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Drug Development & Delivery®

March 2015 Vol 15 No 2

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Enhanced Bioavailability & Solubility Technologies

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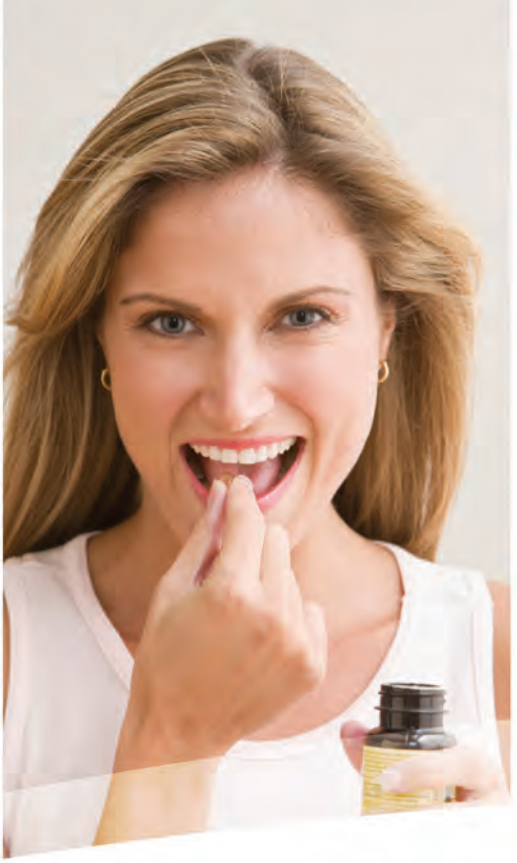

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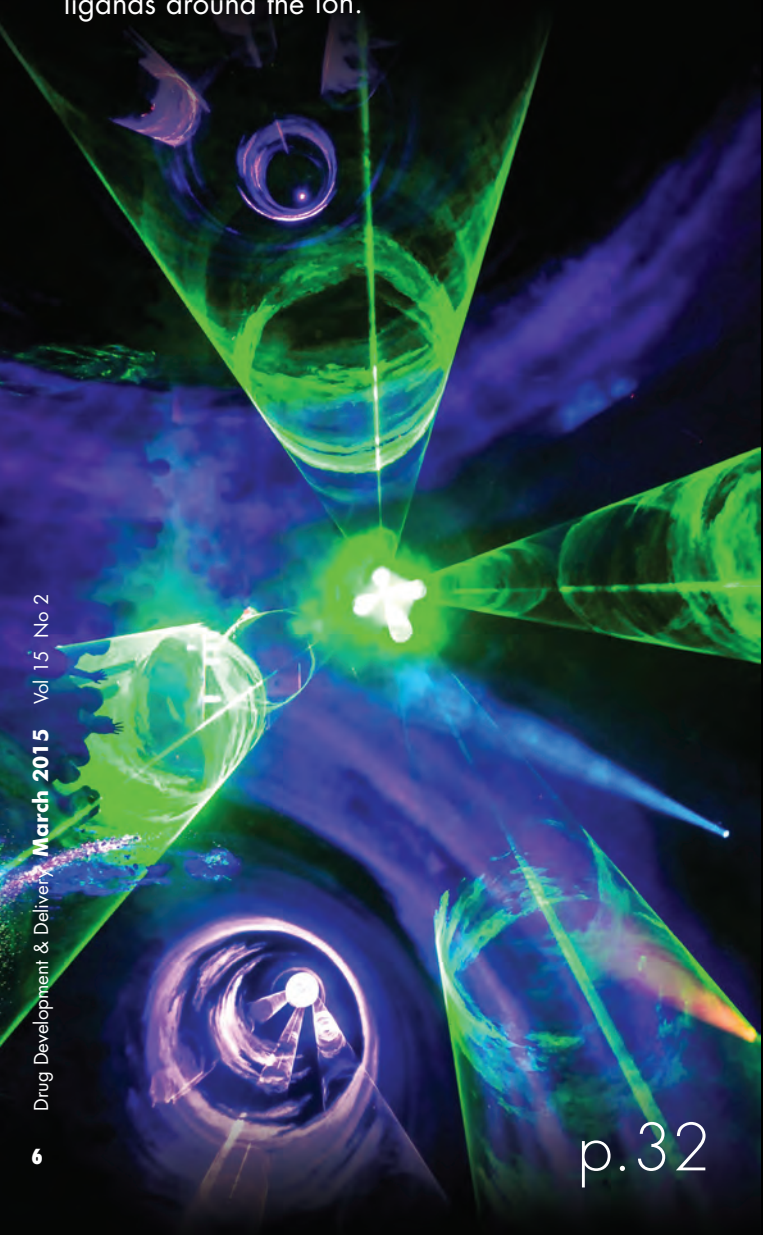
Dynamic Light Scattering

"A number of properties of colloidal gold make it well-suited for nanomaterial-based clinical applications. Its chemical and physical inertness ensure the material is toxicologically safe in vivo, while its fine size allows particles to cross a cell membrane without harming the cell. Furthermore, gold nanoparticles suspended within aqueous media form negatively charged ions that have a strong affinity for biological macromolecules, such as proteins and antibodies, which form biological ligands around the ion."



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Bioavailability & Solubility

"A new report identifies 30 poorly soluble drugs with low bioavailability recently launched in the US that represent a huge business opportunity for specialty pharmaceutical, drug delivery, as well as generic companies using these technologies. In fact, the authors of the report believe that poorly soluble and poorly permeable drugs are valued at $145 billion. Thus, demand for novel technologies and materials to improve solubility and permeability of drugs is only going to rapidly increase over time."

