful competitive advantage."

Capsugel is a global leader in delivering high-quality, innovative dosage forms and solutions to its customers in the healthcare industry. Cardax is a development-stage life sciences company that devotes substantially all of its efforts to developing consumer health and pharmaceutical products that provide many of the anti-inflammatory benefits of steroids or NSAIDS, but with exceptional safety profiles, as conferred by US FDA Generally Recognized as Safe (GRAS) designation at certain doses.

Seventh Sense Biosystems Closes $16-Million Financing

Seventh Sense Biosystems, Inc. (7SBio), the pioneering developer of virtually painless blood collection and diagnostic platforms, recently announced a $16-million Series B financing from a syndicate of global leaders in diagnostic technologies, pharmaceuticals, and clinical diagnostic laboratory services. New investors, the Venture Capital unit of Siemens Financial Services (SFS VC), Novartis, and Laboratory Corporation of America Holdings (LabCorp) participated in the financing with existing investors Flagship Ventures and Polaris Partners. 7SBio will use the proceeds from this financing to complete the development of its Touch Activated Phlebotomy (TAP) platform, which is designed to significantly improve the convenience and efficiency of blood collection.

"The addition of world-class strategic partners Siemens, Novartis, and LabCorp provides strong support to the company's momentum in bringing this revolutionary technology to market," said Howard Weisman, Chief Executive Officer of 7SBio. "The need for improving blood collection for point-of-care diagnostic testing in hospitals, doctor's offices, and clinical trials is significant as innovation in pre-analytical sampling methods has not kept pace with improvements in instrumentation and analytical methods. Our TAP products are intended to make diagnostics more comfortable, manageable, and ubiquitous for patients, transforming blood-based testing regardless of geography or setting."

"We believe strongly that the 7SBio technology will enable the next big wave of point-of-care blood collection and testing," said Ralf Schnell, General Partner at SFS VC. "The 7SBio management team has demonstrated a deep understanding of market requirements and has the vision and execution capabilities to capitalize on this massive market need. It was this combination of innovative technology and sound business strategy that drove our investment decision. We are excited to join the team and contribute to the company's success."

In the past month, 7SBio received notices of allowance for three US patents for its proprietary technology. The company received its first patent in October 2013. When fully commercialized, the TAP platform is expected to incorporate additional capabilities for sample separation as well as dried blood spot and on-board diagnostic abilities.

Touch Activated Phlebotomy (TAP) is a proprietary platform that draws capillary blood in a virtually painless, one-step process without having to access a vein. The TAP system penetrates the uppermost layers of skin through the use of micro-needles, collects capillary blood using a novel microfluidic extraction process, and stabilizes the blood with anticoagulant if required. The device has a visual indicator to confirm that collection is complete. The TAP platform is designed for fully automated, high throughput manufacturing.

Coherus' Biosimilar Meets Primary Endpoint In Pivotal Pharmacokinetic Clinical Study

Coherus BioSciences, Inc. recently announced that CHS-1420, its proposed biosimilar of adalimumab (Humira), met the primary endpoint in a pivotal clinical pharmacokinetic (PK) similarity study that compared CHS-1420 to Humira in healthy subjects. The parallel-group, single-dose study met the criteria for clinical PK similarity on all three required, prospectively defined, PK endpoints: maximum serum concentration (Cmax), area under the time-concentration curve from first to last time point measured (AUC0-t), and area under the time-concentration curve from first time point extrapolated to infinity (AUC0-inf), with all three geometric mean ratios fully within the 90% confidence interval from 80% to 125%. Both agents were well tolerated and there were no differential safety findings observed between the two agents in this study.

"An essential global regulatory requirement is the completion of a clinical study directly comparing the originator and our biosimilar candidate establishing PK similarity," said Barbara Finck, MD, Chief Medical Officer of Coherus. "We are pleased to have achieved robust results, which we believe represents a significant reduction in development program risk."

"Adalimumab is a very complex molecule. Achieving this clinical milestone further validates Coherus' development platform and demonstrates our ability to advance biosimilars across our portfolio," added Denny Lanfear, President and Chief Executive Officer of Coherus.

Coherus is a late-stage clinical biologics platform company focused on the global biosimilar market. Headquartered in the San Francisco Bay Area and composed of a team of industry veterans with decades of experience in pioneering biologics companies, our goal is to become a global leader in the biosimilar market by leveraging our team's collective expertise in key areas such as process science, analytical characterization, protein production and clinical regulatory development.

US-Manufactured API Urea From FDA-Registered Facility Available Q4

BioSpectra recently announced its cGMP, US-manufactured ICH Q7-based Urea, intended for use as an Active Pharmaceutical Ingredient, will be produced in its new FDA-registered facility in Bangor, PA, in fourth quarter 2014. Regulatory Packets, Validation Reports, and Type II Drug Master File Authorization are scheduled for contract customers of Bio Active Urea during second quarter 2015.

BioSpectra's Bio Active Grade Urea, Product Code UR22, will be manufactured in a qualified and validated ICH Q7-compliant API manufacturing suite as a highly purified crystal with optimum solubility, purity, and traceability. Future versions of Bio Active Urea will include liquid and spray-dried forms, both of which are currently scheduled for release in third quarter 2015. This product will be added to the current portfolio, which already includes BioSpectra's Bio Excipient Grade Urea, Product Code UR32, which is an ICH Q7-compliant Excipient supported by a Type IV Drug Master File.

"BioSpectra is committed to making highly pure, compliant, and traceable Active Pharmaceutical Ingredients and Excipients available to our industry," said Richard Mutchler, President of BioSpectra. "UR22 Urea is one of the legacy products we intend to offer as an aggressively priced, exceptionally pure material, designed for its intended end use to support the biopharmaceutical and pharmaceutical industries."

In keeping with BioSpectra's history, contract customers of this API will receive preferential pricing and early access to this essential material. BioSpectra is committed to serving its target industries by launching a series of safe, US-manufactured, highly purified and synthesized alternatives to existing key ingredients not currently supported by Drug Master Files.

BioSpectra is a FDA-registered cGMP-compliant contract manufacturer and commercial producer of amino acids, biological buffers, carbohydrates, pharmaceutical excipients, and active pharmaceutical ingredients. BioSpectra manufactures products for the biopharmaceutical industry in its state-of-the-art Pennsylvania facilities. Excipients manufactured by BioSpectra are produced in accordance with cGMP guidelines to provide the highest quality materials available to the biopharmaceutical industry. Active pharmaceutical ingredients manufactured by BioSpectra are produced in accordance with ICH Q7 guidelines to provide the highest quality materials available to the biopharmaceutical industry.

Charleston Laboratories & Daiichi Sankyo Announce Major Collaboration

Charleston Laboratories, Inc., through its wholly owned subsidiary LOCL Pharma, Inc., and Daiichi Sankyo recently announced the parties have entered into a strategic collaboration for the development and US commercialization of Charleston Laboratories' novel hydrocodone combination products, including CL-108, being studied for the treatment of moderate-to-severe acute pain as well as the reduction of Opioid-Induced Nausea and Vomiting (OINV).

CL-108 combines 12.5 mg of immediate-release promethazine with 7.5 mg of hydrocodone and 325 mg of acetaminophen. Charleston recently completed a 465-patient Phase III trial studying the effects of CL-108 as a treatment for moderate-to-severe acute pain and the reduction of OINV, where CL-108 demonstrated high statistical significance ($P<0.01$) in both primary endpoints relative to pain reduction and the symptoms of OINV.

Hydrocodone is the most widely prescribed medication in the US, with more than 131 million prescriptions annually. Opioid-induced nausea affects up to 30% of these patients, with approximately 15% experiencing vomiting. These unwanted side effects can result in poor pain control related to difficulties with compliance or return visits to the physician or the hospital for further treatment. As a consequence, OINV poses a significant burden for patients and prescribers, while contributing significant costs to the healthcare system.

With this collaboration, under the terms of the agreement, Daiichi Sankyo, Inc., the US subsidiary of Tokyo-headquartered Daiichi Sankyo Co., Ltd. (TSE: 4568), will be the exclusive commercialization partner for CL-108 in the US. Charleston Laboratories will be responsible for manufacturing activities for CL-108 and will receive the right to co-promote this and other hydrocodone products in the US.

Under the terms of the agreement, which is pending HSR clearance, Charleston Laboratories will receive $200 million split evenly between an upfront cash payment and a near-term milestone, and up to an additional $450 million in milestone payments connected to FDA filing and approval of its novel fixed-dose hydrocodone products in the US. In addition, Charleston Laboratories will receive escalating, tiered, double-digit share of the gross operating margin from the products, and will be responsible for supplying all product.

Charleston Laboratories, Inc. is a privately held, specialty pharmaceutical company focused on the research and development of novel pain products to significantly reduce the burdensome side effects related to opioid analgesics and other products. Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address the diversified, unmet medical needs of patients in both mature and emerging markets.

SHL GROUP

RESEARCH & INNOVATION OF AUTO INJECTORS TO ENHANCE PATIENT COMPLIANCE

The enhanced features and convenience provided by auto injectors has increased patient acceptance towards such self-injection devices in recent years. With a wide range of auto injectors already on the market and more entering soon, patients are now more familiar with this type of technology and expect devices to offer key fundamental features such as dose accuracy, ease-of-use, safety, and related feedback systems.

FUNDAMENTAL FEATURES

While designing such devices with the end-user in mind has always been part of most auto injector developments, the traditional emphasis on this relatively new medical device was more focused on features and related specifications. These features would be the incorporation and realization of the pharmaceutical companies' original injection specifications into the device's mechanical mechanisms and exterior design. For example, injection time would be dependent on the spring force or adjustments made to the power pack built into the device, whereas feedback forms can be the result of intricate component interactions before, during or after an injection. Other details including information on the primary container, injection depth, viscosity range, and more, were some of the key inputs behind the design of the auto injectors at the time. Today, these features have become mandatory benchmarks upon which new designs are realized, but now with an added emphasis on usability and human factors engineering (HFE) to help enhance the patient experience and to support compliance.

R&D WITH USABILITY IN MIND

With numerous biologics coming to market, timeline is especially critical to pharmaceutical companies when it comes to developing competitive combination products such as auto injectors. As the development of customized auto injectors can often take many years before launch, device partners are under more pressure to innovate technologies and manufacturing processes either to help shorten time-to-market or to be prepared for the pharmaceutical company's future portfolio needs. Since auto injector products are usually custom-built projects tailored to the drug's therapeutic specifications and targeted user preferences, considerations with regards to HFE and usability compliance are typically implemented during development stages. To stay proactive in providing patient-centric solutions, device manufacturers now need to examine usability studies as early as possible during R&D stages and innovate accordingly.

Figure 1. SHL's Amber is an intuitive 2-step auto injector designed with a unique ergonomic exterior.

An experienced device partner should already have a team of industrial designers skilled in optimizing product architectures while complying to design processes. Optimization considerations include integrating safety features, controlling costs, use of enhanced ergonomic designs and so on. It used to be the case that device components were added whenever a new function or feature was desired. Now, designers have to continuously research and innovate to minimize and simplify features for ease-of-use and manufacturability even before a pharmaceutical customer comes knocking on the door with a request. These designs should be ready to comply with standard HFE and usability guidelines and be reflective of basic usability studies conducted. To achieve this, the ideal device partner needs to have a strong R&D team and sufficient manufacturing capabilities in-house for support. By having both under one roof, conceptual designs can be quickly realized through prototype production and verified for manufacturability.

For example, as part of an internal user study, the mechanisms of a specific proven platform (disposable auto injector with single dose and no button) was placed inside 5 other specially designed prototypes with unique cap, body and rear cap. The purpose of the study was to perform qualitative research and observe the relationship between different device designs and the

user's perceptions, with the ultimate goal of further improving the current mechanism and for future design reference. Since the study was conducted for R&D and not intended for a device with a specific drug, a generic group of users unfamiliar with auto injectors was chosen instead of a targeted patient group. Including the original auto injector, a total of 6 devices were made available during this structured study. The results provided design insight into various aspects of usage including ways users removed the cap, how the device body was gripped, angles at which the device was held during injection, activation sequences and more. The users were also interviewed to gain a thorough and in-depth understanding of their behaviors, all of which were grouped and analyzed accordingly to help establish new design guidelines that were communicated back to the designers and engineers.

The investment in similar internal programs reflects a device manufacturer's dedication to partake in the on-going goal of designing intuitive auto injector devices in addition to just technical implementations. However, the latter example is for internal R&D only and is quite different from the human factors design processes required during an actual development program with a specific drug.

BEYOND THE DEVICE: TRAINERS AND LABEL INNOVATIONS

A medical device such as an auto injector can go through rigorous usability studies and embody as much human factors engineering as possible, yet still potentially result in patient's mishandling any device. Aside from user interface related causes, this can be the result of anxiety during injection and/or miscomprehension of the instructions included with the device. Traditional supplementary tools such as Instructions for Use (IFUs) can often consist of comprehensive information, pictures, icons and diagrams that the patient may not be able to fully follow at first use, especially when under stress. To provide more education and guidance for these patients, tools such as needle-less trainers and enhanced labels are now often encouraged for most device programs; especially those that are single use disposable devices.

Figure 2. Needle-less Trainers allow users to familiarize with the injection process and also help reduce anxiety.

Auto injector trainers generally simulate the look and feel of the actual device, but without any drug or needle inside. For many patients who are used to receiving treatments administered by trained healthcare professionals at clinics or hospitals, the idea of unsupervised self-injection can be intimidating. Trainers allow them to practice at home without the risk of potential injury and thus helps to give patients a clear understanding of how a device should function, relieving some potential anxiety. Even just one unsuccessful attempt can prompt the patient to develop concerns about future injections and may have a significant impact on their compliance with regards to the drug and device itself. Developing trainer devices has thus become an essential component of device programs, and a number of device suppliers have made it a goal to assist their pharmaceutical partners in providing more comprehensive toolkits for patients.

In addition, with digital technology and electronic devices quickly advancing and readily available around us, device labels can now be much more robust than just a sticker with mainly textual information. One example is a near field communication (NFC) integrated label, which allows the individual device to have its own digital signature. Reading the signature with a smartphone can give patients access to a range of alternative tools such as video instructions, voice-guided steps and treatment records, all with the goal to enhance patient education and compliance. These functions would have been otherwise difficult to build into the device without a significant impact on cost.

A NEW ROLE FOR DEVICE MANUFACTURERS

The self-injection device market has quickly matured in recent years and device designs are now often driven by patient usage behaviors and compliance. As a device manufacturer, it is no longer sufficient to directly translate the technological aspect of the specified design input requirements into a device. Both new and existing pharmaceutical players now expect that a device partner can offer not only a knowledge base but the proactive application of the data in their R&D innovations and available device platforms. This is especially essential for pharmaceutical companies that are developing an auto injector product for the first time. This way, the pharmaceutical companies can not only leverage the key established capabilities, which are still the foundation of all development projects, but also benefit from the past project experiences as well as the device manufacturer's on-going evolution to improve device usability and to provide support.

Figure 3. Looking at innovative technologies in areas such as labelling can help the patient experience.

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The Second Quadrant

Bioavailability Enhancement: Potential for Expanding Chemical Space

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

"Simplicity does not precede complexity, but follows it." – Alan Perlis

There are an estimated 6.9 billion unique mobile phone users in the world today, and it is widely thought that this number will exceed the human population by the end of 2016.[1] It is clear that mobile phones are no longer just a convenient way to keep track of your teenager via texting, but they are now shaping the very fabric of the global society. Significant discussion is underway regarding the role of mobile phones in everything from the search for democracy to managing the threats of disease outbreak. But did you ever stop to really think about how we got to the point where a mini-computer in your pocket can influence an entire society?

This journey starts at the infancy of modern, transistor-based computing, which is believed to have taken place in November 1953 with the first working prototype at the University of Manchester.[2] Initially computer circuit layout was done entirely manually and with only a few connections, thereby it was a tractable problem. But quickly, transistors began to shrink in size and correspondingly the design of the circuits became increasingly complex. The seeds of electronic design automation (EDA) emerged in the 1960s out of the necessity to automate integrated circuit design and virtual prototyping and perform analyses of functionality, performance, and manufacturability - all before manufacturing the actual circuit. This took serious investment in scientific, technical, and engineering innovation, to be sure. As the EDA industry emerged in the early 1980s, in addition to the innovations in manufacturing and the EDA software itself, not inconsequential were new approaches to partition the designs phases, discipline the methodology of design, encapsulate expertise through the use modeling, and accelerate the process using automation. While these four aspects of circuit design were not the only components propelling progress, they were an integral part of enabling circuits integrating a doubling of transistor count every 2 years. In addition to accelerated performance and expanded capacity and capabilities of integrated circuits, with EDA software and the methodologies it imposed, time-to-market timeframes could be accelerated on extremely complex projects. To get an idea of the complexity of a modern electronic circuit, there are now approximately 5 billion transistors on a microprocessor chip - a mere 2 billion less than the number of humans on the entire planet!

Obviously, the growth in computing power has not only enabled the mobile phone but has benefited society in countless ways: from IBM's Watson to dealing with Big Data in pharmaceutical discovery. All of these things were unimaginable even 20 to 30 years ago. They key point here is that those pioneers of the electronics industry had a vision for the potential computing could have on society, and they employed a disciplined approach to invest in the basic science and technology necessary to create a completely new industry. Without that, we might still be using slide rules.

BIG CHALLENGES, BIG OPPORTUNITIES

In recent columns, we've explored the adoption and diffusion of new technologies, and the cultures and character traits that foster innovation itself. In this month's column, my goal is not to focus on scientific and technological breakthroughs in solubilization, but on considering what might be achieved if we borrow best practices and processes that have assisted other industries facing growing complexity.

These are exciting times in our industry. Rapidly evolving technology, such as solubilization, targeted delivery, nanotechnology, and robotics has enhanced drug discovery and development. This, coupled with exciting new research in the areas of systems biology, genomics, proteomics, epigenetics, and computational modeling, has expanded the potential target space for new therapeutics with the promise of addressing currently untreatable diseases and improving the quality of life. Personalized medicine is becoming a quantifiable goal that many believe will be realized, and we are beginning to see treatments that are curative in cases where the standard of care was thought to be chronic therapy. At the same time, and perhaps because of these changes, the molecules in development are presenting unprecedented challenges for formulators and drug delivery experts.

THE POTENTIAL FOR SOLUBILIZATION

The growing need for enhancing the bioavailability of drugs to meet unmet medical needs is obvious. Industry data shows that 70% to 90% of drugs in development are poorly soluble. We have performed an analysis using a database of over 1300 marketed drugs, analyzing compound solubility and logP (water-octanol partition coefficient) that revealed that the (log normal) distribution centers on a solubility of 100 micrograms/mL and a logP of nearly 2.2. Assuming a similar density of compounds compared to historical trends, shifting this distribution to just a slightly higher logP and lower solubility, e.g., a solubility of 10 micrograms/mL and logP of ~4, we estimate that 450 new, yet-to-be-discovered drugs could be enabled using solubilization technologies.[3] And we calculate that this would expand the accessible market by 35%, representing nearly $140 billion in industry revenue in today's dollars. This is promising, as our analysis assumes no breakthroughs in solubilization technologies themselves, but only better utilization of those in place today.

LEVERAGING LIMITED RESOURCES

There is a significant amount of solubilization expertise in the industry, but it would be difficult to keep up with demand given the growing number of insoluble drugs in clinical development, estimated at between 2,300 and

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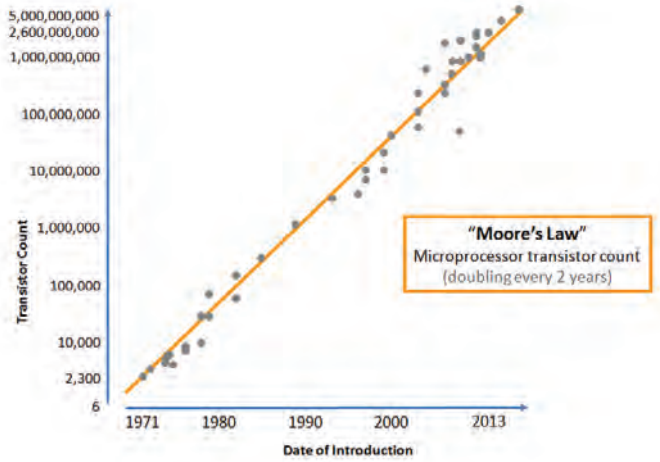
FIGURE 1



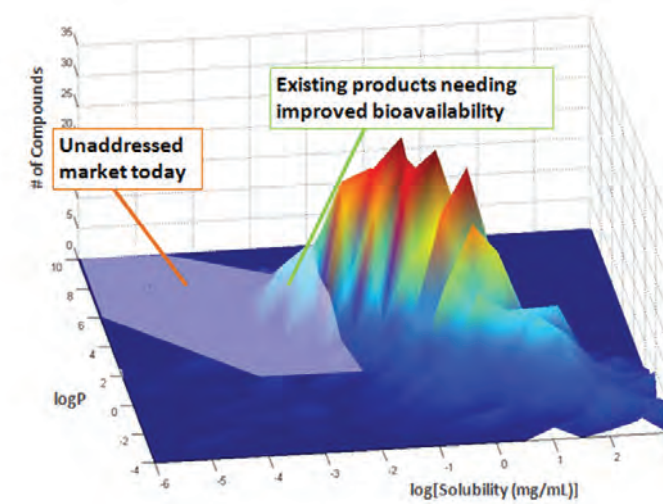
3,200.[4] In addition, no matter how much human expertise exists, the pressure for fast-tracking formulation and then subsequent clinical trials materials manufacturing underscores the cost and time-to-market pressures that are directly correlated with human and financial resources. The standard methodologies for formulation development in use today could benefit from ways in which existing expertise is leveraged and no quality is lost while handling an ever-increasing volume of drugs requiring solubilization.

CREATING KNOWLEDGE FROM DATA

The complexity involved in bringing modern medicines to the clinic today exceeds the abilities of any one person or even teams to apply empirical approaches in search of the best solution. Wherever experience-based methodologies are employed as the primary method development process, there's a significant opportunity for improvement. With the combination of specifications as noted above and robust modeling, formulating for greater bioavailability can be done in a manner that is faster and more repeatable. Accelerated, more rigorous and more accurate in silico exploration of drug and excipient combinations unimagined today can enable us to explore the chemical space that needs to be accessed for all of us to achieve greater solubilization success. Automation, combined with modeling, can deliver greater predictability and result in a higher-proportion of drug candidates that successfully navigate through the clinic.

Certainly, much of the advances in accelerating our solubilization processes are already borrowed from other industries, in many cases even the technologies themselves.[5,6] And more directly related to the electronics industry, we benefit from the computational power that continues to provide us the engines to accelerate our solubilization efforts. As a group tackling bioavailability challenges, let us be inspired by our potential to add similar disciplines and practices as those adopted by others. In so doing, we can more easily benefit from advances in computer technologies, and propel the development and delivery of solubilized drugs across the finish line. ◆

FIGURE 2



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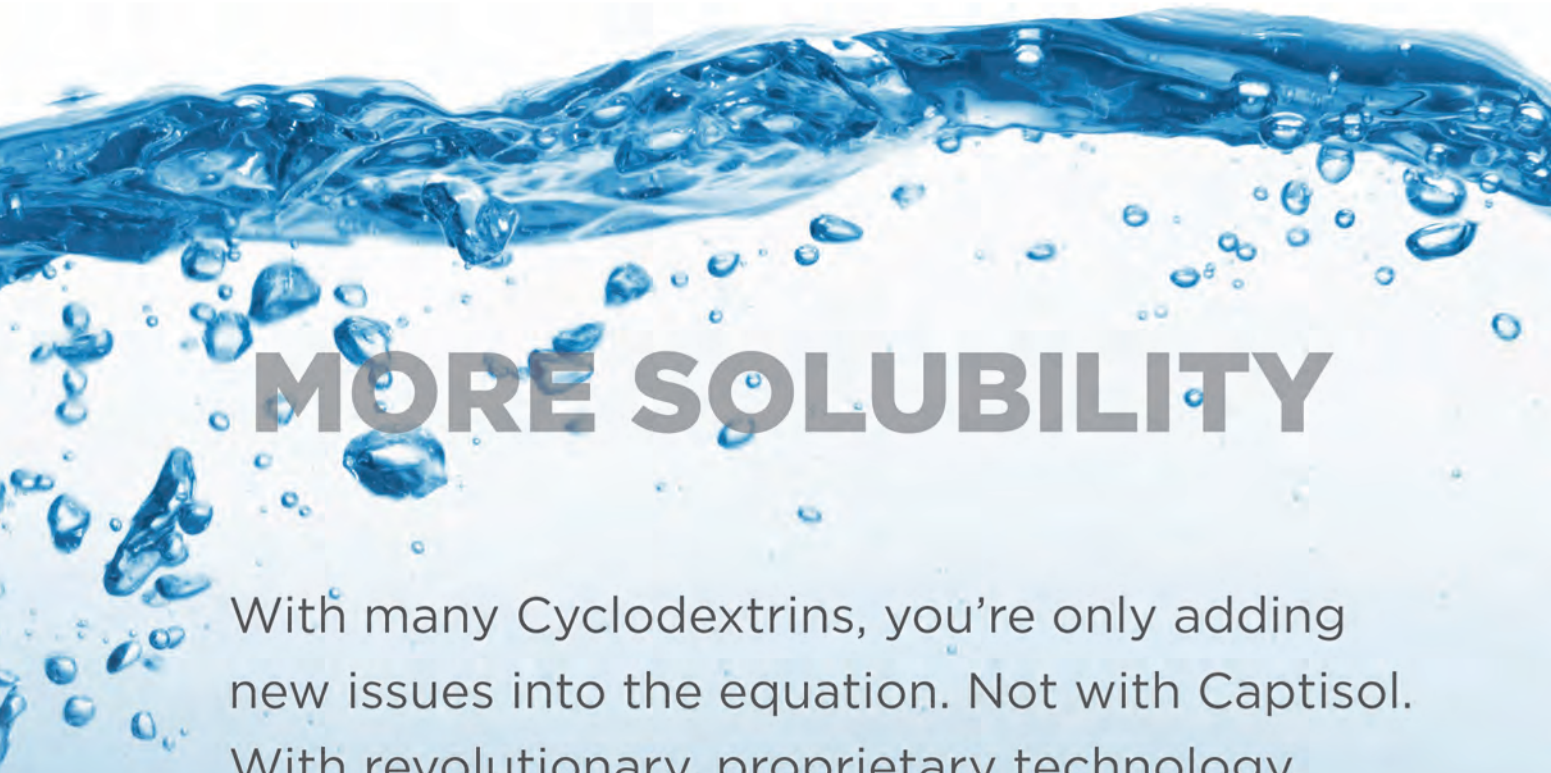

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Management Insight

The Davids of Drug Development

By: Derek Hennecke, CEO & President, Xcelience LLC

Inspiration from Malcolm Gladwell's latest book, *David and Goliath*

We are an entire industry of Davids. Every one of us is a little guy, facing insurmountable odds, scouring the countless compounds of the universe in search of a cure. Every scientist in every lab labors through the seasons in pursuit of that single spark. Every project manager, receptionist, human resources officer, and manager works in tandem for the same cause. Once in a while, we achieve a flicker of light, and spirits soar. Most of them sizzle and die out. And yet we move on, like addicts in search of a buzz, pursuing that moment again; that one incredible high that is drug discovery.

Malcolm Gladwell's latest book, *David and Goliath*, is a feel-good book to inspire our industry. It isn't remarkably new. It is about the concepts of creative destruction and disruption. We've seen it in Richard Foster's, *Attacker's Advantage*, and in some of the concepts from Nassim Taleb's Antifragile.

The author of *Tipping Point, Blink and Outliers* begins this book by telling us that everything we know about the story of David and Goliath is wrong. We've learned about a scrap of a shepherd boy who was the only Israelite brave enough to take on the massive Goliath. Powered by faith, he met his better on the field of battle and bested the mighty giant with only a slingshot.

Actually, writes Gladwell, Goliath never had a chance. Sure, David broke the rules, but he knew he had a good shot at taking Goliath out if he did. As a shepherd, David was skilled with the sling. Not a slingshot - that's a child's toy. A sling is a leather pouch with two long cords and a pouch. He would swing that pouch around a few times and let fly his projectile at speeds approaching 35 meters per second. That's much faster than the best pitcher in major league baseball. He would slip a piece of local stone into the sling: barium sulphate is twice as dense as a normal rock. This combination gave his weapon the stopping power of a 45-mm handgun. He was practiced at using it at great distances for the protection of his flock.

Goliath, meanwhile, was nearly immobilized by metal. He was also almost certainly visually impaired. The text hints at this, and so does the science. Whenever an individual deviates largely from the cultural norms of height, the most likely explanation is

acromeglia, a disease in which the body never ceases producing growth hormones. Measuring 6 feet 9 inches, Goliath almost certainly suffered from acromeglia and its common side effect—double vision or debilitating near sightedness, caused by a pituitary tumor compressing visual nerves. The result is double vision or debilitating near sightedness.

This is the problem with giants, Gladwell surmises. "The same qualities that appear to give them strength are often the sources of greatest weakness." Underdogs, meanwhile, take risks and chart paths that the powerful elite would never contemplate.

Gladwell provides numerous anecdotes demonstrating how the underdog tries harder. A David, by his definition, is someone who doesn't have the resources or the authority to make a difference in the conventional way; and yet, they are so desperate to succeed that they think differently than Goliath. Therein lies their strength. They see the world differently, and that mindset frees them to come up with unconventional ideas.

Disadvantage becomes advantage. Dyslexia, for example, is abnormally prevalent in high-performing people - Richard Branson, Charles Schwab, and Brian Glazer among others. Such individuals are forced from a young age to work differently from others. The early loss of a parent is another disadvantage, yet nearly a quarter of all US Presidents (12 of 44) lost a parent at a young age - including George Washington and Barack Obama. The impressionists of Europe were a largely impoverished group of artists with a shocking artistic style. Tossed out of conventional salons, they created their own art shows. Eventually, their works surpassed in popularity most of the greatest traditional artists of that time.

Drug developers fight incredible odds every day. Every step in our path is fraught with failure. Here are three moving stories of Davids who overcame significant challenges to advance medical science.

JAY FREIREICH – LEUKEMIA: DAVID VS. THE ESTABLISHED BODY OF MEDICAL OPINION

Born to Hungarian immigrants, Dr. Jay Freireich's father died in his youth, and his family lost everything in the Great Depression. He scraped through medical school. A notoriously bad-tempered and callous man, he made few friends. His disinterest in social niceties thwarted his career. He was fired seven times.

In 1955, he began work in the children's leukemia ward of the National Cancer Institute. It's hard to imagine a more heartbreaking place to work. Ninety percent of his patients bled to death within 6 weeks of arriving. They bled from their ears, skin, mouth, and noses. Medical science was failing them.

But Dr. Freireich cared nothing for the usual way of doing things. Like so many Davids, he didn't feel constrained by his colleagues' opinions. In fact, Gladwell asserts that his previous suffering was essential to his later achievements. His colleagues couldn't do or say anything he hadn't seen or heard before. He had nothing to lose. He launched a series of unorthodox methodologies, including the daily sampling of bone marrow from his young patients without anesthetic. He wasn't intentionally cruel, it was simply that anesthetic had little effect in this procedure.

His priority was to stop the bleeding, which he was certain was caused by low platelet counts. His supervisors disagreed. Against their objections, he transfused patients with platelets. He succeeded in temporarily stopping the bleeding. Once the children weren't bleeding to death, he could consider treatment. Frustrated by the lack of success with a single chemotherapy drug, Freireich proposed a mix of four medications: Methotrexate (an antifolate), vincristine (a Vinca alkaloid), 6-mercaptopurine (6-MP), and prednisone - together referred to as the POMP regimen. Again, his colleagues rigorously objected. If a single chemo served only to prolong a child's agony, four was inhumane! When the NCI approved his regimen for initial testing, several doctors on the ward refused to participate. But by giving the doses in combination, he was able to reduce the dose to 60%. This lower dose reduced toxicity while maintaining efficacy.

Today, combination chemotherapy is the basis for any chemotherapy regimen. The cure rate for the type of leukemia Freireich treated is 90%. We owe both of these advances largely to the fact that Dr. Jay Freireich had nothing to lose, and so was willing to risk everything to find a cure only he believed in.

SYNTA – ELESCLOMOL: DAVID VS. STATISTICAL IMPROBABILITY

This story, particularly relevant to our industry, comes from Gladwell's blog. A

Taiwanese-born cell biologist in his mid-60s, Dr. Lan Bo Chen, a founding partner of Synta Pharmaceuticals, saw countless compounds in industries outside of drug development just sitting around untested. He felt the search for new drugs should be as far and wide as possible.

The first improbability Dr. Chen surmounted was in finding a philanthropist to give him $4 million dollars to spend as he saw fit. He immediately purchased a batch of 22,000 chemicals gathered from all over Russia and the Ukraine and a machine to screen 96 compounds at a time, a hundred batches a day.

At first, the chemicals killed everything, normal and cancerous. When he found a compound that killed only cancer cells, he reduced the amount of chemical on the plate a 1000-fold and tried again. One chemical withstood the tests. The cancer cells reacted to it "like a blowtorch." It was a strange little chemical called elesclomol, something no one ever would've thought to try. The chemical gathered up copper from the bloodstream and deposited it in the mitochondria, causing an electrochemical reaction. The idea of using copper to cause this kind of reaction was bizarre. No one ever would have come up with it through a rational approach.

Still more improbabilities lay ahead. No one had any idea what the new drug should target. It showed promise for ovarian cancer, sarcoma, even melanoma. But cost was a factor. They couldn't test it on everything. They zeroed in for Phase II on lung cancer, soft-tissue sarcomas, and melanoma.

Still more decisions had to be made - decisions that could significantly affect the trial's outcome. What if the drug only worked on low-LDH patients and not high-LDH? What if it worked against a melanoma that adhered to the skin but not the kind that invaded the liver? What if it only worked well in second-stage cancers, or on patients who have not been treated with other forms of chemo? Even a major pharma house can't afford multiple Phase II trials on a single disease. The company settled on a single trial allowing for the presence of the full myriad of variables.

In the world of cancer research, melanoma is something of a holy grail. It's one of the most complex and variable cancers, and in the previous 35 years, there had been some 70 large-scale Phase II trials for metastatic-melanoma. None made it to the next phase. Synta, meanwhile, had other problems. Its other, more statistically probable candidates had all failed. The company began discussing lay-offs.