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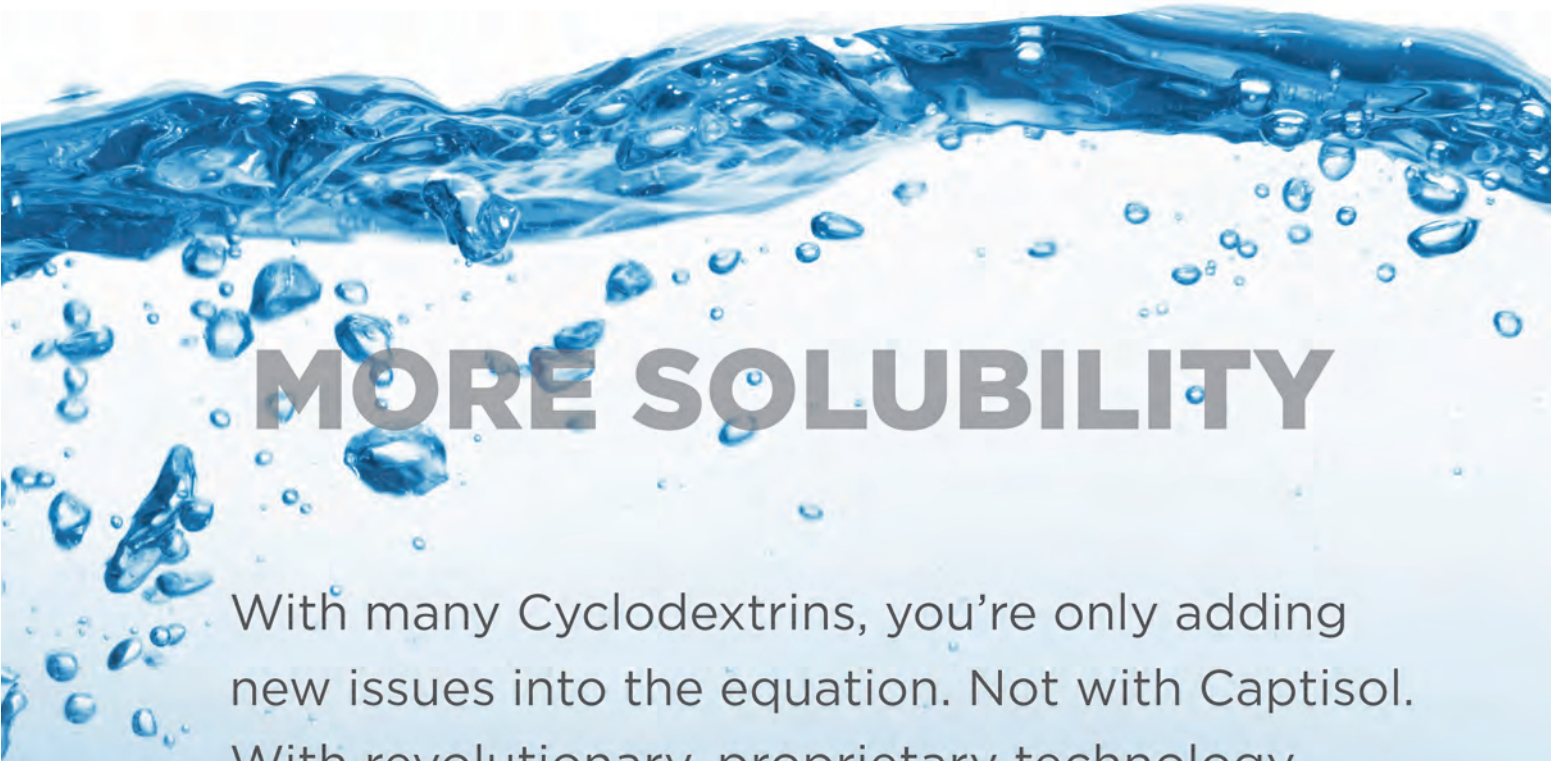
MORE TECHNOLOGY.



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Dipexium Announces Successful Completion & Initial Results of Phase I Trial

Dipexium Pharmaceuticals, Inc. recently announced successful completion and initial results of DPX-120, a Phase I skin sensitization trial of Locilex (pexiganan cream 0.8%), the company's novel, broad-spectrum topical antibiotic peptide.

DPX-120 was a single-center, double-blind study in healthy adult subjects with the primary objective of evaluating the potential of Locilex and its vehicle cream to induce contact sensitization by repetitive application to human skin. Volunteers received applications of Locilex, vehicle cream, and a low irritant control 3 times each week for 3 weeks during an induction phase, followed by 2 weeks without dosing and then a single challenge dose to intact skin. Visual skin irritation assessments were performed by trained and blinded evaluators using a well-established, FDA-recognized standardized rating scale.

In total, 203 evaluable healthy adult subjects were assessed for contact sensitization. The low irritant control showed no contact sensitization as expected, indicating a successful trial. Vehicle cream also showed no induction of contact sensitization. Locilex demonstrated low potential for inducing contact sensitization. In total, only 3 out of 203 evaluable subjects were characterized as sensitized, which was better than anticipated by the company and its scientific consultants based upon published studies conducted with other topical antibiotics.

"We are pleased with the results of this trial, and we expect these data will satisfy the regulatory requirement for evaluating the contact sensitization potential of Locilex with our new formulation," said Dipexium's Chief Executive Officer, David P. Luci. "With the completion of both this trial and our recently completed contact irritation trial, DPX-110, we are confident that Locilex will continue to demonstrate excellent local tolerability. This is particularly relevant in view of published studies that indicate that other topically applied antibiotics, such as neomycin, may produce local skin reactions in a clinically important percentage of patients."

Novasep Selected to Commercially Biomanufacture Mydicar API

Novasep recently announced it has entered into an agreement with Celladon to supply the drug substance for MYDICAR. The €4.7M deal covers scale-up and prevalidation studies. It includes the facility enhancement engineering Novasep will make at its Seneffe (Belgium) bioproduction plant to enable it to bring advanced heart failure drug MYDICAR into commercial production.

In addition, Novasep and Celladon have agreed to negotiate further terms for a commercial supply agreement until December 31, 2018. This is subject to the early termination of certain specified MYDICAR regulatory and development outcomes, with extension options until 2020.

MYDICAR is an innovative, genetically targeted enzyme replacement therapy for advanced heart failure based on AAV/SERCA2a, an Adeno-Associated Virus (AAV). MYDICAR is currently undergoing several clinical phases, including a Phase IIb study in the US.