Two days later, Chief Medical Officer Dr. Eric Jacobson gathered Sytna's 130 staff in the company lobby to present the Phase II results for elesclomol. The data was rigorously detailed. The staff was silent slide after slide, waiting for the one and only thing that mattered: the Kaplan-Meier graph. This two-line graph would show patients who received treatment on one line, and those who received the control on another. If the two lines separated, the drug was a success.

When Dr. Jacobson flipped to the Kaplan-Meier, his audience gasped. He continued talking. A few slow claps erupted, Gladwell reports. There were tears. Their lives had changed. Patient lives had changed. Their little company had a chance to win. It was the type of moment drug developers live for. But it was only Phase II.

The trials moved to Phase III, enrolling 650 patients in 15 countries, backed by GlaxoSmithKline. There were problems with making a water-soluble version of the drug, but compromise was achieved, and the trial continued.

Too soon, another call came. More patients in the treatment group were dying than in the control group. The study was halted. The data revealed that the drug was failing patients with high-LDH tumors. Glaxo ended the collaboration.

Synta, like so many biotechs, continues to fight the odds. The company has regrouped and is moving forward with further clinical trials on elesclomol for other cancers, and their website reports early promise. They've since added another drug, ganetespib, to their oncology portfolio. They continue to pursue that high. It takes a certain kind of person to drive forward through such unbearable odds. It takes a David mentality. In drug development, we see this attitude everyday.

DR. DEVI SHETTY - HEART TRANSPLANTS: DAVID VS. POVERTY

Dr. Devi Shetty, a cardiothoracic surgeon, has been dubbed "The Henry Ford of Heart Surgery" by *The Wall Street Journal*. When he first returned to his native India in 1989, very few patients could pay the $2,400 cost of his surgery, even if their lives depended upon it, writes Davis Lui, a physician blogger who expanded on Gladwell's ideas in a recent blog. This combination of urgency of need

and lack of resources begged for Dr. Shetty's David mindset, says Lui.

Many surgeons before him had walked away from the problem, but Dr. Shetty chose to explore a different tact. Maximizing economies of scale to reduce costs, Dr. Shetty now oversees 42 cardiac surgeons who performed 3,174 cardiac bypass surgeries in 2008, more than double than the 1,367 performed by the Cleveland Clinic in the US that year, according to Dr. Liu's blog.

The sheer volume of surgeries performed at Dr. Shetty's hospitals allows each doctor to zero in on a specific area of specialty. Surgeon Colin John, for example, has performed nearly 4,000 Tetralogy of Fallot procedures, a complex procedure that corrects four different heart defects simultaneously. He has almost certainly achieved the 10,000 hours of practice necessary to achieve mastery of a field.

Dr. Shetty's team now performs 12% of all cardiac surgeries in India. That reality gives him tremendous buying power. When a European manufacturer failed to lower the cost of hospital gowns, he convinced a group of Indian entrepreneurs to take up the job, reducing costs by 60%. A new hospital cuts costs by pumping air conditioning only into operating theaters and intensive care units.

Urgency and lack of resources combined to create an environment ripe for a David mindset. Dr. Shetty reduced the cost of surgery to $1600. Compare that to the $106,000 regularly paid for the same surgery in the US. Even accounting for differences in the cost of living (Delhi's cost of living is 54% of Atlanta's), this achievement is staggering.

THE IMPORTANCE OF GOLIATH

Innovation involves taking risks and breaking rules. This is something individuals do. Companies do the opposite. The larger the company, the more the rules. Gigantic cash flows can smother the incentive to find better ways of doing things. Institutional memory can inhibit new ideas at their source. Lipinski's Rules, hERG liabilities, and other rules of drug selection do more to stifle development than to facilitate it.

Goliath shouldn't try to be David. And yet, we very much need our Goliaths in this industry. So too did the armies in the time of David. In fact, as Gladwell points out, every army had their massive foot soldiers, clad like Goliath with swords and armor, leading the army into battle. But they also had infantry - those sling-bearing soldiers like David, in the rear. Together they formed a powerful combination.

We have thousands of Davids out there slogging away at their science in pursuit of a spark. Most of them are in biotech. But biotech needs big pharma to takes those ideas that work to the next level. Only big pharma can bankroll a trial of hundreds of rare patients across 15 nations.

Drug development is an industry uniquely replete with Davids. They provide the spark that drives development. David and Goliath, working for the same common cause, form a potent army in the war against disease. This is the model for our generation. ◆

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BIOGRAPHY

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

LEACHABLES STUDIES

Investigating Leachables in Oral Solid Dosage Forms

By: Chris Connolly and Niculae Miron

INTRODUCTION

Discovering at a late stage of development that a contaminant leached into your drug product is a biopharmaceutical sponsor's nightmare - and can be extremely costly. As drug products become increasingly potent, more-sensitive analytical methods are needed to determine lower acceptable levels of contaminants. The US FDA and European Medicines Agency (EMA) have issued directives to identify and quantify contaminants, such as genotoxic and carcinogenic impurities, at increasingly lower levels, nanogram or lower.

Advanced, highly sensitive testing technologies available today, such as high- performance liquid chromatography (HPLC), can detect extremely low levels of leachables, enabling sponsors or their contract research organizations (CROs) to detect more contaminants in their drug product. For every leachable detected, they must determine whether to conduct extractables and leachables (E&L) studies and the extent of testing necessary to ensure regulatory approval and the safety of their product for patients.

For drug products dispensed from medical devices, sponsors need to know whether any contaminants have leached into the drug from the device components, secondary packaging, or other materials. When leachables are detected, investigators must determine their identity and the level to which they will accumulate in the finished drug product over its shelf-life, as well as the impact of storage conditions, and whether the level of leachables is acceptable. They also need to develop appropriate methods for E&L analyses that are adequately sensitive and specific to the compound. While E&L studies are usually not relevant for solid dosage forms, there are times when these investigations are advisable.

E&L studies can be challenging, and regulatory guidances are not specific. As part of the studies, investigators must develop test methods appropriate to detect, identify, and quantify potential leachables, and if found, assess their toxicity. Consequently, sponsors often outsource these studies to a highly qualified CRO.

In this article, Patheon explains the importance of conducting leachables studies for solid dosage forms in certain situations, and describes its leachables study of an oral solid dosage form delivered in a medical device.

WHAT ARE LEACHABLES & EXTRACTABLES?

Leachables are chemical compounds that migrate into the drug formulation from any product contact material, including elastomeric, plastic, glass, stainless steel, or coating components as a result of direct contact with the drug formulation under normal process conditions or accelerated storage conditions and are found in the final drug product.[1] They can increase the toxicity and impurity levels of the drug product and react with product components. Extractables are chemical compounds that migrate from any product contact material when exposed to an appropriate solvent under exaggerated conditions of time and temperature.[1]

REGULATORY GUIDANCE

The FDA Guidance for Industry, Container Closure System for Packaging Human Drugs and Biologics, provides guidance on principles for submitting information on packaging materials used for human drugs and biologics. For oral tablets and capsules, the degree of concern associated with the route of

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administration is low, as is the risk of interaction between packaging components and a solid oral dosage form. For tablets, appropriate reference to the indirect food additive regulation for each material of packaging construction can be submitted.

For medical devices, extractables and leachables testing is required by the Center for Devices and Radiological Health (CDRH) of the FDA. The CDRH requires a 501(k) premarket submission: an assessment of the stability and compatibility of each drug or biologic intended to be used with the medical device, and a safety evaluation of any leachables, extractables, impurities, and degradants from the medical device into the drug product.

Various ISO guidelines address the issue of impurities. The following are four key guidances for the biological evaluation of medical devices:

- ISO 10993-13: Identification and quantification of degradation products from polymeric medical devices.
- ISO 10993-15: Identification and quantification of degradation products from metals and alloys.
- ISO 10993-17: Establishment of allowable levels for leachable substances.
- ISO 10993-18: Chemical characterization of materials.

Development, validation, and testing of components must be carried out under International Conference on Harmonization (ICH) and US Pharmacopeia guidelines.

The ICH Tripartite Q6A guideline Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances indicates that an extractables study is only recommended for oral liquid and parenteral drug product, but not for tablets or hard capsules.

In addition to various ICH guidances on impurities, the FDA Guidance for Genotoxic and Carcinogenic Impurities in Drug Substances and Products recommends approaches to characterize and reduce the risk of patient exposure to these impurities. The guidance references the threshold of toxicological concern (TTC) as 1.5 micrograms per day.

STUDY OF TABLETS DISPENSED FROM A MEDICAL DEVICE

Patheon conducted a study to determine the source of the leachables discovered in a low-strength tablet (label claim: 10 micrograms/tablet and 15 micrograms/tablet) packaged in a medical device, and whether the drug product met the acceptable level of contaminants for the particular compound.

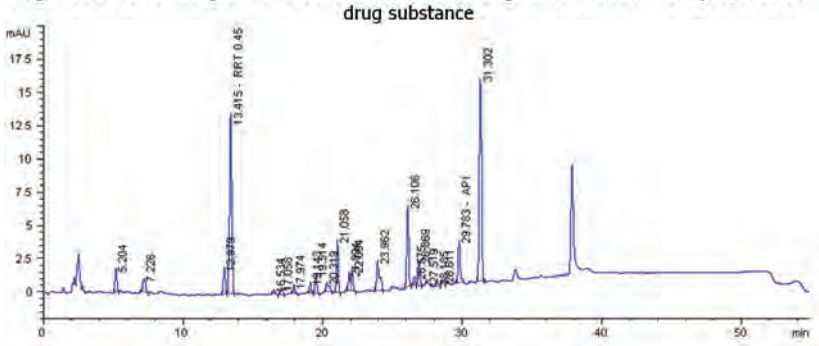
During Phase II studies to test the chemical and physical stability of the product, two unknown impurities were detected in products packaged in a polycarbonate cartridge in a foil pouch with oxygen-scavenging sachet. One of the key chemical attributes tested was changes to the profile of related substances (impurities), which indicate degradation of the active pharmaceutical ingredient (API). The related substances method was developed to detect and quantitate impurities down to the ICH reporting threshold for the lowest tablet strength.

The investigators conducted a study to determine the source of two unknown impurities detected at relative retention times (RRT) of 0.45 and 0.76 RRT and tested under accelerated and long-term storage conditions. RRT is an analytical parameter used in chromatographic procedures to control impurities in a drug product, correcting variation in peak retention time related to HPLC system variance. The RRT relates each impurity peak retention time to that of the reference standard of the API.

When testing the impact of storage conditions on drug product stability, the investigators found that the relative magnitudes of these peaks were higher in samples stored at 40°C/75% Relative Humidity (RH) compared with those at 25°C/60% RH, and increased with storage

FIGURE 1

Figure 1. A chromatogram of extract solution of the Original Foil Pouch in the presence of drug substance



time for products packaged in cartridges. When testing the product in different secondary containers, they found that neither of the impurities was detected in the product packaged in plastic HDPE bottles. Because the impurities were not detected in the bottle configuration, the investigators suspected they might originate from the cartridge components or pouch material.

Related substances of the low-strength solid dosage form were determined using an HPLC method with a diode array detector (DAD) and quantitation at 235 nm (limit of quantitation ~ 0.05 micrograms/mL). To identify the source of the two impurities, pouch materials and each of the cartridge components were separately extracted in an aqueous buffer solution at 50°C for 72 hours and in an organic medium at room temperature for 24 hours. Extracted solutions were analyzed with the product-related substances test method. Both the RRT of the peaks and UV spectra collected from the DAD were used for peak identification.

Based on the RRT and UV spectra analysis, the RRT 0.45 was found to be a leachable from a pouch material, while RRT 0.76 was a leachable from two of the cartridge components and identified as Bis-Phenol A (BPA).

TABLE 1

Table 1: Peak Area Count of Impurity RRT 0.45 detected in pouch material extracts

Extraction Condition	pH 2.2 Buffer 50°C 72 hours	pH 2.2 Buffer 50°C 72 hours With Drug Substance	ACN/Water 2 hours Sonication	ACN/Water 2 hours Sonication With Drug Substance	ACN/Water 24 hours 50 °C	ACN/Water 24 hours 50 °C With Drug Substance
Original Pouch	450.2	562.5	109.63	140.0	1059.5	1821.1
Alternate Pouch	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected

FIGURE 2

Figure 2. A chromatogram of the drug product with the impurity at RRT 0.45

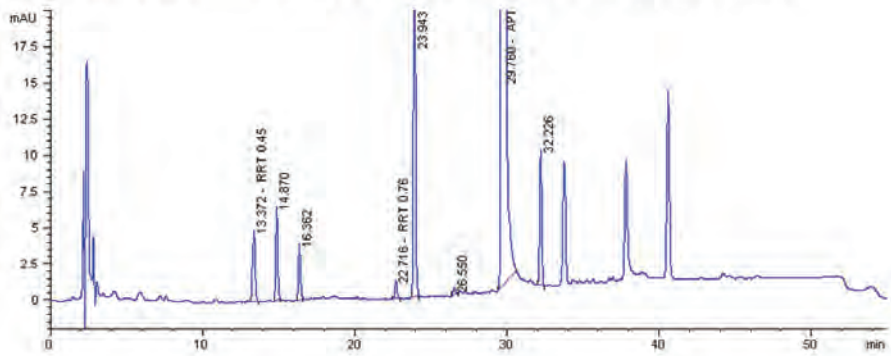
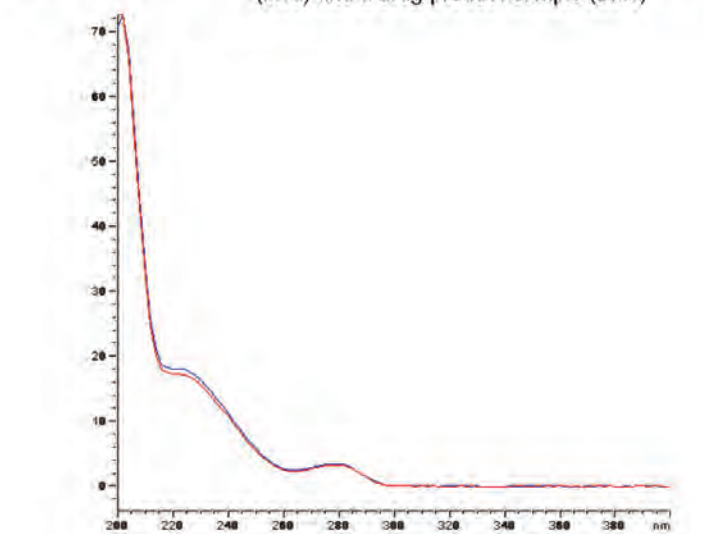


FIGURE 3

Figure 3. UV spectra collected from the peak of RRT 0.45 of original foil pouch extraction (Red) and a drug product sample (Blue)



RESULTS

Leachable Study for Impurity Peak at RRT 0.45

In chromatograms of the extracts of a pouch material in both aqueous buffer and organic medium, a peak was observed at RRT 0.45 (Figure 1). As a comparison, a typical chromatogram of a drug product sample with the impurity at RRT 0.45 is shown in Figure 2. UV spectra of these peaks also matched that of the RRT 0.45 impurity in the drug product (Figure 3). This peak was not observed in the chromatograms of extracts from the cartridge components. Therefore, the impurity was determined to be a leachable that migrated from the pouch material into the dosage form during drug product stability storage.

A new alternate foil pouch material was extracted under the same conditions, and the impurity was not detected under any tested

TABLE 2

Table 2: Peak Area Count of Impurity RRT 0.76 detected in extract solution from cartridge component and pouch material (ND: Not detected)

Extraction Condition	pH 2.2 Buffer 50°C 72 hours	pH 2.2 Buffer 50°C 72 hours With Drug Substance	ACN/Water 2 hours Sonication	ACN/Water 2 hours Sonication With Drug Substance	ACN/Water 2 hours sonication and 24hours 50 °C	ACN/Water 2 hours sonication and 24h hours 50 °C With Drug Substance
Base	ND	ND	28.3	30.7	410.3	401.2
Shuttle	2.3	2.8	ND	ND	ND	ND
Shipping Tablets	1.9	2.1	ND	ND	ND	ND
Cover	ND	ND	35.9	24.7	1680	283.4
Spring	ND	ND	ND	ND	ND	ND
Shuttle Catch	0.9	1.4	ND	ND	1.8	2.1
Recon Dome	1.7	2.2	ND	ND	ND	ND
Dowel Release	ND	ND	ND	ND	2.0	3.1
Original Pouch	ND	ND	ND	ND	ND	ND
Alternate Pouch	ND	ND	ND	ND	ND	ND

conditions (Table 1). Therefore, in the absence of any other consideration between the two pouch materials, the original pouch was replaced by the alternate pouch for future packaging.

Leachable Study for Impurity Peak at RRT 0.76

Two of the cartridge components contributed to a peak at RRT 0.76, which was identified as BPA, a plasticizer known to be present in the polycarbonate cartridge components. Table 2 summarizes results of the RRT 0.76 impurity extracted from cartridge components and foil pouch material in an aqueous medium and organic solvents. Aqueous extracts of cartridge components showed a small peak at RRT 0.76, whereas the foil pouch material extracts did not show any peak. Organic extracts of most of the components did not show any significant peak at RRT 0.76. However, the cartridge base and cover extracts in organic solvent had the RRT 0.76 peak in large amounts. A typical chromatogram of extract solution from a cartridge component is depicted in Figure 4.