"With this agreement, Novasep will support Celladon's plans to produce MYDICAR on accelerated timelines," said Alain Lamproye, President of Novasep Biopharma BU. "We are leveraging over 10 years' experience in developing and manufacturing viruses and viral vector products to enable Celladon to meet its goal of bringing MYDICAR to the market as soon as possible. We consider this contract a reward for our strategy of developing custom manufacturing capabilities for novel virus and viral vector-based therapies. We are delighted to have the opportunity to establish this partnership with Celladon aimed at bringing this potentially life-changing therapy to patients sooner."

Vaxxas Raises $20 Million to Accelerate Commercialization of Novel Vaccine Platform

Vaxxas recently announced it has secured equity funding of $20 million from new and existing investors. These funds represent the first closing of a Series B venture financing round, the proceeds from which will be used to advance a series of clinical programs and develop a pipeline of new vaccine products for major diseases using Vaxxas' patented Nanopatch platform. This new round of financing brings the total capital raised by Vaxxas to $33 million.

"As we have advanced the development of our Nanopatch needle-free vaccination technology, we have seen tremendous opportunities to create our own proprietary pipeline of Nanopatch-based vaccine products as well as those with partners," said David L. Hoey, President and CEO of Vaxxas. "This funding creates an important inflection point for Vaxxas, as we are now poised to create significantly increased value through our first clinical studies."

Vaxxas' proprietary Nanopatch platform induces robust immune system activation by targeting vaccine to the abundant immunological cells immediately below the surface of the skin. Vaxxas' plans call for applying its patented needle-free vaccination technology against major diseases, such as influenza, polio, bacterial infections, and cancer.

"OneVentures is proud to lead this Series B financing, which reflects the tremendous potential of Vaxxas through commercialization of the Nanopatch platform," said Paul Kelly, MD, Chairman of the Board of Directors of Vaxxas Pty Ltd and Managing Director at OneVentures Pty Ltd. "The funding positions the company to establish a high-value vaccine product pipeline and initiate clinical programs."

Midatech Pharma Announces Positive Study Results for OpsiSporin

Midatech Pharma recently announced positive results from a proof-of-concept in vivo study with OpsiSporin, a sustained-release treatment for uveitis.

Uveitis is an inflammatory process affecting the iris, the ciliary body, the choroid layer, or all or part of these structures of the eye. Whilst treatments exist, including corticosteroids and the immunosuppressant compound Cyclosporin A (CsA), a therapeutic that permanently controls inflammation, with a good short- and long-term safety profile, has yet to be developed.

OpsiSporin applies Midatech's Q Sphera microencapsulation technology platform to precisely encapsulate CsA within polymer microspheres for sustained and extended release. The product has the potential to offer an effective alternative to steroids for the treatment of uveitis and a concomitant reduction in associated adverse effects, such as cataracts and glaucoma.

The in vivo preclinical study sought to determine the efficacy of OpsiSporin microspheres following a single intravitreal injection, in the treatment of autoimmune uveitis, compared with oral administration of CsA, an intravitreal microsphere suspension vehicle and untreated controls. Intravitreal injection, a technique by which a drug is injected into the eye, has become a common method of treatment for many retinal diseases, including AMD, Diabetic Retinopathy, and Retinal Vein Occlusions.

Results of the study showed a significant reduction in the severity of the disease when intravitreal injection with 4.5 micrograms OpsiSporin was compared with microsphere suspension vehicle. The study also demonstrated a comparable reduction in severity when a single intravitreal injection of 4.5 micrograms OpsiSporin was compared to the daily oral administration of 6.7 mg/kg/day CsA (a dose more than one thousand-fold greater). These results show the potential of OpsiSporin to offer patients with autoimmune uveitis a therapeutic alternative to steroids and CsA with high efficacy and reduced adverse effects.

Midatech Pharma is a nanomedicine company developing and commercializing multiple therapeutic products to enhance the delivery of medicines in major diseases with high unmet medical needs. The Group has a strong pipeline of product candidates in clinical and preclinical development with a clear focus on the key therapeutic areas of diabetes, cancer, and neurological/ophthalmological diseases.

N-of-One Becomes Oracle Silver Level Partner

N-of-One, Inc. recently announced it has become a Silver Partner in Oracle PartnerNetwork (OPN) Specialized program. By attaining Silver Level membership, N-of-One will benefit from integrated access of N-of-One clinical interpretation solutions with the highly scalable Oracle Health Sciences Translational Research Center. Oracle's comprehensive platform aggregates omics data and data from electronic health records and can be leveraged to accelerate biomarker identification for drug discovery and clinical development to facilitate translational medicine research.

N-of-One, combined with Oracle's TRC, can now add N-of-One clinical interpretation to enable the delivery of molecularly guided treatment strategies to the point of care for providers that are launching and growing a precision medicine program.

N-of-One provides clinical interpretation and analysis of next-generation sequencing (NGS) and companion diagnostic test results of each patient's cancer. N-of-One's clinical interpretation links the relevant biological and clinical evidence and insights related to the mutation profile of each tumor to possible therapeutic strategies for the physician.

With this new relationship, N-of-One can gain the ability to integrate its clinical interpretation solutions with Oracle Health Sciences Translational Research Center, a comprehensive platform that normalizes, aggregates, controls, and analyzes all the diverse clinical and molecular data needed to support the complete biomarker lifecycle. This allows mutual customers to incorporate all relevant clinical and scientific data, including patient-specific EMR content, in the clinical analysis to identify each patient's therapeutic options for physician treatment decisions.

"We are pleased to work closely with the talented team at Oracle Health Sciences as they develop the Oracle Health Sciences Translational Research Center platform and other precision medicine tools that easily adapt to and address clinical environments for oncology patients," Chris Cournoyer, CEO of N-of-One. "As precision medicine becomes an integral part of providing outstanding cancer care, oncologists increasingly are looking for insight on molecularly guided therapeutic options for each patient."

N-of-One, a leader in enabling precision medicine for oncology, leverages its world-class team of experts coupled with a highly proprietary platform that allows us to provide clinical solutions and services , such as molecular interpretation, to clinicians at the point of care. N-of-One's team of experts has interpreted thousands of samples for oncologists and patients worldwide, through partnerships with leading diagnostic companies, hospital systems, directly to oncologists, and through employee access benefit programs.

BioSpectra Welcomes New Director, Offering Direct Access to the Highest Compliance Excipients & APIs

BioSpectra recently announced the appointment of Thomas Donnelly as Director of Sales and Marketing. Mr. Donnelly will manage direct sales and business activities for BioSpectra and will serve on BioSpectra's Leadership and Senior Management Teams. The hiring comes as BioSpectra moves into a new phase of business development, which expands its product line offerings to include the new Bio Excipient and Bio Active Grades. These ICHQ7-based products are intended for use in drug products and are available directly through BioSpectra.

"Tom brings significant sales and marketing experience to the position, but his professional leadership and interpersonal skills make him the first person to represent the BioSpectra name and entire product line," said Richard Mutchler, President of BioSpectra. "We look forward to Tom's contribution to our strong, existing capabilities as we increase the value we deliver to our customers through new products and innovative solutions."

Among Mr. Donnelly's new responsibilities will be the development and implementation of sales and business strategies to support BioSpectra's rollout of new pharmaceutical ingredient offerings – chiefly Amino Acids, Carbohydrates, and US synthesized Life Science products. Additionally, he will spearhead a drive to not only sustain the company's surging momentum, but also to aggressively develop additional strategic business opportunities that will advance the BioSpectra brand through products that are intentionally manufactured for the most demanding end uses.

BioSpectra is an FDA-registered, cGMP-compliant, manufacturer and commercial producer of biological buffers, pharmaceutical excipients, and Active Pharmaceutical Ingredients. For more information on the Bangor, PA, company, visit www.biospectra.us.

West Launches High-Quality Flip-Off Plus Seals

West Pharmaceutical Services, Inc. recently announced the availability of a new sterile drug vial seal, the Flip-Off® PlusRU seal. Part of West's Flip-Off® seal product family, these new ready-to-use seals help pharmaceutical and biopharmaceutical manufacturers protect the safety and integrity of their drug products while meeting regulatory requirements for increased drug cleanliness and safety.

Seals play an essential role in keeping injectable drugs safe. They ensure that drug products in vials are sterile and free of contaminants and particulates that could present risks to patients. For more than 90 years, West has been a leader in this field, producing high-quality drug containment and delivery components and systems that help pharmaceutical and biopharmaceutical companies provide medicines to patients more efficiently, reliably, and safely. West's newest innovation, the Flip-Off® PlusRU seal, continues this legacy by providing drug manufacturers around the world with sterile, high-quality seals that consistently achieve reproducible and safe container integrity for drug products while ensuring low levels of bioburden and particulates, which may help make drugs safer for patients.

Flip-Off® PlusRU seals are manufactured using the TrueEdge® manufacturing production process providing precise, consistent, and reproducible seals with a smooth, even bottom edge, which addresses requirements for high-speed filling and reliable capping success. The seals are assembled in a CNC (Controlled, not Classified) environment. They are sterile and support clean crimping under Grade A air supply in order to exclude bioburden. A certified bioburden prior to sterilization allows cGMP-compliant sterilization validation, thus enabling clean crimping processes in accordance with the latest quality trends and regulations.

XstalBio Issued US Patent for Stabilization of Therapeutic Proteins

XstalBio Ltd a biologic formulation and drug delivery company recently announced the United States Patent and Trademark Office has issued US Patent, US 8,932,715, covering the use of precipitation stabilizing additives for manufacture of dry powders of therapeutic proteins, including monoclonal antibodies (mAbs). Applications in development include proven multi-year intermediate storage of protein drugs as bulk dry powders (API stable for >7 years) and production of high concentration mAb solutions suitable for subcutaneous injection. The proprietary technology allows delicate protein drugs, unstable in aqueous solution, to be rapidly and cost effectively precipitated into very stable dry microparticles with full retention of bioactivity. XstalBio has exclusive rights to the patented technology and is developing a commercial process suitable for GMP manufacture of tonne per annum quantities of protein powder.

"The stabilizing additives described in this patent have enabled XstalBio to develop an exciting platform technology for processing delicate therapeutic proteins into dry powders with exceptional shelf-lives," said XstalBio R&D Director Barry D. Moore. "Compared to lyophilization the XstalBio precipitation process offers advantages of speed, cost, and dose-flexibility, and it produces humidity- and temperature-stable powders that are much easier to handle than spray-dried particles. Drug substance can be stored as a bulk dry powder without freezing for over 7 years, and the same platform formulation has been applied to multiple human and animal health proteins. We anticipate in the future this disruptive technology will provide significant benefits to patients by helping pharma companies to bring a new generation of more convenient protein medicines to the market faster and at significantly lower cost."

XstalBio is a privately held company founded in 2004 and based in Glasgow, Scotland. XstalBio works collaboratively with international clients to help drive biopharmaceuticals and vaccines to market by enabling delivery of products to patients. The company provides its experience, innovative technologies, and expert consultancy to find efficient solutions to complex bioformulation challenges and accelerate the development of biologics.

XstalBio has successfully formulated over 50 APIs working with many of the world's top pharmaceutical and biotechnology companies as well as leading vaccine and animal health companies. APIs include mAbs, mAb fragments, cytokines, hormones, plasmids, and peptides spanning a broad range of molecular weights and physical characteristics. In addition, the company has generated novel adjuvant formulations of many types of antigens, including recombinant proteins, bacterial lysates, toxoids, and polysaccharides. Its scientists routinely take on challenging formulation issues and seek to solve them by applying innovative, straightforward, and scalable formulation technologies.

SteadyMed Raises $12.2 Million

SteadyMed Ltd. recently announced it has secured $12.2 million in an equity financing. The financing was co-led by funds advised by subsidiaries of Federated Investors Inc. and Deerfield Management Company L.P., and the company's largest existing shareholders also participated in the financing.