Because a significant amount of RRT 0.76 impurity was extracted from the cartridge base and cover made from polycarbonate, BPA, a plasticizer for polycarbonate manufacturing, was analyzed using the liquid chromatography (LC) method (Figure 5). The investigators observed that the retention time of BPA was very close to the RRT 0.76 impurity extracted from cartridge base and cover in organic solvent. The UV spectra of BPA, the impurity of RRT 0.76 from cartridge base extraction, and the impurity of RRT 0.76 in the drug product are displayed in Figure 6.

UV spectra collected from the three sources have identical UV absorption profiles. We concluded that the impurity of RRT 0.76 in the drug product sample is BPA, a leachable from the cartridge base and cover.

Recently, BPA has been the subject of health concerns. During product development, the highest BPA amount detected was 0.34% for a 15-microgram strength product, which equates to 0.001 mg intake per day. According to the EPA's Integrated Risk Information System, the reference dose for chronic oral exposure (RfD) of BPA is 5 x10-2 mg/kg-day. For a 50-kg adult patient, BPA intake from the drug product is 2500 times less than the threshold at which a health concern will be raised. Therefore, there is low risk in the cartridge/pouch system for the dosing device.

Because the BPA levels in the packaged product were several orders of magnitude lower than the EPA's acceptable limit, no changes were determined to be necessary for the cartridge materials.

FIGURE 4

Figure 4. A chromatogram of extract solution of the Cartridge Base in the presence of drug substance

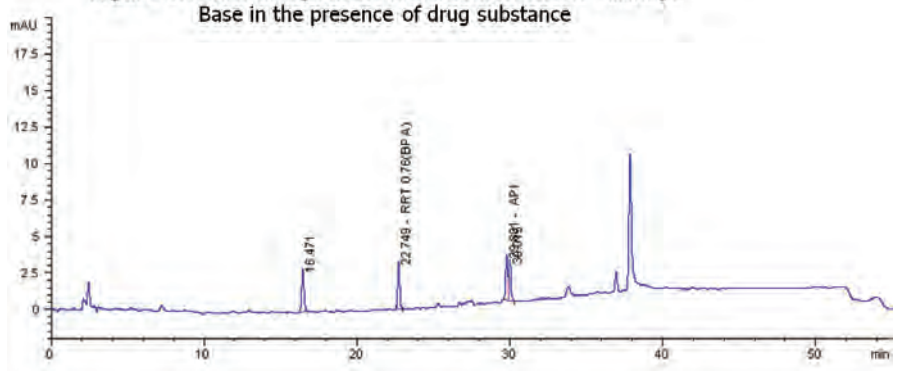


FIGURE 5

Figure 5. A chromatogram of Bis-Phenol A (BPA)

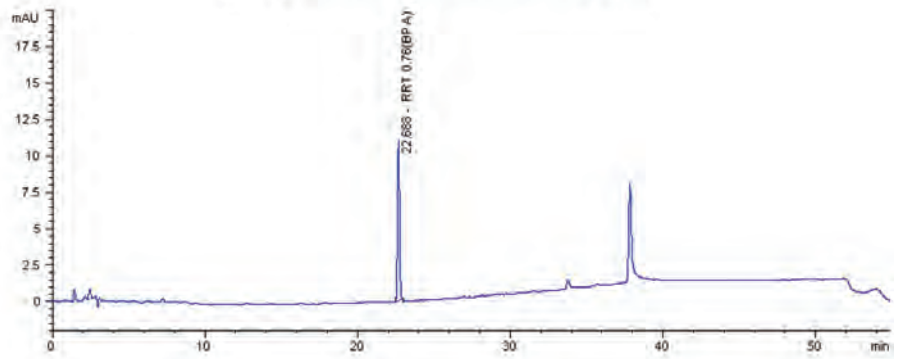
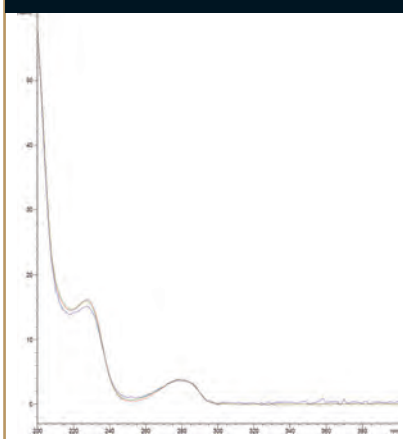


FIGURE 6



UV spectra collected from peak RRT 0.76 of cartridge base extract (Red), BPA (Green), and a drug product sample (Blue).

Study With Modified Packaging Configuration

An experimental lot of drug product was packaged in a polycarbonate cartridge sealed in the alternate foil pouch (the pouch that did not display the RRT 0.45 impurity in the leachable study) and stored at accelerated conditions (50°C/75% RH). At the 3.5-month time point, a review of chromatographic traces of this sample did not show any impurity peak at RRT 0.45, and the amount of the RRT 0.76 impurity was 0.053%.

CONCLUSION

With increasingly potent drug products and lower acceptable levels of contaminants today, more-sensitive analytical methods must be used to detect and analyze leachables and determine drug product safety. Although the risk of interaction between packaging components and a solid oral dosage form is small, E&L studies may be necessary for low-dose products when the related substance profile is monitored with a very sensitive method. For drug products in medical devices, investigators must understand E&L testing methods and make sure the devices are unadulterated to the drug products they deliver. A highly experienced E&L partner can help you conduct these sensitive and specific analyses, mitigating risk at this late stage in product development. . ◆

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BIOGRAPHIES

Chris Connolly earned his BSc in Biochemistry and has worked in the biotechnology and pharmaceutical industries for 19 years, starting as an analytical chemist, and rising to be manager of analytical chemistry and of operations excellence. He joined Patheon in 1999, and is Manager of Analytical Development for Pharmaceutical Development Services. He has worked on dozens of early-to-late clinical-stage development projects for solid and semi-solid dosage forms, leading activities including development and validation of analytical methods, formulation evaluation, development of product specifications, clinical batch release, stability studies, and CMC reviews.

Niculae Miron earned his BSc in Chemical Engineering from the University of Ploiesti, Romania. He has worked as an analytical chemist for more than 15 years with various Canadian pharmaceutical companies. He has been working as a Senior Chemist since 2008 with Patheon Inc., within the Analytical Development Laboratory of Pharmaceutical Development Services.

A Novel Approach to Mitigating Oxygen Permeation in Prefilled Syringes

By: Peter Sagona, MS, Rómulo Romero, MS, and Adam Breeland

SiO_2 Medical Products (SiO) is a vertically integrated manufacturer of primary containers. Using advanced materials science, SiO has developed a line of parenteral drug containers that offer improved performance and consistency over existing containers. SiO's containers are precision-molded from medical-grade plastics, and the interior surface has a thin, transparent, silicon-oxide based coating system. Our containers combine the durability of plastic with the high-purity and barrier properties of glass, while eliminating the shortcomings of existing glass and plastic containers.

INTRODUCTION

Parenteral drug containers are multicomponent systems designed to safely store a drug until it is ready for administration to the patient. Historically, parenteral drugs are first launched in vials, with subsequent development of prefilled delivery options. Recent trends in the industry, however, show an increase in the use of prefilled syringes as the primary container of choice.[1] There are several factors to consider when selecting the components for a drug delivery system, such as the nature of the active pharmaceutical ingredient (API) (eg, molecule size and complexity), oxygen sensitivity, formulation pH, cytotoxicity, and stability, among others. In this article, we will focus on oxygen permeation into a sealed syringe and detail how the individual system components (syringe, needle shield, and plunger) contribute to the overall Oxygen Transmission Rate (OTR). Whole article testing refers to an experimental design in which the OTR of a fully assembled syringe is measured, mimicking the environment that a drug product would be subject to in a prefilled, ready-to-use syringe. Glass has historically been the material of choice for the syringe, and while glass provides an excellent oxygen barrier, other factors should also be taken into account when selecting components for a prefilled syringe system. More complex formulations reaching the market today, such as proteins, monoclonal antibodies (mAbs), and other biologics can have compatibility issues with the silicone oil that must be used to provide lubricity for glass. Oxygen ingress is not limited to the syringe wall; the other components of the prefilled syringe (the plunger and needle shield) also contribute. SiO offers an alternative to traditional glass primary packaging, namely cyclic olefin polymer (COP) parenteral containers with an internal coating of pure silicon oxide providing glass-like oxygen barrier properties.[2] As part of a Quality-by-Design (QbD)-driven development process, SiO has developed a means for quantitatively

measuring oxygen ingress into prefilled syringes, and furthermore, we are able to measure the OTR contribution from the individual components (barrel wall, plunger, and needle shield).

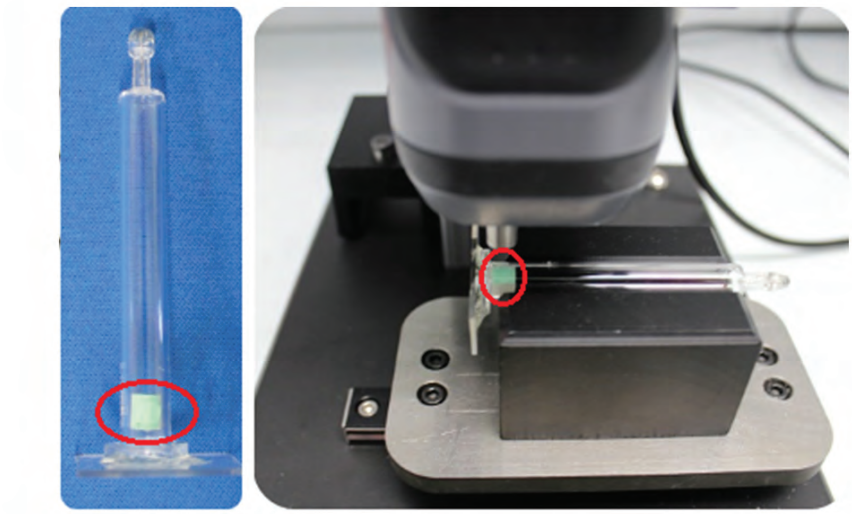
UNDERSTANDING THE NEEDS OF THE PRODUCT

Understanding the nature and requirements of the drug product is a key step in designing a prefilled syringe system. Every drug product has unique needs to be met. At a basic level, a container must protect the API purity and stability. Accelerated stability testing and forced degradation studies of the API/drug product will reveal potential liabilities for the drug that must be considered. Borosilicate glass is a material with a long track record in parenteral containers; however, it has many disadvantages, such as the potential for breakage and a high count of visible particles, which have led to costly recalls. Newer formulations reaching the market now, such as proteins, monoclonal antibodies, etc., have complex requirements, such as higher sensitivity to silicone oil and aggregation from high particle counts, thus requiring a more cautious approach. For purposes of this discussion, we will focus on understanding drug product oxygen sensitivity and controlling oxygen ingress into the prefilled syringe. Forced degradation and early accelerated stability studies should provide the development team an indication of the areas of concern for API stability, including oxygen sensitivity. Once an initial basic understanding of the API sensitivity to oxygen is obtained, there are several approaches that can be taken to further understand the oxygen sensitivity and determine the maximum allowed oxygen ingress into the prefilled syringe system (ie, not adversely affect the drug product). A quantitative approach can be taken that involves stability testing of the API at various O_2 partial pressures and determination of the rate of oxidation. A complete discussion of this approach; however, is outside of the scope of this discussion. A more general approximation could be determined by placing the API/formulation in an oxygen-enriched environment and submitting it to accelerated conditions (eg, 40°C/75% RH). This approach should provide the development team enough information to select candidates for the optimal container. At a basic level, the oxygen sensitivity of the API will be categorized as none, slight sensitivity, or high sensitivity.

RATIONAL CONTAINER DESIGN

The understanding of the drug product needs gained by early stability and degradation studies will allow for a rational approach to container design in which individual components are selected according to how they meet those needs. Prefilled syringes have the advantage of delivering an accurate dosage to the patient in a safer, easy-to-use format; to do so, they have to be sterilizable, maintain CCI, protect the drug product from possible extractables and leachables from the container (labels, adhesives), and also provide some protection against breakage. Depending on the nature of the API, some concerns (such as breakage in the case of cytotoxic drugs) can be of greater importance than others.[3] Components should be selected that address the specific needs of the drug product. This discussion focuses on whole article oxygen permeability and, therefore, we need to consider the oxygen permeability characteristics of the syringe wall, plunger, and needle shield. Other more general considerations are outside the scope of this article.[4]

FIGURE 1



Oxygen sensor inside an epoxied syringe (left) and on fluorescence reader (right).

METHODOLOGY

The OTR is determined using an optical oxygen analyzer. The Mocon system uses an optical sensor containing a platinum metal complex that fluoresces directly proportionally to the amount of oxygen present in the environment. Working in an oxygen-depleted environment, the oxygen sensor is placed in the container to be tested, and the container is then sealed using an epoxied glass slide. The samples are then exposed to standard atmospheric conditions at room temperature, and the fluorescent quenching of the metal complex, specific to oxygen, is measured non-destructively over time to determine the increase in the concentration of oxygen in the test article. The ingress of oxygen is measured daily for a week or longer. In the early stages of container optimization, only the coated wall area was tested for OTR, excluding contributions of the needle shield and plunger. Once our development process achieved consistent oxygen-barrier properties along the wall, comparative studies were performed on a variety of whole article assemblies to evaluate SiO's performance relative to that of other commercially available products. The differential in the observed OTR, when testing whole articles, led to the determination of the individual contributions of each component (ie, plungers and needle shields) to demonstrate the additive effect of each component to the whole article OTR.

CALCULATIONS

The OTR into a whole article syringe at a given time t is given by:

$$\frac{dp_{O_2}}{dt} = \frac{RT}{V} P_{wa}\left(p_{O_2,outside} - p_{O_2,t}\right)$$

Where V is the syringe internal volume, P_{wa} is the whole article permeation coefficient (moles time^{-1} pressure^{-1}), $p_{O_2,outside}$ is the oxygen partial pressure outside the container, $p_{O_2,t}$ is the oxygen partial pressure inside the container at a particular time t, T is the absolute temperature, and R is the gas constant. The whole article permeation coefficient is dependent on the syringe component permeation characteristics and syringe geometry:

$$P_{wa} = \overline{P}_{wall} A + P_p + P_{ns}$$

Where A is the syringe wall area, $\overline{P}_{wall}$ is the average permeance of the wall (moles time^{-1} wall area^{-1} pressure^{-1}), P_p is the plunger permeation coefficient (moles time^{-1} pressure^{-1}), and P_{ns} is the needle shield permeation coefficient. On integration of the rate equation:

$$ln\left(p_{O_2,outside} - p_{O_2,t}\right) = ln\left(p_{O_2,outside} - p_{O_2,0}\right) - \frac{RT}{V} P_{wa} t$$

where $p_{O_2,0}$ is the oxygen partial pressure in

the container at time zero (typically near zero). Plots of $In\ (p_{O_{2,outside}} - p_{O_{2-t}})$ vs t should be linear with a slope for the whole article (time^{-1}):

$$slope_{wa} = -\frac{RT}{V} P_{wa}$$

The whole article permeation coefficient (moles time^{-1} pressure^{-1}) calculated from this slope is the key experimentally determined value from the measurement. From the permeation coefficient, the OTR can be determined and then converted to any unit desired. In an effort to standardize, the units cc/package/day, including the measurement conditions, were chosen.

DISCUSSION

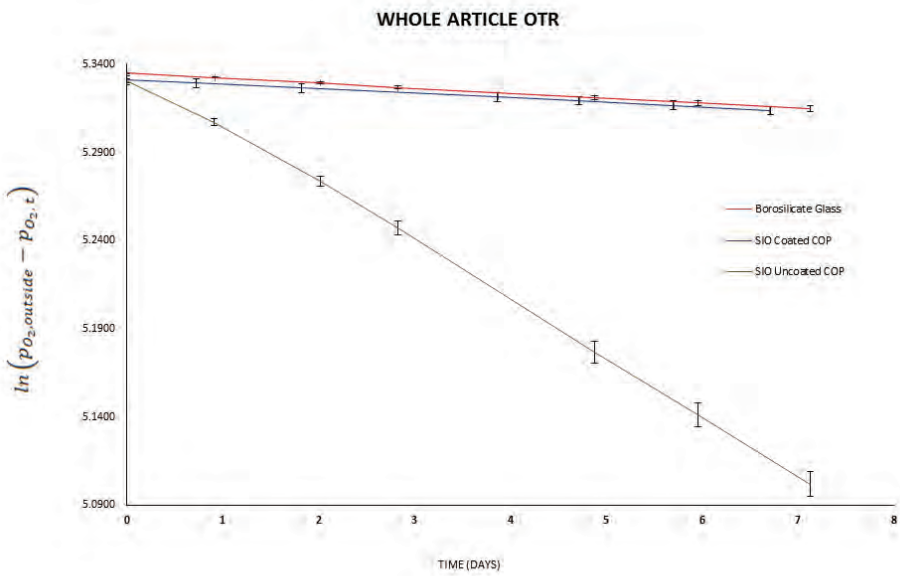
Once a drug product reaches the level of development when the primary container selection process begins, the development team should have some understanding of the drug product sensitivity requirements. For purposes of this article, we will focus solely on oxygen sensitivity. The team will be faced with a number of options

TABLE 1

OTR (cc O_2/Package/Day (25°C, 60% RH@0.21 atm)		
	Whole Article	Wall Only
Glass	0.0009	0.0000
Competitor Uncoated COP	0.0217	0.0181
SiO-Coated COP	0.0011	0.0003

Whole article vs wall OTR.

FIGURE 2

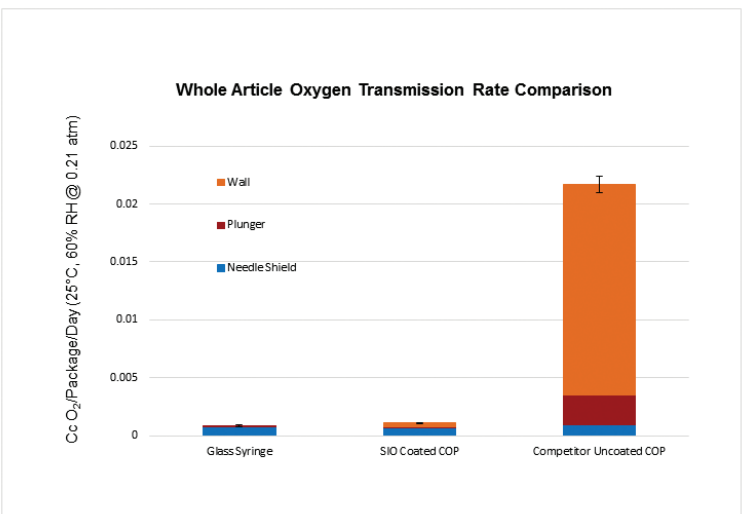


Representative data from OTR measurements.

regarding the choice of wall materials because in response to market requirements, manufacturers have developed new syringe wall materials that offer alternatives to glass. We will focus our discussion on a comparison of the oxygen-permeance properties of glass, uncoated COP, and coated COP containers from SiO.

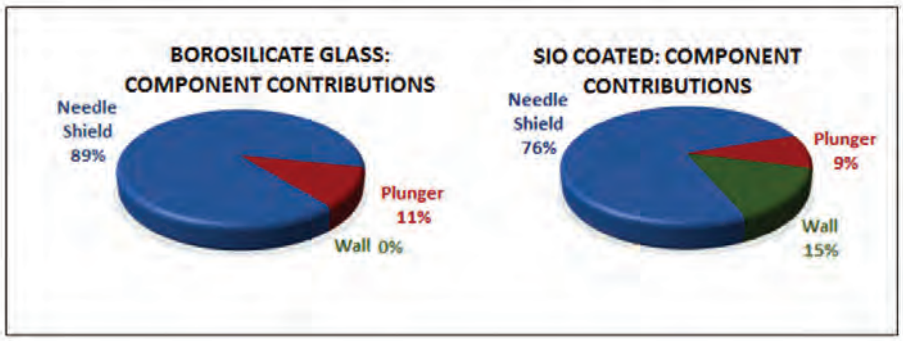
Whole article OTR measurements show that uncoated COP syringes are at a clear disadvantage when compared to glass (Table 1) due to the oxygen permeability of COP. SiO-coated COP syringes show much lower OTR compared to uncoated COP due to the unique internal barrier coating that gives the syringes glass-like properties. However, when we look at the oxygen permeance from the wall alone, it is evident

FIGURE 3



Whole Article OTR Comparison

FIGURE 4



OTR component percent contributions.

that the wall contribution is not the major contributing factor to oxygen ingress.

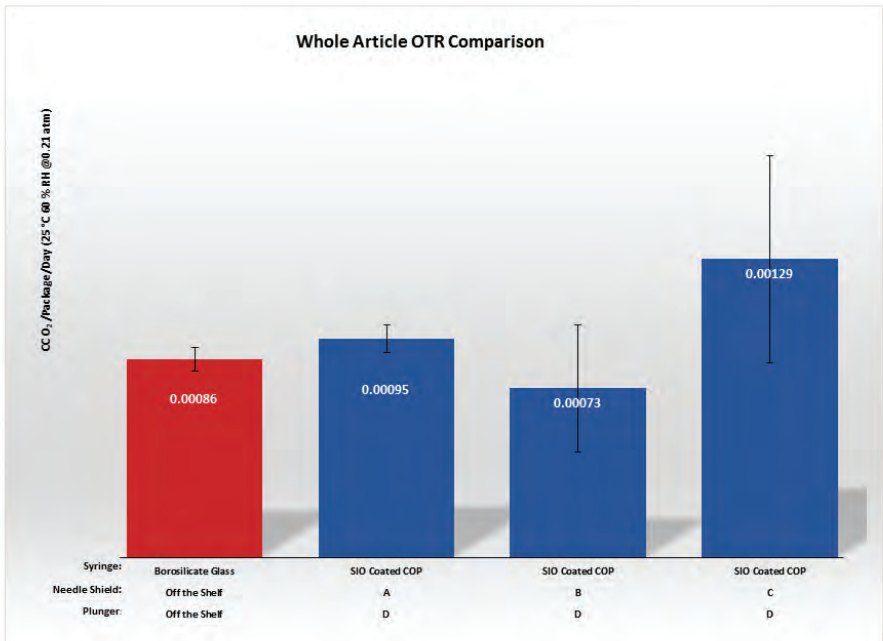
A detailed analysis (Figure 3) shows the individual component contributions to oxygen ingress: the data shows that for glass and SiO-coated COP syringes, the component with the greater contribution to oxygen permeance is the needle shield. Contributions from the wall and plunger are minimal in comparison (Figure 4).

Container closure components and their assembly have an effect on whole article OTR. Figure 5 demonstrates that OTR varies with needle shields using a coated COP syringe barrel. Additionally, a reference value for a purchased commercial glass syringe system is shown. The selection of appropriate closure parts can allow whole article SiO parts to approach glass syringes, and in one example, yield an even lower oxygen ingress. With rational design and selection of components, coated COP syringes can protect oxygen-labile drug products. The data shown in Figure 5 was produced using a single condition and was not optimized for closure part assembly. Thus, the observed variability in the data is a combination of the needle shield design, assembly conditions, and elastomer properties.

CONCLUSION

With biological systems entering the market place at an increased rate, oxidation sensitivity is an issue that will need to be considered further. The novel materials with improved performance entering the marketplace offer a new variety of options that should be examined and understood by development teams. In this article, we have focused on designing a primary container system (prefilled syringe) for the minimization of oxygen exposure to the drug product. Initial stability studies will provide the formulation team an idea of how sensitive the drug product is to oxidation, and this should be taken into account when selecting a container for the

FIGURE 5



Whole Article OTR comparison.

drug product. The oxygen contributions from the various components available need to be accounted for - simply choosing a wall material that is impermeable does not ensure good oxygen inertness. The oxygen permeability of COP-molded syringes for use as prefilled syringes has been investigated at the whole article and the individual component level. With a more thorough understanding of the individual contributions to OTR, a rational approach can be taken to designing a container system that meets the needs of the API. We have demonstrated that the COP syringes from SiO (coated with an internal barrier liner) offer oxygen permeation characteristics that are glass-like. Furthermore, once the OTR for whole article coated is taken into consideration, COP syringes from SiO can approach (and in one case surpass) the oxygen permeation of glass prefilled syringes. The new coated COP syringes from SiO offer the advantages of plastic containers (resistance to breakage, more precise molding, and low particulates) along with the advantages of glass (good gas impermeability, chemical resistance, no organic extractables). Utilizing QbD principles, SiO_2 Medical Products has developed a process that produces superior products through our leading-edge technology, superior quality, and consistent product performance. ◆

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BIOGRAPHIES

Peter Sagona is Senior Vice President at SiO2 Medical Products, responsible for program management, including overall project coordination of deliverables and timelines. Mr. Sagona also oversees the intellectual property strategy associated with the program. Prior to joining SiO, Mr. Sagona spent 11 years with CV Holdings LLC, and 7 years at SmithKline Beecham Clinical Laboratories managing automation development projects. Mr. Sagona earned his MS in Engineering Management from Drexel University.

Rómulo Romero is a Senior Applications Scientist at SiO2 Medical Products and an analytical chemist with over 15 years of experience supporting the pharmaceutical discovery. Mr. Romero earned his MS in Organic Chemistry from Florida State University. He was with Bayer Pharmaceutical in West Haven, CT, for 13 years supporting medicinal chemistry by solving purification challenges, and previously with Neurogen Corporation in Analytical Development and Merck in Boston, carrying out purifications of compound libraries and learning SFC.

Adam Breeland is an Analytical Chemist at SiO2 Medical Products, responsible for method development and validation, writing test methods, and training lab technicians. He collaborates with internal engineers and consultants on a variety of new product development projects as well as existing product enhancements aiding in experimental design and test output matrices. Mr. Breeland earned his BS in Chemistry from Millsaps College.

Special Feature

Safer, Simplier, and Smarter Devices

By: Cindy H. Dubin, Contributor

Current estimates value the global market for injectable drugs at $240 billion, giving injectables a 28% share of the overall drug market worldwide. This annual *Drug Development & Delivery* report on hand-held devices reveals that the injectables sector is witnessing some very specific trends that are affecting the market's growth.

For example, biologics are being attributed as the main driver for this growth because these are larger molecules that need to be administered by injection given their size and profile. The biologic drug market is expected to grow to $251 billion by 2018 and $900 billion by 2024.[1] For these larger and more viscous biologic products, wearable injectors could prove invaluable. Single-use wearable or bolus injectors deliver precise amounts of drug in doses as high as 30mL. With approximately 250 molecules identified by Roots Analysis requiring wearable injectors, the bolus market is projected to generate $8 billion in device sales by 2024.

Another trend is a move toward more customized hand-held devices that take advantage of platforms that have already been developed. Customizing these platforms differentiates them from the competition and enables pharma/biopharm companies to reach the clinic and, ultimately, the market faster.

Finally, manufacturers are developing hand-held devices with the user in mind. This Human Factor Engineering provides detailed understanding of how the devices will be used, identifies safety risks, and is expected to help ensure patient compliance.

This year's report explores the products from a variety of device developers that are incorporating one or several of these abovementioned offerings into their devices.

The Pro-Ject® auto-injector from Aptar Pharma incorporates human factors into its design.

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APTAR PHARMA PRESCRIPTION DIVISION—INTEGRATING THE HUMAN FACTOR IN THE DEVELOPMENT CYCLE

It is generally accepted that Human Factor Engineering is an integral part of developing any new drug delivery device. Human Factor studies address many different "human elements," such as perceptual, cognitive, ergonomic, emotional, social, and even cultural. The outcome of Human Factor studies should provide a clear understanding of how to avoid errors, identify safety risks, improve patient education/training and competence, and eventually patient compliance.

In addition, clear regulatory guidance has emerged from various government authorities, including the U.S., Europe, and others, over the last few years. This guidance outlines how to integrate Human Factor studies into drug delivery devices during their development in order to optimize their design and gain successful regulatory approval.

Aptar Pharma applied Human Factor guidelines to the Pro-Ject® development cycle. Aptar Pharma's Pro-Ject is a novel auto-injector that has been designed and developed with input from patients and healthcare professionals to ensure patient convenience and compliance.

During the initial Pro-Ject concept phase, Aptar Pharma carried out several investigations and market studies with patients and healthcare professionals. The main objective of these studies was to better understand users' and healthcare professionals' experiences, expectations, and preferences for auto-injectors.

Once a prototype of Pro-Ject was developed, additional user acceptance studies and investigations were performed to deepen the understanding of how rheumatoid arthritis patients interacted with Pro-Ject. Results demonstrated that both training nurses and rheumatoid arthritis patients confirmed the benefits of Pro-Ject in terms of ease of use, ergonomics, and design. Features include push-on-skin activation, slow injection, hidden needle, highly visible indicator window, and audible feedback.

"Patient-centric development of drug delivery devices is now the accepted norm. Applying Human Factor principles means that the outcomes should benefit all the stakeholders involved," says Dr. Gerallt Williams, Director Scientific Affairs, Aptar Pharma Prescription Division. "Aligning Pro-Ject with patient needs during its development is a major step forward in delivering this benefit.

The Credence Companion's modular 'snap-on' approach simplifies the development path to a passive needle-retraction, automatically disabling safety device.

CREDENCE MEDSYSTEMS INC.—DIFFERENTIATING BIOSIMILARS WITH HAND-HELD DEVICES

FDA's recent acceptance of Novartis' application for a biosimilar version of Amgen's Neupogen marks a new stage in the race to the U.S. biosimilar market. This race, fueled by the $50-plus billion worth of biologics coming off patent by the end of this decade, as well as the cost pressures and market reaction from the Affordable Care Act, will create an opportunity for hand-held delivery devices. Biosimilar developers aim to be as "biosimilar as possible"

to the FDA-licensed biologic while still offering meaningful market differentiation from the innovator product. In this effort, biosimilar manufacturers have an opportunity that is not as readily available to generics manufacturers: they can differentiate on something other than price. The ace-in-the-hole is the hand-held delivery system, explains John A. Merhige, Chief Commercial Officer, Credence MedSystems Inc.

"With biosimilars, FDA has anticipated the use of delivery systems that are different from those approved with the innovator products, allowing for the well-known advantages of delivery devices such as prefilled syringes or auto-injectors, even if the innovator was approved in a vial," he says. "This brings with it the obvious requirement to demonstrate compatibility with the drug formulation, but perhaps also the onus and opportunity to demonstrate the advantages of the new device. With evidence to support improved safety, better compliance, proper dosing, etc., the delivery device becomes a meaningful and valuable source of differentiation for biosimilars and other drugs, as well as a powerful lever for biosimilar manufacturers. Even with the tangible upside afforded by the device, it is important to remember that drug manufacturers will still need to minimize the development path complexity and sourcing risk associated with launching in a new delivery device."

Credence MedSystems will launch the Companion Safety Syringe System later this year. Initial meetings with a select group of biopharm manufacturer partners indicate that the value the Companion brings lies not only in the end-user benefits of the final device, but also in the simplified path for biopharm partners to bring their drug to market in the Companion System. For the end-user, the Companion System is a best-in-class safety device with passive needle-stick prevention features, explains Mr. Merhige. At the completion of the injection, the needle automatically retracts into the syringe barrel and the syringe is automatically disabled. The Companion allows the choice of any size needle, offering passive safety, even with needles two inches or longer, which Mr. Merhige says is unique in the market.

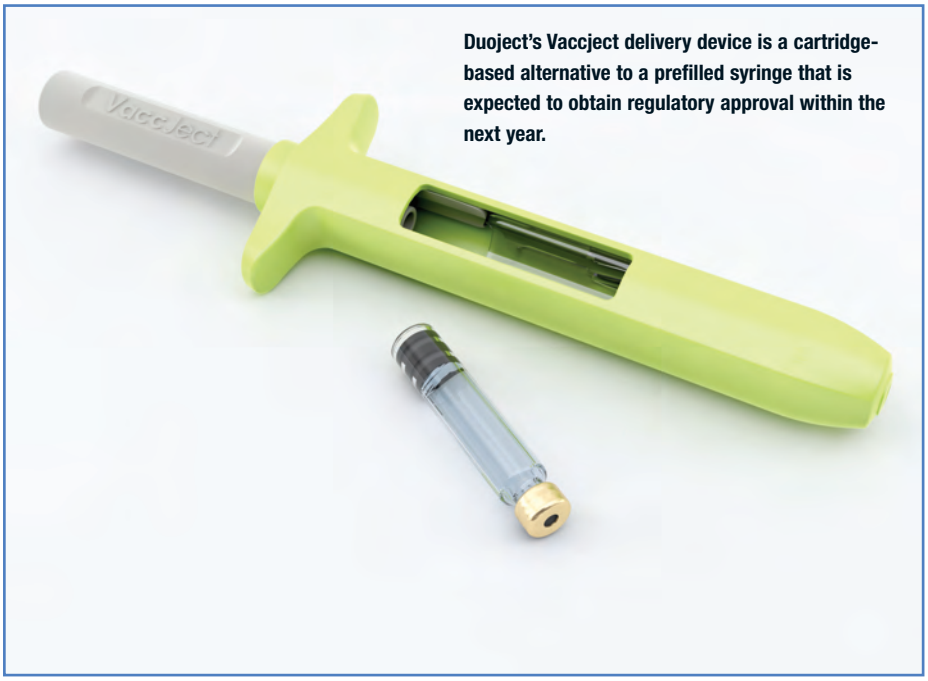
Also unique is its role in lyophilization applications where conventional safety devices tend to fail due to premature activation of the safety features during aspiration or reconstitution. The Companion, prefilled with a diluent, allows delivery into the vial for reconstitution followed by drawing up of the drug solution into the syringe, all while maintaining the passive safety intact for the injection into the patient. This, says Mr. Merhige, is critical given the wide array of biologics that require a lyophilized presentation to achieve appropriate shelf life.

"Whether for the growing number of inexperienced home injectors who need needle-stick safety and prefer the naked prefilled syringe to the auto-injector, or for the traditional caregiver dealing with time pressures, the Companion provides safety and flexibility in drug delivery," he says.

Of further importance to drug manufacturers is the modular approach of the Companion Syringe System. Biopharm manufacturers have complete freedom to choose and source the critical syringe, plunger/stopper, and tip cap primary package components from any vendor(s) they choose. The Companion plunger rod, Flex Finger Flange, and Guide-On Needle components accompany and snap on to the prefilled syringe. The primary drug container is undisturbed and there is no contact between the Companion components and the drug product before use. This approach dramatically impacts the development and regulatory requirements, as well as the sourcing risk profile, for the biopharm partner, he says.