In conjunction with the closing of the financing, William Slattery, Partner at Deerfield, will join SteadyMed's Board of Directors. Mr. Slattery has been a Partner at Deerfield Management since 2000. Deerfield is an investment firm dedicated to advancing healthcare through investment, information, and philanthropy. Mr. Slattery has been an investor in public and private companies seeking to develop therapeutic options for many forms of disease, including for the treatment of Pulmonary Arterial Hypertension (PAH), an orphan disease with no known cure.

"We are very pleased to have completed this latest round of financing, and I welcome Federated and Deerfield to our top-tier group of investors," said Jonathan M.N. Rigby, SteadyMed's President and Chief Executive Officer. "This year promises to be an important time for SteadyMed as we take the necessary steps to file for regulatory approval for Trevyent, our lead drug product candidate that utilizes our proprietary PatchPump technology in combination with treprostinil to treat PAH."

"I look forward to contributing to SteadyMed's mission, as a Board member and healthcare investor," stated Mr. Slattery. "This investment recognizes the clear potential of Trevyent for PAH and the benefit to patients that it may someday provide."

SteadyMed Therapeutics, Inc. is a specialty pharmaceutical company leveraging its PatchPump platform to develop its own therapeutic portfolio and partners to optimize the delivery of high-volume (greater than two mL), high-value, small molecule or biologic drugs. The company's family of PatchPumps can be customized to deliver liquid drugs, including biologics, with a wide range of volumes and viscosities, in a consistent and controllable manner. SteadyMed aspires to redefine the parenteral therapeutics experience for patients dependent upon large doses of intravenous and subcutaneous medications: extending the limits of parenteral therapeutics to restore freedom, joy, and dignity to patients' lives.

Management Insight

The Specific Peck Response & How Express Scripts Has Changed the Future Course of Drug Pricing

By: Derek Hennecke, CEO & President, Xcelience

In the book, *The Bird*, author Colin Tudge describes how his favorite pub once ran out of peanuts and lamely proffered a medley of Japanese biscuits in their place. The tiny, pretty crackers, he reports, were brightly colored in hues of yellow, red, and blue, and thoroughly revolting. He tossed them across a lawn in disgust, to where a nearby flock peacocks waited for just such a possibility.

Tudge watched with interest as the peacocks wandered through the field of crackers, eating first all the yellow ones and only the yellow ones. Then they returned over the same area only for the red, and finally lapped the area a third time for the blue. Why?

Birds, it turns out, are pattern followers. Their eating rituals follow what scientists call the specific peck response, which is an optimal foraging strategy. Animals that feed on small foods face two logistical challenges: that no single seed (or biscuit) is worth lingering over, and that in any one scattering of items, only some will be edible. Most often there will be gravel, rocks, and other debris mixed among them. Rather than wasting time

making choices, the birds will test the most prevalent item and go after those, before switching to the next most populous item.

You can conduct this experiment at home, if you're so inclined. Toss a cup of sunflower seeds mixed with a half cup of peas onto your lawn or driveway. I promise you that whichever species of bird arrives first, it will ignore the peas and eat only black sunflower seeds before switching to the peas. Then, reverse the experiment and throw a cup of peas and a half cup of sunflower seeds out. The birds will first eat the peas, then the sunflower seeds. Every time!

The specific peck response system was forged by evolution, and it works. We may reasonably expect that birds will continue this pattern unless and until it no longer works for them.

We humans aren't so very different. We develop certain ways of doing things, and we generally stick to those patterns unless and until they no longer work for us. Then we are forced to adapt or die. In nature, change is slow. In business, it can happen overnight.

THE END OF SKYMALL

Just ask SkyMall, which filed for bankruptcy in January. Remember this magazine? For 25 years, it's been tucked into the back of every airline seat. It's full of whacky, oddball innovations — paper towel holders with USB ports, wine glasses with built in aerators and the like. SkyMall died because of a single regulatory change that destroyed them overnight.

You may not have realized it, but the reason you perused SkyMall was because you were forced to turn off your electronic devices during takeoff and landing. There wasn't much else to do, so you flipped open the magazine. Just like everyone else.

But last year, the regulations changed, and airlines were able to allow passengers to power up during takeoff and landing. SkyMall's sales numbers fell out of the clouds. From $33.7 million in revenue in 2013, the company saw only $15.8 million in the 9 months ending Sept. 28, 2104, according to *The Wall Street Journal*.

The fortunes of a magazine, or indeed an industry, can change significantly based on a single event. In drug development, we are ever on the lookout for this type of change induced through changes in FDA policy. Or healthcare laws. Or economic downturn.

But this time, we've been broadsided by a new player in drug pricing policy, and many of us still haven't recognized the impact this single deal will have on prescription drug pricing. I'm talking about AbbVie and Express Scripts.

A NEW PRICING ENVIRONMENT

Allow me back up a little first, before I get to the meat of the matter. Until 2015, price wars didn't happen among patented prescription drugs. Insurance companies offered a selection of drugs, with varied accompanying payment plans. Some drugs weren't covered to encourage patients to use more cost- effective options — usually generics. The insurance companies exercised some pricing pressure, but their main concern was that the treatment offered be less expensive than the alternative of no (or different) treatment. Express Scripts, CVS, and Walgreens distributed the drugs to the patients. The drug companies, as a result, could set their prices to what the market would bear; within the context of other treatment options.

In the case of Hepatitis C, any solution that mitigated the need for liver transplants and/or prolonged end-of-life care was preferable, and hence, when Gilead came out with Solvadi with a 90% success rate and priced the pills at $1,000/pill or $84,000 for a full course of treatment, the insurance companies swallowed it.