A major challenge to biopharm manufacturers lies in the inherent difficulty of making any changes to existing commercially available products, whether innovator drugs or generics, due to the traditional development and regulatory requirements to modify a drug/device product. "While the resistance to change is understandable and often warranted, it has had the undesirable effect of keeping technological advances in delivery systems out of the market," says Mr. Merhige. "With a new approach and significantly simplified commercialization path, the Credence Companion addresses this challenge and offers the biopharm partner a new option to differentiate their products by delivering to their patients and providers the best technologies available."

Looking ahead in the market, the near future will likely bring new ISO standards for small-bore luer connections, intended to improve the reliability of connections and reduce the likelihood of mistaken connections between unrelated delivery systems. Mr. Merhige says: "The recent past shows a surprising prevalence of needle-to-syringe luer



Duoject's Vaccject delivery device is a cartridge-based alternative to a prefilled syringe that is expected to obtain regulatory approval within the next year.

connection failures, stemming often from incorrect user procedures due to poor ergonomic design, unsatisfactory user instructions or simple user error. Regardless of the reason, the results include needles being left in patients after injections, spilled and wasted drug product, inaccurate dosing, etc."

He adds that Credence has approached this issue by developing the Guide-On Needle Cover. The cover is designed to allow easy attachment by dexterity-challenged users; fingertips are not needed but rather the needle can be attached by holding the cover in a fist or in a thumb/forefinger wedge. Further, the user receives audible, tactile, and visual feedback of a successful needle-to-syringe connection. Finally, the cover cannot be removed until the needle has been mounted successfully with a pre-determined torque level, ensuring that the aforementioned failures will not occur.

DUOJECT—IMPLEMENTING CLIENT NEEDS INTO DESIGN

In order to design the optimal device for an application, it is important as a design firm to not only fully understand the client's requirements and expectations but also understand the overall scope of the project and application, i.e. the operational context, the end user, the geographical setting, etc.

"This is what has enabled Duoject to incorporate features in its device that might not have been considered had the company only focused on meeting the mechanical aspects of the project," explains Dan MacDonald, Vice President, Engineering Services, Duoject. "Through the years, Duoject has developed a design methodology that ensures all aspects of a project are considered and evaluated for incorporation in a specific device design."

Duoject has successfully transitioned into manufacturing by completing the validation phases of production for two of its reconstitution devices: the E-Z-Link and PenPrep EVO. The cartridge-based PenPrep EVO reconstitution device will be part of a major pharma company's combination product and will be entering into production in the fall for market launch in early 2015. The E-Z-Link, currently used in clinical trials, received regulatory approvals this past year in the form of a 510k and CE Mark and is now available for commercialization.

Duoject's Vaccject delivery device is a cartridge-based alternative to a prefilled syringe, including a built-in auto-retract needle safety feature. One advantage of this device is that the compact 1mL cartridge drug container can be kept separate from the device until moment of use, greatly improving cold-chain storage, says Mr. MacDonald. Its integrated safety feature ensures that the injection needle is never exposed to the user, either before, during or after injection. It is intended for vaccines as well as any other drug that requires safe injection.

Vaccject has undergone a range of testing and user studies these past years with the goal of obtaining regulatory approval within the next year. Duoject has partnered with a major contract filler to offer cartridge filling services to pharma companies interested in its Vaccject device.

During this past year, Duoject concentrated its efforts in obtaining regulatory approvals for its reconstitution devices as well as its ISO 13485 certification. The company also entered into development of a novel hand-held injection device for a client, details of which are still confidential at this time, but should be available to the public within the next year, says Mr. MacDonald.

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SGS Life Science Services is pleased to announce the upcoming opening of its new GMP/GLP laboratory in the Los Angeles area of California. The new facility will house 7,500 square feet of dedicated laboratory space to deliver analytical development and quality control testing to West Coast clients. With a grand opening scheduled for the Third Quarter of 2014, services at this facility will include:

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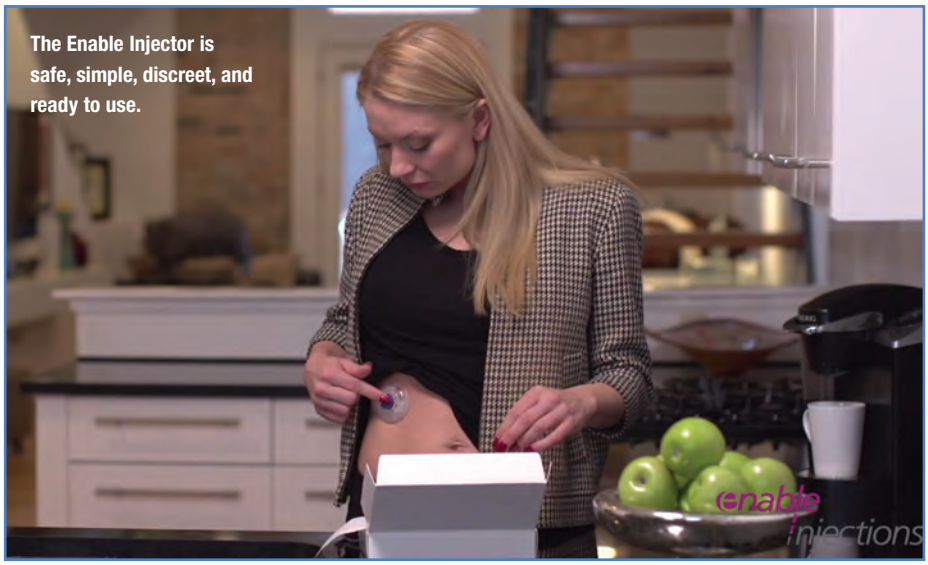
ENABLE INJECTIONS—BOLUS INJECTOR DELIVERS HIGH VOLUME AND MIXES LYOPHILIZED SOLUTIONS



The Enable Injector is safe, simple, discreet, and ready to use.

Enable Injections is a start-up company that has developed a disposable body-worn bolus injector to deliver high-viscosity/volume payloads up to 20cc to the subcutaneous tissue. The company has completed its 16th Human Factors study and continues to conduct HF studies in parallel with design work. "Our findings are that our Enable Injector is strongly preferred by users over the conventional cartridge-based products. The key advantages of our device vs. cartridge-based products, as expressed by the users are numerous," says Michael D. Hooven, President and CEO, Enable Injections.

First, he explains the Enable injector is significantly smaller, lighter, lower profile, and more discreet than cartridge-based products. The long-term container closure is not contained within the device, allowing an optimum size, weight, and profile. And, the 20mL device is smaller than competitive 5mL devices.

Second, a "pause" function has been incorporated that allows the user to pause the injection if they are experiencing any pain or discomfort. The user holds the button down until they are comfortable. Once the button is released, the injection is continued with no further discomfort.

Third, the Enable device automatically warms the drug and can be used immediately. "Our transfer package automatically warms the drug to room temperature during transfer and the patient can use the injector immediately after drug transfer," says Mr. Hooven. "Other devices containing refrigerated drugs must be warmed prior to patient use; typical wait times of 30-45 minutes."

He adds that patient pain is increased with colder drug; refrigerated drug viscosity can increase more than threefold; and battery power is significantly reduced in a refrigerated device.

From a pharma/biotech perspective, Mr. Hooven says that the Enable Injector offers several advantages. For example, by utilizing absolutely standard container closure–vial, cartridge, or prefilled syringe–there is no change to manufacturing filling lines or processes; no need for long-term stability testing of a new container closure; no need for an aseptic manufacturing facility to combine the container closure with the device; and the container can be combined with the device at the optimum point in the supply chain.

In addition, the injector offers high-volume dosage: 1-10mL for the standard product and up to 20mL for high-volume product. A change in volume does not require any change to the device. "This is especially important in clinical studies where dosing volume has not yet been determined," he points out.

Finally, according to Mr. Hooven, the injector is the only high-volume device that can achieve completely automated mixing of lyophilized solutions. The Enable transfer system completely automates the mixing process without requiring user input. It allows up to 10mL of reconstituted solution and mixing time of up to 1 hour. "This is a significant cost savings because our system allows in-home user mixing of solutions previously requiring a healthcare professional," he says. "And it provides for earlier release of drug formulations that may not be stable in liquid form."

Enable expects to conclude limited clinical studies later this year.

The LISA™ smart reusable auto-injector from Unilife Corp. provides user-selected injection speeds, needle-free disposal and the option of Bluetooth connectivity.

UNILIFE CORP.—A BROAD, FLEXIBLE PORTFOLIO HELPS CLIENTS SELECT THE BEST DEVICE

There is a growing trend for subcutaneously administered therapies, such as biologics, that are best suited to a dosage volume somewhere between 1mL and 6mL, depending on factors such as drug viscosity and delivery rate or duration. Traditionally, the optimal dose volume for a hand-held device, such as a prefilled syringe or auto-injector, has been around 1mL. "We work with many pharmaceutical companies to help them evaluate what device platform is most suitable for a target therapy," says Stephen Allan, Vice President of Marketing and Communications, Unilife Corp. "Having a portfolio including prefilled syringes, auto-injectors, and wearable injectors provides pharmaceutical customers with the flexibility to work with one partner that is neutral when it comes to the final device platform that is selected."

He adds that many trends are converging to spark a shift in how hand-held devices are leveraged by pharmaceutical companies to enhance and differentiate their injectable therapies. The specific needs of biologics have increased demand for platform-based devices that can be customized to address specific molecule, commercial, and patient requirements. With many of these therapies being targeted for patient self-injection, devices must be as safe, simple, and convenient to use by the target population as possible.

"Pharmaceutical companies recognize they can use these device benefits to drive preference amongst patients, prescribers, and payors to build market share against the competition," says Mr. Allan.

Unilife is experiencing accelerating customer demand for all of its product platforms, which offer various features that can accommodate the needs of virtually all injectable therapies outside of insulin. For example, the company is rapidly expanding the manufacturing capacity for its broad platform of Unifill prefilled syringes. Its wearable injectors are generating significant demand for use with large-dose volume biologics unsuited for use with hand-held devices, says Mr. Allan. The wearable injectors, which are prefilled, pre-assembled, and ready-to-inject, represent a solution for customers with portfolios of drugs best suited to the subcutaneous self-injection of doses between 2mL and 15mL.

And LISA, a smart, reusable auto-injector is being pursued for its benefits over conventional disposable systems. LISA represents a solution for patient self-injection of therapies requiring regular injections. "LISA overcomes many of the issues patients face using conventional, disposable auto-injectors, provides needle-free disposal, and is highly customizable with a variety of options, including Bluetooth connectivity," he says. It features true end-of-dose indicators that allow users to select the speed of injection to minimize pain or discomfort while its reusability with Unifill syringes improves portability and the convenience of disposal.

For drugs that cannot be made liquid-stable, Unilife developed the EZMix platform of drug reconstitution delivery systems, which enable automatic reconstitution that is ventless and orientation-free. This platform brings the process for reconstitution down from

around 12 steps to one, opening the door for easy patient self-injection, says Mr. Allan.

He explains how one customer required a hand-held device for the injection of lyophilized therapy in a complex and challenging environment. Users were experiencing significant errors during reconstitution with conventional systems. Multiple components were required and there were concerns of needle-stick injury from a high-risk patient population.

"What our customer desired was an intuitive, integrated device that provided one-step reconstitution of their therapy, fit into standard filling processes, and provided automatic needle retraction. We addressed that customer's need via the provision of a customized product from our EZMix platform of drug reconstitution delivery systems."

Looking at the hand-held sector as a whole, Mr. Allan comments that the market for hand-held injectable devices has been fragmented for a long time. He says that many companies have focused on only one or a few market segments, such as auto-injectors. "This has required pharmaceutical companies to work with multiple device and component suppliers. There are very few device companies that take responsibility for the entire product and provide a broad portfolio that covers virtually all segments for injectable drug delivery. We've developed our portfolio to accommodate dose volumes from microliters to 50mL or greater, with customer-centric platforms for liquid-stable, lyophilized or liquid-liquid combination products."

The Vetter Dual-Chamber Syringe Lyo-Ject®, whereby lyophilized drug resides in one chamber and diluent in the other.

VETTER—A PACKAGING SOLUTION FOR PRODUCT DIFFERENTIATION

The ascendency of the global injectable market is one of the most significant trends in the drug manufacturing industry today. According to an October 2013 Datamonitor forecast, the injectable market as a whole, which includes hand-held devices, is quickly becoming the single largest driver of the pharma/biotech market. However the injectable market is a dynamic and continuously changing industry with ever-growing cost pressures, intensifying competition, and increasing regulatory demands, says Peter Soelkner, Managing Director, Vetter Pharma International GmbH. And, because product variety will continue to increase, the need for special requirements provided by novel fill and final packaging solutions will be paramount. To stay competitive, product differentiation is critical and demands high priority.

"Vetter sees a growing need for support in early-stage development of injectable drugs," he says. "More progressive biopharmaceutical companies are looking beyond the traditional methods of drug delivery in clinical phases using vials as the primary method. Launching directly in a syringe can set a drug product apart from the competition and offer an advantage that other companies may not be able to beat."

He adds that a user-friendly system like a syringe may actually improve trial appeal, making it easier to recruit medical clinics for clinical trials that use prefilled syringes instead of traditional vials. Yet another advantage of using syringes includes precision single-unit dosing, which saves valuable API compared to vials. "As a consequence, our latest developments are dedicated clinical syringe packages that make it easier to start the use of syringes earlier in the drug development process. The modular, self-contained packages are designed to provide our customers with a clear roadmap through the syringe development process to reduce time-to-market."

The growth of biotechnologically drugs has created new challenges for the pharmaceutical manufacturer. Such drugs are often very delicate and tend to be unstable, which has a negative impact on their shelf life. One solution is freeze-drying. Vetter's dual-chamber technology provides the basis

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The West SmartDose® electronic wearable injector, designed for patient convenience, uses a Daikyo Crystal Zenith® cartridge and can deliver a dose of up to 3.5mL, which may allow for viscous biologics to be administered over longer periods of time.

for the patented Vetter Lyo-Ject® syringe and dual-chamber V-LK® cartridge. The dual-chamber design allows the differing ingredients and solvents to be prefilled and stored separately, then easily mixed and administered as needed just prior to administration. These all-in-one solutions also mitigate the residual risk of needle stick injuries allowing non-professionals like patients and family members to safely use the device, says Mr. Soelkner.

"The use of dual-chamber technology has other advantages beyond simplification of drug delivery. The system allows for product differentiation within the crowded and competitive drug delivery market, whether it is at the initial launch of a product or as part of a product lifecycle management strategy. For drugs with multiple dosing, dual-chamber cartridges can be inserted into modern pen systems. And, the all-in-one design also allows precise dosing and reduced overfill, minimizing reconstitution errors and packaging waste."

When asked what he sees for the future, Mr. Soelkner says: "Manufacturers of hand-held devices need to balance time to market, costs, business goals, and other factors to determine the appropriate fit for each product. Quality will continue to be the most important element of our business. Combination products involving safety features, auto-injectors, and new primary packaging materials have to perform every time to prevent incomplete injection, glass breakage, and other failures. Also, regulatory requirements regarding product safety and drug devices have a strong impact on prefilled syringe use and design. Soon, new regulatory requirements for 'track and trace' of drug products will be introduced to support a safer, more secure, and more efficient drug supply chain. Only through continuous investment in new technologies, processes, and staff training that allow for the highest possible product quality while offering flexibility, CDMOs can stay competitive and relevant, offering medical devices that meet rigid regulatory standards."

WEST PHARMACEUTICAL SERVICES, INC.—WEARABLE INJECTOR FOR HIGH-VOLUME, HIGH-VISCOUS PRODUCTS

Market uptake of biotechnology drug products is growing rapidly worldwide. Many of these products are intended for chronic conditions and represent breakthroughs in treatment and outcomes. Self-administration, assisted by delivery systems, offers patients a safe and cost-effective means to help improve adherence to treatment regimens. Some of the newer products require dosing above 1mL, which has been the limit of commercial auto-injectors designed for use with 1mL glass prefilled syringes. Also, several new drug products require higher concentrations to achieve therapeutic dosing, which results in more viscous solutions that may be difficult to inject.

"A new kind of electronic wearable injector for subcutaneous bolus delivery is required to meet the demands of this high-volume and high-viscosity biologic products," states Zach Marks, Director, Strategic Marketing, West Pharmaceutical Services, Inc.

He says that the SmartDose® electronic wearable injector is the first and only electronic wearable bolus injector to have

completed a first-in-human clinical study. The single-use, disposable system is currently cGMP manufactured in clinical trial quantities with ongoing investment in scale-up and dual-site manufacturing to meet the commercial needs of the market.

Utilizing a Daikyo Crystal Zenith® polymer cartridge along with Flurotec® barrier film-coated elastomers as the primary container, the SmartDose injector is also the only silicone-oil free system, ideal for sensitive biologics, claims Mr. Marks. The Daikyo Crystal Zenith cartridges and closures are available ready-to-fill in industry-standard filling tubs and nests.

The SmartDose electronic wearable injector is designed for high-volume (>1mL) and/or high-viscosity protein formulations for subcutaneous bolus administration. "With the growing number of biotechnology products for treatment of chronic disease, the SmartDose injector can extend the time between dosing and may improve patient compliance (versus daily injections)," he says. "Based upon market research and Human Factors analysis, the majority of patients prefer the convenience of less frequent dosing in the home environment, leading to greater adherence to treatment regimens, lower costs, and better outcomes."