Even when AbbVie came along with a similar product, Viekira Pak, the new competitor signaled reluctance to compete solely on price by giving it a sticker of $83,300 for 12 weeks; not a hugely significant difference, particularly for a product with the downside that it requires 4 to

"The industry's pattern of pricing behavior has long been strained by high prices, but there's a pretty good argument to be made that the Hep C drugs were the straw that broke the camel's back. Even though there have been more expensive drugs, the combination of high prices and a huge patient population is new. Those record-breaking revenues are someone else's costs, and that someone else is the insurance companies. Something had to change."

6 tablets a day versus Solvadi's single-daily dose.

Then, in January, AbbVie entered an exclusive deal with Express Scripts. In exchange for exclusive access to Express Scripts 25 million customers, AbbVie agreed to significantly discount the price of its Viekira Pak.

Soon after, CVS Health Corp. and Anthem Inc., the biggest provider of health insurance plans to US employers, made an exclusive deal with Gilead for the use of Harvoni (which combines Solvadi and another Gilead product), at a significant price discount.

This changes everything! Not so much for Gilead; Gilead will still make a breath-taking profit. It's the rest of the players in the industry who are going to be most affected.

Gilead, if we do the math, will still come out extremely well, albeit less well than before. This is true even despite the astronomical costs of developing Solvadi. For most drugs, it now costs about $2.6 billion to gain market approval, according to the Tufts Center for the Study of Drug Development. If things go spectacularly well, the most any drug might reasonably (or perhaps unreasonably) expect to earn is peak year sales of $13.7 billion and lifetime sales of $131 billion (according to *Forbes*); that being the record set by Lipitor, Pfizer's LDL-cholesterol lowering drug (now generic).

Solvadi has been on a different playing field since the day Gilead bought the drug candidate from a company called Pharmasset in November of 2011 for a whopping $11 billion dollars. Gilead's shareholders were, understandably, shocked and amazed. Gilead became the worst-performing big cap biotech in December 2013, down 8.38% that year compared to Celgene's 12.59% increase. The company then proceeded to push millions of dollars more into the Hep C drug candidate to get it through clinical trials. How could a gamble like that possibly pay off?

All you really need to know is this: In July of last year, revenue guidance for the drug was between $22 and $24 billion/year, and Solvadi isn't set to come off patent for more than a decade. Even factoring in AbbVie's competition and the new exclusivity agreements, no one need be overly concerned that Gilead will fail to do anything less than rocket

past Lipitor to become the best selling drug in history.

Let's be clear about one other thing also: Solvadi is not the most expensive treatment out there. There are several more expensive, most notably Shire's Idursuflase, approved for use as enzyme replacement therapy in patients with Hunter Syndrome. This drug goes under the tradename Elaprase, and the cost for treatment of a 35 kg individual is estimated at $657,000.

It isn't just the cost of Solvadi that has brought it into the spotlight, but the combination of cost and market size. With its broad existing customer base (estimates of the global population with chronic Hep C range from 130 to 150 million), a whole lot of people are clamoring for this drug all at once. Over time, those numbers will settle to include only those newly diagnosed, but right now the backlog of people demanding this drug simultaneously is putting a lot of pressure on insurers.

The industry's pattern of pricing behavior has long been strained by high prices, but there's a pretty good argument to be made that the Hep C drugs were the straw that broke the camel's back. Even though there have been more expensive drugs, the combination of high prices and a huge patient population is new. Those record-breaking revenues are someone else's costs, and that someone else is the insurance companies. Something had to change.

ENTER EXPRESS SCRIPTS: A NEW PLAYER ON THE DRUG-PRICING SCENE

In the drug pricing system, drug companies set the prices, and insurance companies determine how much of that price they are willing to cover. There are only two players. Or rather, there were only two players. Now Express Scripts, CVS, and Walgreens have arrived. Any drug that has a competitive form of treatment will now be subjected to a new form of competition. This new player isn't interested in the cost effectiveness of one treatment relative to another; only in reducing the price of the drug as much as possible so customers will shop with them.

You can bet this is the tip of an iceberg. Express Scripts has already announced its next target will be the $37.2-billion cancer drug market. At the moment, Express Scripts doesn't cover cancer drugs, which are administered by doctors and hospitals and aren't sold by pharmacies. Express Scripts plans to expand its coverage to include these drugs, which can cost hundreds of thousands of dollars. Bristol-Myers Squibb and Merck's PD-1 Inhibitors, a new class of treatment approved for skin cancers, which is currently being tested for other types of cancer, may be targeted. Bristol-Myers' Opdivo and Merck's Keytruda are also in the crosshairs; both drugs cost $150,000/year.

Already the chances of any particular idea making it through the decades-long process of drug development, gaining funding, surviving regulatory screening, and showing efficacy beyond existing treatments are slim at best. The risks are huge. We need a vast field of sparks if we are to see any flames of discovery at all.

Now we have a new risk factor: a drug that makes it all the way to market and then fails to negotiate a good enough deal with the drug distributors to generate a profit. This will affect the number of drugs that are developed, and the willingness of venture capital to get behind a good drug candidate. The drug industry's old foraging patterns have been disrupted. We haven't seen anywhere near the full impact of what just happened. ◆

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Derek G. Hennecke
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COMBINATION PRODUCTS

Human Factors & Combination Products

By: Richard Featherstone

INTRODUCTION

Manufacturers of combination products are increasingly being asked by regulators to perform human factors (HF) testing alongside the clinical trials program. This comes as a surprise to many pharmaceutical companies, in particular those who are developing their first combination product. As an active HF practitioner who works with combination products globally, I see first-hand the confusion caused when manufacturers of combination products are suddenly asked by regulators to present a report of their HF data. Often, this is because the client has realized very late in the product development cycle that HF studies are likely to be required. But there are some very clear principles to follow, and in this review article, I will discuss the most important considerations when setting out to perform HF studies with combination products.

WHAT ARE COMBINATION PRODUCTS?

Combination products sit in a grey area between medical devices and pharmaceutical products, with features of both product types. The US Food and Drug Administration (US FDA) defines combination products as "diagnostic or therapeutic products that combine drugs, devices, and/or biological products." This means that some type of technology (such as a hand-held injection device) is used to deliver a measured amount of drug from a container through an exit port and onto the administration site. This dual aspect to combination products is one reason why regulators often try to address both the clinical and HF programs with the same review team.