The target therapeutic areas can include autoimmune diseases such as rheumatoid arthritis, psoriasis, and Crohn's, as well as hyperlipidimea and oncology. In the future, as more long-acting products are approved, the market may expand with therapies for other chronic conditions requiring self-administration such as diabetes, multiple sclerosis, and hemophilia.

"Developing a sterile electronic device, along with a primary drug container compatible with today's biotechnology products, is a project requiring expertise in many areas, as well as an understanding of our customers' filling environment," says Mr. Marks. "With the SmartDose electronic wearable injector, we have built upon West's expertise in complex packaging and delivery systems for injectable drugs, including injection molding and high-speed device assembly. The primary container utilizes the expertise of our partner Daikyo Seiko Ltd. for the polymer cartridges, and Flurotec-laminated elastomers to provide the cleanliness, high-quality, and minimal container interaction necessary for stability of biotechnology products. To facilitate filling, the primary container components are provided in industry standard configurations compatible with installed equipment."

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

SmartDose® is a registered trademark of Medimop Medical Projects, Ltd., a subsidiary of West Pharmaceutical Services, Inc.
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YPSOMED—CUSTOMIZING PLATFORMS SAVES TIME TO MARKET

More customers want to customize an existing product platform for their specific drug. By choosing from an existing platform, a pharma customer wins critical time to clinic and market launch, as the major development phases have already been completed by the device company. Therefore, the platform product only needs to be adapted to the primary container, its filling volume, and the dosing requirement. Customer-specific designs may also be implemented and verified during the customization of the platform within certain limits and manufactured using the same device assembly equipment.

"Platforms are ideal for many pharma customers to enter the field of self-injection devices as they do not have the resources or the experience to initiate a device development program from scratch. Platform products are built on a solid patent base," says Tobias Nemeth, Business Development Manager, Ypsomed.

Ypsomed offers several platforms, such as the UnoPen™, a disposable pen platform for both insulin and other liquid drugs, and the YpsoMate®, a disposable, single-use auto-injector platform for

Ypsomed Custom Products: UnoPen™, a disposable pen platform for both insulin and other liquid drugs; YpsoMate®, a disposable, single-use auto-injector platform for prefilled 1mL syringes; and LyoTwist™, a disposable, single-use pen platform for the reconstitution, priming, and injection of freeze-dried drugs.

prefilled 1mL syringes made of glass or plastic.

The UnoPen is suited to insulin suppliers that are competing with the major suppliers in established markets, but it is also suitable for administering GLP-1 drugs as well as parathyroid (PTH), growth (hGH), and fertility hormones (FSH). "The user-friendly and yet economically priced disposable pen is very well accepted by users and is an important marketing tool that allows pharmaceutical customers to clearly set themselves apart from their competitors," he says.

The YpsoMate auto-injector is compact and ergonomic to handle. The needle is invisible to the patient at all times and shielded after use, enhancing safety and compliance. The clearly audible start and end click, and the large viewing window, through which the drug can be seen, increase patient confidence and provide confirmation that the full dose has been injected. The YpsoMate enables the drug to be injected comfortable and automatically as soon as the auto-injector is pressed against the skin.

Customer-specific versions of the UnoPen and YpsoMate are in the final stages of customization. UnoPen has gone through formative handling studies for a range of patient groups and the results of one study were recently published. The study took advantage of a broad user population, including different user characteristics across a range of indications.

With regard to customization, one customer project involved the customization of the Ypsomed LyoTwist™ platform for GlaxoSmithKline's (GSK) once-weekly GLP-1 agonist (albiglutide). Mr. Nemeth explains: "LyoTwist is the ideal device platform for reconstitution, priming, and injection of a freeze-dried drug in only a few easy steps. The LyoTwist monodose device family for dual-chamber cartridges is based on Ypsomed's twisting method for reconstitution and priming and sets a new standard for preparation and injection of a freeze-dried drug in a disposable device. It was GSK's intention to implement a state-of-the-art injection system that is convenient and safe to use for the patient."

The product was recently launched as Tanzeum™ in the U.S. and will be launched in Europe under the trade name Eperzan®. ◆

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

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Larry Acquarulo
CEO
Foster Corporation

"With every project, we seek to leverage our vast experience in melt extrusion to develop the optimal process for the application. Our first step is to develop a clear understanding of clients' objectives and molecules. With a clear understanding of the desired outcomes and API limitations, we begin our systematic approach to process development. This includes extruder and feeder selection, screw design, die design, processing conditions, pre- and post-blending operations, and design for future scale-up."

Hot-melt extrusion (HME) has been widely utilized in the development and manufacture of pharmaceutical and combination products, including formation of solid molecular dispersions to increase the bioavailability of poorly soluble drugs and drug/polymer implantable devices. Foster Delivery Science specializes in HME for pharmaceutical and medical device applications offering contract services from formulation development to clinical supplies and manufacturing. Foster Delivery Science is a wholly owned business unit of Foster Corporation, a leader in melt extrusion of biomedical polymers for more than 25 years. *Drug Development & Delivery* recently spoke to Larry Acquarulo, CEO of Foster Corporation, about the history of Foster Delivery Science, their highly focused strategy in melt extrusion, and future plans for the business.

Q: What is the history of Foster Delivery Science?

A: Foster Corporation was founded 25 years ago to provide highly specialized melt extrusion and material blending services to the healthcare market. At that time, interventional catheters were emerging as a primary method for treatment of blockages in the coronary arteries using balloons and, later, stents. We played a key role in formulation development, process development, and contract manufacturing of polymers to make catheters visible under fluoroscopy during these procedures.

Over time, the demand for highly specialized polymer blending services emerged in other areas, including implantable devices, drug delivery devices, and combination drug/device products. To support the demand for drug delivery applications, we invested in dedicated equipment, cleanroom operations, cGMP capabilities, and highly trained pharmaceutical personnel to complement our polymer processing expertise. This resulted in a dedicated business unit, Foster Delivery Science, to serve these applications.

At the same time, there was an increase in newly discovered drugs with high crystallinity and poor solubility within the pharmaceutical industry. Hot-melt extrusion (HME) began emerging as a viable process for enhancing the bioavailablity of these drugs. HME involves twin-screw extrusion processing of active pharmaceutical ingredients (APIs) and water-soluble polymers. Foster Delivery Science was one of the few contract development and manufacturing companies that had extensive expertise in extrusion processing and the facilities to support APIs. Providing contract HME services to pharmaceutical companies is a core competency of our business today.

Q: What are the services that Foster Delivery Science offers today?

A: Foster Delivery Science provides contract melt extrusion services throughout the product life cycle, including formulation, analytical characterization, process development, process improvement, scale-up modeling, and optimization for clinical and commercial supply. Our twin-screw extrusion lines range from 16 mm to 27 mm, offering the ability to produce extrudate from lab sample to production quantities.

We have a variety of post-extrusion equipment that allows us to convert extrudate into shapes that include powder, pellets, film, fiber, and rods. This allows us to support a variety of delivery systems, such as oral dose, patches, implants, and more.

Q: What are the company's core areas of expertise?

A: We offer expertise in engineering critical polymer blending and extrusion processes and providing solutions to complex design engineering requirements. Our strategy has always been to provide the highest quality melt extrusion services to our customers by leveraging the expertise and know-how we have developed during the 2.5 decades in the extrusion blending business. We believe our focus and expertise in melt extrusion results in a premium service to those customers for which the technology is applicable.

Polymer process design engineering is one of our primary areas of expertise. Our top people have strong backgrounds in extrusion process engineering, which has contributed to our expertise in process development, optimization, and scale-up. This process expertise ideally complements the chemistry background of many of our pharmaceutical customers, and provides for a highly collaborative and effective interaction partnership that maximizes project outcomes.

Q: How has pharmaceutical HME evolved over the years?

A: Within the pharmaceutical industry, early HME applications involved extruding rods which were milled into granules for oral controlled drug delivery, which were subsequently tableted or encapsulated. Melt granulation had been investigated for solid dispersions, and HME was a natural fit for the processing technology. Currently, HME has emerged as a standard processing technology to create molecular dispersions of APIs into various polymer or/and lipid matrices for improved bioavailability, controlled release, and targeted drug delivery. Pharmaceutical scientists have used HME to produce a range of pharmaceutical dosage forms, such as tablets, capsules, films, and implants for oral, transdermal, and transmucosal routes of administration. HME is now used to prepare commercial pharmaceutical products with

enhanced bioavailability (Norvir) and to provide abuse deterrent properties for narcotics (OxyContin).

Within the medical device industry, melt extrusion of APIs into polymers used in the manufacture of devices are also rapidly evolving. New materials, such as bioresorbable polymers, are ideally suited for drug delivery. These materials have melt temperatures below the degradation temperatures of many drugs such that they can be processed into shapes and provide slow, localized release over time.

Q: What is your unique approach to solving pharmaceutical HME challenges?

A: With every project, we seek to leverage our vast experience in melt extrusion to develop the optimal process for the application. Our first step is to develop a clear understanding of clients' objectives and molecules. With a clear understanding of the desired outcomes and API limitations, we begin our systematic approach to process development. This includes extruder and feeder selection, screw design, die design, processing conditions, pre- and post-blending operations, and design for future scale-up.

It is not uncommon for APIs to have low degradation temperature, and in some cases, these are below the melt temperature of the polymer. Our technical team is composed of experts in twin-screw extrusion, which allows us to develop process solutions to these complex problems.

For example, one client asked to incorporate an API that degrades 90°C into a polymer that has a processing temperature of 150°C. Our team was able to develop a process that minimized residence time of the materials in the extruder to achieve good mixing between the drug and polymer yet avoid drug degradation.

Q: How do you manage projects with your clients?

A: Our approach to project management is to be pro-active and collaborative. We understand our clients' success is dependent on the success of the projects we work on for them. Conversely, our success as an organization is dependent upon our clients' success in developing products to bring to clinical trial and ultimately commercialization. We utilize project management tools, including Gantt charts, to manage the timeline of projects. Our intranet calendar system provides a communication platform for our internal project team and ensures the entire team remains on schedule.

Q: What are your plans for future growth?

A: Foster Delivery Science is in the process of constructing a 32,000-sq-ft, cGMP facility, directly across the street from our current building. This facility will provide the necessary resources for development and manufacturing of pharmaceutical and medical device components using highly engineered polymer extrusion technologies. The new facility will be complete with a new Process Manufacturing Area (PMA), equipment wash and clean areas, equipment storage, as well as a designated space for weighing and dispensing. Additional areas will be allocated to research and development, as well as a comprehensive QC laboratory. The new PMA will allow for more efficient handling of equipment and will provide our customers with the confidence to expand orders and entrust Foster Delivery Science as a leading supplier for their unique polymer needs. ◆

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For more information, visit www.deliveryscience.com. Visit Foster Delivery Science at AAPS in San Diego booth # 3604, November 3-5.

Recruitment Challenges for Proof-of-Concept Viral Challenge Trials

By: Robert Lins, MD

INTRODUCTION

There is a common perception that finding sufficient healthy volunteers for early phase clinical trials is a fairly straightforward process. On the contrary - patient recruitment is a difficult process, and finding adequate numbers of suitable subjects is frequently the biggest barrier to trial success, and the most common reason why most clinical trials face delays.

Viral challenge tests are an important proof-of-concept technique for new drug treatments or prophylactic vaccines directed against viral infections. They can also be of value in proving mechanisms for new targets for non-viral diseases that might be exacerbated by a viral infection, such as asthma attacks. For viral challenge tests, the recruitment situation is even more difficult than for traditional clinical pharmacology studies, even for healthy volunteers, because of the additional criteria subjects must meet to qualify.

Some recruitment challenges remain constant across all clinical trial types. Lack of volunteer awareness that the trial is happening is common, particularly in later stage trials in sick people. They might be afraid of being exposed to experimental drugs; they may also be concerned about receiving a placebo. And there is a whole host of access, language, literacy, cultural, insurance, and administrative barriers. For example, if the potential subject cannot read, it is difficult for them to give their informed consent. Even practical considerations like the ability to travel to the trial center may be an issue.

Challenges also exist around the site and protocol design. Inclusion or exclusion criteria may be overly restrictive, and a site involved in running the trial might find they have fewer eligible subjects than they expected or claimed they would be able to recruit. There may be other competing studies being run that deplete potential patients, physicians may have personal wishes, sites may have so many studies running already that they are understaffed, and there may be funding restrictions that impact on recruitment.

Trial sites use a number of tactics to assist in patient recruitment. They may advertise, whether in print, on the radio or TV, or even via advertisements on public transport. Call centers or direct mailings may be employed. Word of mouth is an important tool, whether from a network of physicians or specialists, patient associations, or via

FIGURE 1

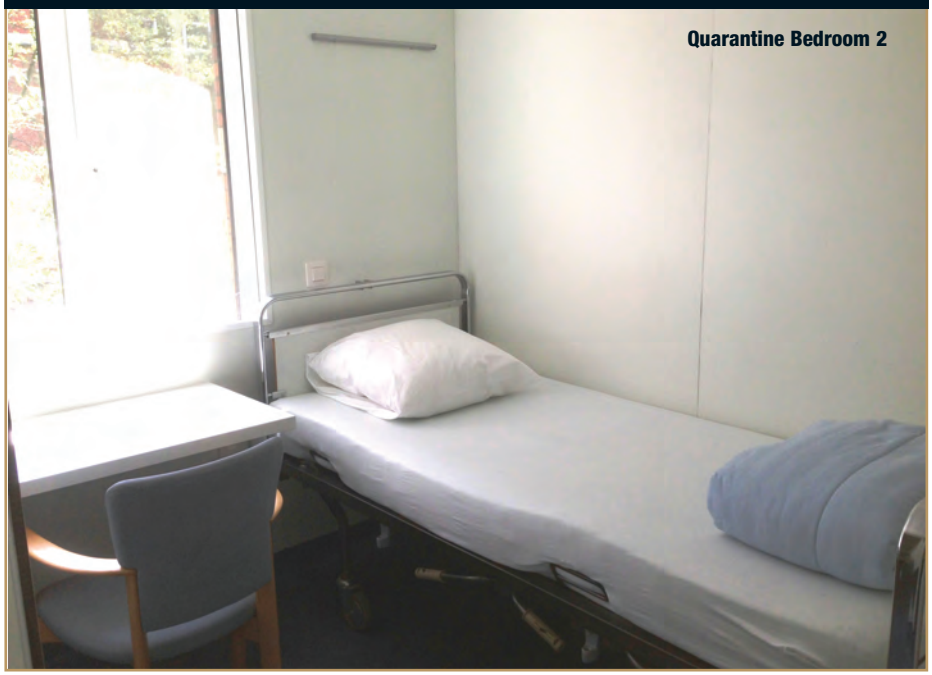
SGS Quarantine Area Corridor

partnerships with universities. Increasingly, social media is an important tool, alongside patient and trial websites, such as clinicaltrials.gov and centerwatch.com. Those running the study may also outsource the task to a third-party recruitment company that specializes in tracking down potential subjects for clinical trials.

Perhaps surprisingly, the additional problems with viral challenge test recruitment result less from a fear among potential volunteers about being infected with a virus, or other ethical or psychological concerns. Rather, most drop out or are not accepted because they have been in contact with the virus that is being tested and have already developed antibodies to it. This is very different from the typical clinical pharmacology study, and for common viruses, it can exclude the vast majority of potential subjects.

Although they are occasionally run in sick patients, most viral challenge studies are carried out in healthy volunteers. Subjects are given a challenge strain, which is normally an attenuated virus that, in theory, produces a milder set of symptoms than would the original virus. The investigational antiviral vaccine or drug is administered to the subject, either before the viral challenge is made if the test is for prophylaxis, or afterward if the aim is treatment. Depending on the virus being tested, the volunteer may then be quarantined for a sufficient amount of time to prevent cross-infection, or spreading the virus to the general population.

FIGURE 2



FACILITY DESIGN

Safety concerns about the potential for wider infection means that a facility where viral challenge tests are run must meet several additional criteria that are not required for more standard clinical trials. It must have a Class II environmental license, and have HEPA filtration, a negative pressure system, and a cleanroom-style airlock with changing room and interlock linked to an alarm to prevent viral egress. This license is granted by the health authority after an auditing process, which assesses the quarantining of subjects within the unit. This was originally a requirement for facilities using genetically modified organisms, which, like viruses, could contaminate the environment.

For example, in SGS's existing Antwerp clinical trial facility, which already had the required Class II environmental license valid until 2023, a dedicated area was installed to enable viral challenge tests to be carried out. It was renovated to provide an area that could be fully quarantined according to biosafety level L2-Q requirements, following the principles of reversed-barrier nursing. There are now 12 and very soon 20 separate one-bed rooms designed for subjects undergoing viral challenge studies, in addition to 80 beds for standard trials.

Implementing a separate viral challenge facility within an experienced clinical pharmacology unit makes running these types of tests more straightforward. The unit already has a large population of healthy volunteers and patients for the other pharmacological studies, increasing the likelihood of recruitment success. Prolonged periods of quarantine are possible, and complex laboratory techniques are available to collect body samples and prepare them for biomarker analysis, whether viral titres, protective antibodies, or cellular immunity are being studied. It also assists in the detailed

assessment of those immune parameters that will aid in the identification of immunological correlations of infection and illness.