The most common types of combination products are pulmonary inhalers (eg, dry powders or pressurized aerosols), injection systems (eg, pen injectors and auto-injectors), and infusion systems (eg, ambulatory syringe pumps delivering continuous subcutaneous drug delivery). Other types include nasal sprays, creams, eye drops, and ear drops.

COMBINATION PRODUCTS & HUMAN FACTORS

The development of combination products is gathering pace, with many of the world's pharmaceutical companies developing them as a key part of their new product pipeline. In many cases, firms are dusting off their older drugs and generating new intellectual property around a new delivery technology. New injection technologies, smaller infusion pumps, and smarter inhalation systems are all being developed.

FIGURE 1

Regulators are catching up, and there is a growing demand on manufacturers to provide evidence that their new technology can be used safely. The FDA in particular is increasingly proactive and is currently updating its guidance to manufacturers on human factors (HF), with combination products very much in their sights.

SO WHAT'S THE PROBLEM?

The science of drug testing is well developed, and there are clear and comprehensive guidelines on how to construct clinical studies, and a well-established body of "best practices" available to industry and researchers alike. There is also a reasonable amount of knowledge (and guidance) on how to perform HF testing for medical devices; however, the science of HF testing for combination products is less well developed, and there is, as yet, no specific guidance from regulators.

Because combination products have only recently become center stage, there is still a lack of clarity about how HF testing should be applied to them. In my experience, there is also a lack of consistency from regulators when they review HF data for combination products.

A common complaint is that regulators seem to be applying an unduly stringent risk-focused approach, even when the drug involved has been used for many years, and also when the product type is widely used. For example, one organization I know has been asked to provide evidence to mitigate use-related risks anew for their auto-injector, even though it is similar to devices that have been available for some time. This is despite the fact there is widespread experience of their use amongst healthcare professionals, and auto-injectors are not generally regarded as high risk devices.

Another complaint we hear often is that there is conflicting guidance from different reviewers within the same regulatory body. For example, one reviewer might request an untrained group to be included in a study, whilst a different reviewer might say that an untrained group is not required.

HOW DOES THE USER EXPERIENCE DIFFER?

The users' experience with a combination product is fundamentally different to traditional oral drug products, such as tablets and capsules. With oral drug products, the drug is presented as a tablet, capsule, or a liquid; often the user needs only perform a very few tasks to administer the drug either to a patient or to themselves, such as opening the packaging, removing a tablet, or pouring a liquid onto a spoon and then swallowing. However, with combination products, the user must master many more of the device's components. This may mean performing 8, 10, 12, or more tasks successfully, such as assembling it, inserting a drug cassette, switching it on, reading the dose counter, priming an infusion line, checking for dose delivery, stopping delivery, switching off, and disassembling. A failure to perform any one of these tasks correctly could mean that the patient does not receive the intended dose, or receives an overdose or some other harm.

WHAT DO REGULATORS WANT?

Regulators require evidence that your combination product can be used safely and effectively by its intended users. As with other medical devices, their focus is three-fold; the intended users, the use environments, and the user interface.

So they will be looking for evidence of safe and effective use of your product from these three perspectives. FDA guidance states that medical devices should be "adequately safe and effective for its intended users to use it for its intended use in its intended use environment(s)."1 In practice, this means providing data in particular from your summative HF testing program, and involves showing the performance outcomes of study participants during simulated use. Specifically, you will need to show that the user interface of your combination product (such as the instructions, labels, dose counters, etc) can guide your product's intended users toward safe use, especially for those tasks that are critical.

ARE YOU EXPECTED TO REMOVE ALL RISK OF HARM?

There is a common belief that regulators expect manufacturers to remove all risk of use-related harm. In our experience, this is not the case; the regulators do understand there may be limits to what you can realistically do with the current state of technology, although they definitely do expect you to demonstrate that you have quantified the risks and done everything you can reasonably do to reduce it.

Thus, you may also need to prepare a justification as to why you do not intend to try to further remove risk. The FDA guidance clearly states that you may provide reasons why you are not intending to continue development; in other words, you may be justified in stating that:

1. Further modifications to the user interface (remember this includes the device itself, plus instructions, patient leaflets, packaging, and labelling) would not further reduce risk.
   AND

2. Further modifications are not feasible or practicable given the current state of the technology (eg, when there is no technology that can anticipate a user's next action, or where there is no way to remove the risk of a user running out of medication during a weekend).
   AND

3. The residual risks are outweighed by the benefits that would accrue to users; this may be particularly the case for novel technologies that address previously unmet clinical needs.

Whether you can use the argument that you cannot afford further changes is debateable; a financial argument alone is unlikely to be accepted, but one that is combined with an explanation as to why further changes are not feasible or practicable given your resources and the state of technology, then that is likelier to be acceptable.

GENERATING THE RIGHT HF DATA FOR COMBINATION PRODUCTS

Human factors specialists approach a combination product in the same way they would do for a medical device. First, by defining some of the basics, such as:

Intended Use: What is the intended use of your combination product? Examples might be "the continuous subcutaneous delivery of drug X for patients with condition Y whilst being mobile."

Intended Users: Who are the product's intended users, and what is known about them? Examples might be "adults over 18 years in the United States with moderate-to- severe rheumatoid arthritis who are currently using a disease-modifying drug by injection" (remember, you will need to be very specific, for example, about age, sex, ethnicity, and any other characteristic that may influence usability).

Use Scenarios: What use scenarios are expected to be most frequently encountered when the product is on the market, and what are the reasonably foreseeable worst-case scenarios? Examples might include "using an inhaler at home during the night in low light conditions whilst laying down in bed" (again, you need to be specific).

Use-Related Risks: What risks of harm are posed by the use of your combination product, and are these clearly documented? These need to link directly to your use-related risk assessment, and you will need to make sure that you are testing at the very least all of the higher risk tasks.