CASE STUDY: INFLUENZA

An example of a viral challenge test is an open label Phase I validation trial run in healthy volunteers. This study was designed to determine the optimum dose of virus to give to subjects in a subsequent trial evaluating the effectiveness of an antiviral drug. The trial involved a dose escalation across three cohorts, and the aim was to recruit 36 volunteers for enrolment in the 29-day study. Subjects would spend 10 days in an isolation unit, and the primary endpoints were safety, viral load in nasal swabs, illness score, and immunogenicity - illness caused by the virus.

Potential subjects could not have had an influenza vaccination within the previous 2 years, and would have no contact with anyone who was immune-suppressed, under the age of 5 or over 65, or pregnant for the 2 weeks following the challenge to avoid them being put at risk. Those that met these criteria were pre-screened for negative antibody titres using an influenza haemagglutination inhibition test.

Following a recruitment letter sent to 6,382 potential subjects on the volunteer database, 239 responded positively, and 213 of these attended the screening process. Of these, 57% failed the first screen because they were positive for influenza antibodies, leaving 90 potential subjects. Of these 90, 61 subjects expressed their willingness to participate in the study, and underwent the study-specific second screening 3 to 5 months later. Ultimately, just 29 of the original panel of volunteers were enrolled in the trial, with many of the drop-outs having failed the antibody titre screen. These dropout rates are significantly higher than in a standard clinical pharmacology trial - about 87%, in contrast to the more typical 50% for a normal trial.

CASE STUDY: RHINOVIRUS

There is a hypothesis that rhinovirus can trigger asthma attacks. One of the pathological mechanisms involves toll-like receptors (TLRs), and it is thought that these can be activated by the virus, provoking asthma attacks. A trial was designed to investigate whether a monoclonal antibody designed to block the TLRs would be effective at preventing asthma exacerbations triggered by rhinovirus infection.

The Phase I randomized, double-blind, placebo-controlled trial aimed to recruit 12 healthy non-asthmatic patients for the first part, followed by 60 asthmatic subjects in the second part. In both parts, subjects would be given the study drug via intravenous infusion prior to inoculation with human rhinovirus Type 16. Subjects would spend 10 days in the isolation unit at the start of the 56-day study. The primary endpoints were determined as safety and tolerability for the first part of the trial in non-asthmatic patients, and efficacy, including pulmonary function and patient-reported outcomes, such as asthma attacks, in the second part of the trial in asthmatic subjects.

The list of inclusion criteria for subjects was more extensive for this trial. Subjects had to have a bodyweight of 40 to 125 kg, with a BMI of 19 to 32. They must not have a positive serum neutralizing titre to human rhinovirus 16, the virus being tested; however, they needed a positive serology for herpes simplex virus 1, but with no signs or symptoms of active infection, and not receiving prescription treatment, as there is otherwise a potential risk of herpes simplex exacerbation and encephalitis. In addition, they cannot have regularly used tobacco within 6 months of screening, have a history of smoking of at least 10 pack years, or a positive urine test for the nicotine metabolite cotinine. This exclusion of smokers is essential, as smoking is an important promoter of bronchial constriction, and thus could affect trial results.

Again, a recruitment letter was sent to the volunteer database to recruit potential subjects for the first part of the trial, in healthy subjects. This yielded 160 volunteers for screening. There was a 92% screen failure rate, leaving just 13 subjects to be enrolled in the study. The main reason for screen failure was serological - a HRV16 positive titre, an HSV-1 negative titre, or both. This first part of the trial has now been completed in this small group of healthy volunteers who met the strict trial criteria.

Recruiting asthmatic subjects proved even more challenging, however. These

were recruited through the patient database, advertisements, flyers, and the physician network. A total of 54 potential subjects were identified in this way, but every single one of them failed the screen. Clearly, patient recruitment has delayed this part of the trial, with none of the required 60 subjects being identified in the first screen. All available sources of subject recruitment, including the database, networks, and advertising, have been exhausted. This highlights the extreme recruitment difficulties that can result from the necessary additional subject requirements for a viral challenge study.

SUMMARY

While recruitment tactics are similar for clinical pharmacology and viral challenge trials, in reality, the pool of potential subjects needs to be significantly larger for a viral challenge trial because of the additional exclusion criteria, and the number that will fail the screening procedure. We have found that the high rate of screen failures is not due to patients' fear of viral inoculation or reluctance to be isolated for a period after virus administration; indeed, there is very little difference in willingness between the two types of trials.

Those experienced in clinical pharmacology will understand that very probing questions have to be asked of volunteers and patients. As long as these are done in an open and honest way, few potential subjects will refuse to answer. The recruiter needs to have the communication skills to facilitate this, and explain why the trial is being conducted and its long-term benefits, and any potential risks they may be exposing themselves to. Trials may involve invasive procedures, and informed patient consent is vital.

Many of the viruses used in viral challenge tests are extremely common, and subjects are very likely to have encountered them at some point throughout their lives. This can cause significant problems in finding "clean" subjects. It's a numbers game. Maximizing success involves approaching a much larger group of potential subjects than normal, and thus adding viral challenge testing to the activities of a large clinical pharmacological unit is the best way to achieve recruitment success.

Viral challenge testing is an important factor in optimizing the overall development process for antiviral treatments. Fortunately, bearing in mind the difficulty in recruiting suitable subjects, the number of patients required to obtain meaningful results in a viral challenge is substantially lower than for community-based studies looking at naturally acquired infection. This can offer savings in clinical development costs by avoiding initial efficacy studies in much larger populations, which also often require an outbreak of that infection to be under way. It also minimizes safety risks for infected volunteers, while simultaneously protecting the outside world from a potential spread of infection. ◆

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BIOGRAPHY

Dr. Robert Lins earned his Medical Degree from the University of Gent, Belgium, specializing in Nephrology and Hypertension. In addition, he holds a Doctor of Philosophy degree in Medical Sciences from the University of Antwerpen, Belgium. Dr. Lins is a European Hypertension Specialist, a Fellow of the Belgian College of Pharmaceutical Physicians, and formerly a Clinical Professor at the Department of Internal Medicine, University of Antwerp. He held the position as the Director of the Nephrology-Hypertension Department at Stuivenberg Hospital in Antwerp, eventually becoming General Manager of one of the hospitals, belonging to the Hospital Network of Antwerp (ZNA). Dr. Lins started a Phase I unit in Stuivenberg Hospital in 1987 that was subsequently acquired by SGS. From 2007 until 2011, he was Managing Director of SGS Life Science Services Clinical Research. Dr. Lins currently continues his activity as Project Director Vaccines and Senior Clinical Adviser for SGS.

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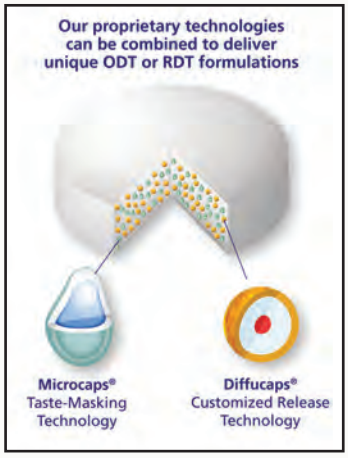

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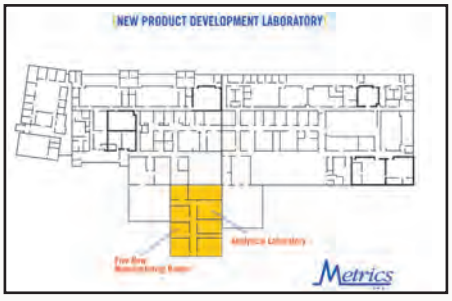

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Technology & Services Showcase

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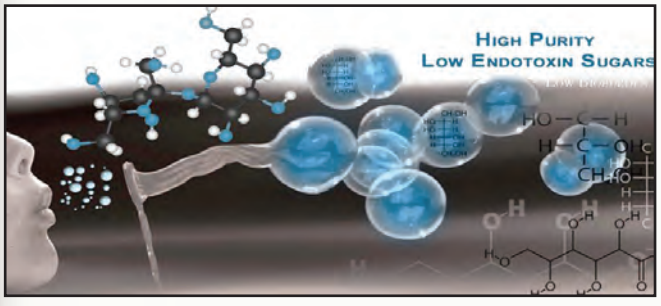

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CRONOS: INNOVATION IN CLINICAL TRIAL SERVICES THROUGH FOCUS ON QUALITY DATA

Guillermo DiClemente

Founder & President

Cronos

"In the current economic climate, sponsors cannot afford to continue to have failed or negative studies for reasons unrelated to the compound. Cronos' services offer Sponsors insight into what is going on in the real world and in real time. We provide situational awareness and institutional memory."

Cronos Clinical Consulting Service is a global provider of centralized risk-based data monitoring and data visualization solutions for neuroscience clinical trials. Its clients achieve high-impact results from their proprietary technology, proven processes, and scientific expertise to assess and confirm the credibility as well as accuracy of data necessary for approval and labeling of pharmaceutical products. For more than 6 years, Cronos has focused on Central Nervous System Phase II/III clinical trials and worked throughout the world with many of the top global pharmaceutical companies. The company was founded by Mr. Guillermo DiClemente as a response to obvious issues with clinical data he was experiencing during his Columbia University days. Mr. DiClemente recently spoke to *Drug Development & Delivery* about the company's unique approach, its relationship with customers, industry trends, and the importance of focusing on quality clinical data.

Q: What is the concept and focus of Cronos Clinical Consulting?

A: The concept is to mitigate clinical trial risks faced by Sponsors by focusing on clinical data. We do this by determining if there are internal inconsistencies when raters assess a patient from a clinical point of view. For example, one can obtain accurate body temperature with a thermometer or measure blood pressure with a calibrated device. There is no such tool for measuring hallucinations or various aspects of depression. The sensitivity of the raters sometimes comes into play, which is what Cronos targets. We try to minimize the subjectivity of the scoring.

Q: How are you able to do this?

A: We developed a set of algorithms that detect inconsistencies within an instrument or across instruments. The concept here is that you may have a psychologist or psychiatrist assessing a patient, and they understand the symptoms very well, but may not be familiar with the instrument or how to arrive at the best possible scores. At the same time, from a research standpoint, they may not

understand the distinction between data gathering and therapeutic clinical practice. Utilizing our algorithms, we detect and remediate those inconsistencies, and we address those issues by talking to the raters about symptom assessment.

Q: Can you give us an example of what your algorithms would measure so we can get a feel for how it is practical?

A: The algorithms detect potential discrepancies amongst and between instrument items and are able to highlight if raters are misconceptualizing one or more items. By improving signal detection and protocol fidelity, we can measure site and rater performance from a clinical point of view. Regarding how practical it is, it allows the sponsor to know if raters are able to capture change in patients in real time and not after database lockout.

Q: Have doctors been receptive? Do they realize they need additional tools? Are they resistant because somebody is taking over what they know best?

A: One of the aspects we took into careful consideration during the creation of our system was the target population. In our case, Sponsors contract us, but the target populations are professionals who have not requested our services but are obligated to communicate with us. This is a sensitive arena and as such, we are always very respectful and careful during our interactions with the doctors and raters. We focus our conversation on symptom assessment and the use of the instrument. We do not aim to contradict their clinical knowledge, but rather to share with them how other raters are using the instrument in discussion. This is a very novel and well-accepted approach. Most raters are grateful of our feedback and glad to speak with someone about a meaningful assessment and not just boring, generic PowerPoint presentations about general training. That is the big difference with what we are doing - how a respectful approach can change the outcome of an interaction - especially because we do not tell them they are doing anything wrong. We are just sharing our opinion and that is it.

Q: Is all this conducted in real time?

A: Yes, it is done in real time. We receive data via FTP or from any mobile devices, such as tablets, collecting data. We run the data through our algorithms and schedule calls or remediations by email in less than 24 hours from data receipt.

Q: What companies are currently implementing your services?

A: Currently, our clients are biopharma companies, including five of the top-tier big pharmas. We work on global trials, for example, we are currently working on a trial that spans data from 43 countries. We can see our brand of data quality approach be interesting to other industries like the insurance space.

Q: Are there competitors and other equipment available that is able to do what you can?

A: From a strictly surveillance perspective, yes, there is competition because there are other people checking data, offering independent rating and recording, and videotaping or audiotaping assessments and feedback. Our system is unique in that we do not interact with the patient or review the interview; we analyze the data and remediate the raters as needed, and that is something unique to Cronos. We are an independent company that does data review, we do not need to justify why or how a rater was allowed to do scorings. I know others will claim they do something similar, but when we see the results, it is evident there is something different there. One of the most important parts is that Cronos is only data monitoring, and this aligns us with Sponsor objectives. Regardless of which company trains raters or selects raters and sites, we are in the unique position to provide real-time study awareness. There is no other company positioned this way.

Q: What has changed over the years since you have developed the product and it has been in use? What have you learned from the usage that has perhaps caused changes or tweaks to what you have available?

A: We have seen significant changes over the 6 years we have been in business. There is a new array of variables that we take into consideration now. For example, Sponsors have moved studies to lower cost locales, which made us consider cultural differences in our score expectations. As more global raters are used, we must be more careful with their familiarity with the scale instrument. In addition, we have seen a growth in patient knowledge and hence we need to be careful with repeated patients.

Q: How do you reach out to potential clients?

A: We have a sales force that focuses on branding, client relationship management, and prospecting. However, we find our most powerful tools include demos and research. The proof is in the pudding, and as such, we typically invite clients to share data and ad-honorem we present our results. Additionally, our publications, posters, and white papers showing the impact of our interventions have had strong results.

Q: Are people surprised that you are able to do this?

A: I believe they were surprised in 2008 when we started. Now that we are well known, I do not believe they are surprised anymore. The feedback we receive from sponsors is that Cronos is a niche company that takes data very seriously and provides information about things that are happening in clinical trials. Sponsors feel supported and they believe they can trust our findings. Usually, our findings drive CRA interactions. The Sponsor communicates our findings with the CRAs, which are addressed at the appropriate site.

Q: Do you work with patient selection as well for trials?

A: Yes, we have actually been in three trials in which we have given our patient selection opinion. We are developing a system that we believe is approximately 6 months away from market deployment. What we are doing right now is determining if patients are appropriate based on the scores developed either by independent raters or by site raters.

Q: Do you find that you are able to identify much that is missed?

A: I believe there is a wide spectrum of missed items or issues in a clinical trial with a varied level of risk severity. I find that strictly speaking from a clinical perspective, yes, we are able to identify all the important issues that may influence signal detection and go against protocol fidelity. We can tell the Sponsor with certainty when there is a problem with their data, and we provide solutions to those problems. What has been a tenet for us is when someone is doing something wrong; it shows up in the data right away.

Q: Put it together for our readers. Why pay attention to Cronos?

A: In the current economic climate, sponsors cannot afford to continue to have failed or negative studies for reasons unrelated to the compound. Cronos' services offer Sponsors insight into what is going on in the real world and in real time. We provide situational awareness and institutional memory. We provide sponsors the ability to make decisions on imperative variables: allow a site to recruit more patients, to retrain a rater, curtail enrollment, or even stop the study. Business is going very well. The company has been growing steadily and organically since 2008. Right now, we have 23 full-time employees and more than 35 consultants around the world addressing raters in their native languages. We are excited about the future prospect of our company. ◆

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Founder's Syndrome

By: John A. Bermingham

Founder's Syndrome is defined as a situation that occurs when an organization operates according to the personality of a dominate person within the organization, usually the founder. This syndrome normally occurs when an organization begins to achieve revenue growth at a level that requires a change in management style and how things get done. This type of problem can be very difficult to deal with. Here's why.

It is not uncommon for the founder of a company to surround himself or herself with friends and relatives to make up the management team, and all too often, the Board of Directors is composed of friends and relatives too! So what you end up with is a management team and/or Board of Directors that are simply yes men and yes women who are in place to approve whatever the founder wants approved.

On two occasions, I was brought in as the CEO to turn around two different companies that were suffering from Founders Syndrome. They were both acquisitions by private equity firms, and the former founders/CEOs were still with the company to act as consultants and help me ramp up as quickly as possible. Two immediate problems with this situation:

1. When you join a company, especially if the company is in distress, the new CEO must establish leadership and control very quickly. This is very difficult to do when the former founder/CEO remains in the building. All or most of the company's people worked under the former founder/CEO and in many cases, were hired by this person. Hence, even with a new CEO on board, the loyalty of the people could still remain with the former CEO, at least for a period of time.

2. A company normally falls into a distressed condition due to bad decisions by the CEO and his or her management team. Company people can become confused and even fall into a personal distressed condition because they are being given direction by the new CEO, which often conflicts with the way the former CEO did things. With the former CEO remaining in the building, the dominate person tends to be the former CEO, not the new CEO.

Yes, people will follow your leadership and direction but not completely in this situation. So what can you do? The first thing that you must do is get the former CEO out of the building. This has to be accomplished quickly and with dignity and respect. People will closely watch how you do things, and this can make or break your leadership and control issues.

On the two occasions when I had to get the former CEO out of the building, I announced his departure at a Town Hall Meeting and had him/her speak at the meeting. I would also set up a dinner for this person to be attended by the management team as well as people from the private equity firm. ◆

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BIOGRAPHY

John A. Bermingham is currently the Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. He was previously Co-President and COO of AgraTech, a biotech enterprise. Previous to that, he was President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. More previously, he was 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. Mr. Bermingham served 3 years in the US Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and graduated from the Harvard University Graduate School of Business Advanced Management Program.

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