GETTING THE TESTING RIGHT

There are some critical questions to ask as you plan your human factors testing program:

Getting the Tasks Right: Are you testing the right tasks? You should be testing those tasks that are associated with use-related risks. But in combination products, you have the additional risks associated with the drug. If the risks are not related to the intended user using the device component, then it is probably not necessary to test them. However, if your risk assessment includes any drug-related risks that are potentially caused by a user handling/using/applying the device component (eg, by controlling the dose delivered), then it should be evaluated.

Test the Right Users: Are you testing the right users? The intended users of combination products may include a healthcare professional (HCP) who teaches the patient how to use it, and may also configure the product. For example, with ambulatory infusion pumps, a healthcare professional may configure the bolus volume and the flow rate. Users may also include a pharmacist who might teach patients how to use their inhalers. Also, with the increasingly elderly and frail patients, there may be a caregiver (such as a partner, child, or friend) who may need to perform some or all of the tasks.

WHAT HF DATA IS REQUIRED FOR COMBINATION PRODUCTS?

In principle, the HF data requirements for combination products are similar to those for medical devices with a few important differences, as follows:

Device or Drug?: Your combination product is designed to deliver a drug safely and effectively. Your focus should be on the use-related risks, rather than the drug-related risks. In other words, your HF program is not intended to provide evidence that the drug itself is safe. Your focus is on the safety and efficacy of the technology. So start with a use-related risk assessment and make sure it focuses on the technology, not the drug. Remember, you are not retesting the drug, you are gathering evidence that users can deliver the drug safely and effectively.

Home Use: Many combination products are intended for use at home. It is possible (or indeed likely) that some users will have received no training. They may rely on your instruction leaflet, or they may need to ask a friend or partner for help. This places additional burden on you to show that the instructions can help an untrained or inexperienced user to use it safely.

Multiple Reviewers: As we have already mentioned, there is a range of experience among regulatory reviewers with regard to HF. Because a combination product involves a drug, it is entirely possible that your HF data gets reviewed by a drug regulator who may have little experience of reviewing HF data. Whilst some reviewers may ask for help from a colleague with HF expertise, you may get asked questions that appear to have little relevance to best HF practices. In practice, this means that you will have to help the regulator by working hard to provide a clear, concise report with suitable references, and a scientific justification for your arguments, in particular, with regard to any residual use-related risks.

Device-User Interface: What elements constitute the interface between the combination product and the user? This is where there is likely to be the most difference between oral pharmaceuticals and combination products, because there will be multiple elements to the user interface. Examples may include a dose counter, a carrying case, a charging port, or perhaps an app. There may be disposable items, such as a needle, and there may be peripheral items, such as a spacer device for aerosol inhalers. Your HF focus is on the interface between your combination product and its intended user, so you will need to gather data on any aspect of the user interface that supports safe use. Your combination product may require the use of disposable items, such as an infusion line, a disposable mouthpiece, or a disposable needle. It may include a carrying case with a window that enables users to view the remaining dose to be delivered. These constitute a system, and whilst you are not expected to prove that someone else's product is safe, you will be expected to test the whole system, including peripheral items.

A FEW FINAL COMMENTS

Manufacturers of combination products are being asked to provide rigorous data on the safety of their product when its intended users use it. These challenges are not going to diminish, but with a focused approach and some sound HF principles, manufacturers can navigate the challenges successfully.

Disclaimer: The opinions expressed in this article are based on the author's experience only and cannot necessarily be taken as specific recommendations. ◆

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BIOGRAPHY

Richard Featherstone is an experienced human factors and usability practitioner and is joint Founder of Medical Device Usability in the UK, where he specializes in combination products. He has 30 years of experience in the pharmaceutical and human factors industries and works globally. He is regarded as an expert on the usability of inhalation technologies, and designs and runs human factors testing programs globally, with extensive experience of summative testing in the US for combination products, including inhalers, injection systems, and infusion devices. MDU is a human factors and usability consultancy that focuses exclusively on medical technologies, such as medical devices and combination products. Based in Cambridge UK, MDU performs human factors and usability testing globally, including extensive experience in the US. To contact Mr. Featherstone, email him at richard@medical-device-usability.com. To contact MDU by phone, call +44 1223 214 044.

MARKET BRIEF

Miniaturizing Healthcare – From Microelectronics to Nanobiosensing

By: Cecilia Van Cauwenberghe, MS, Technical Insights Senior Research Analyst, Frost & Sullivan

INTRODUCTION

Technology miniaturization has challenged scientists for decades. Starting with microelectronics, the concept of miniaturization has been studied and applied to life sciences and biotechnology with prospective results. Molecular behavior at micro- and even nanoscale has demonstrated to be substantially different than at the bulk scale. Under this scope, micro- and nanofluidics technology allows researchers to achieve a more profound understanding of these variations aiming to optimally exploit their benefit in a broad spectrum of application fields.

The principal impact of this technology keeps highest levels for high-throughput screening (HTS) methods for DNA sequencing, in which nanobiochips are mainly used to stretch DNA strands. Similarly, nanofluidic devices are strategically targeted to be used as disposable devices, specially applied to point-of-care (POC) diagnostics.

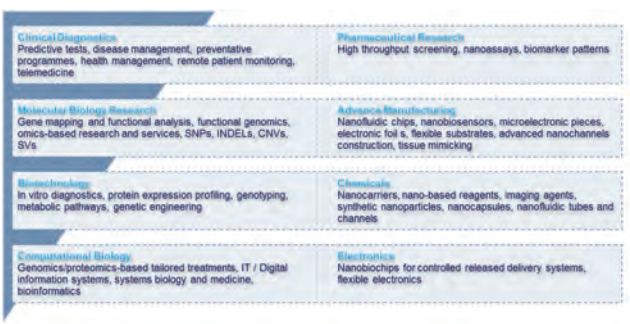
In other words, as the information revolution has constituted the predominant event in the economy of the 20th century with the silicon microchip or semiconductor, the past decade has evidenced the simultaneous advances in miniaturizing microchip elements on one hand and self-assemble nanoparticles on the other. In fact, performed with the aim of reducing costs while enhancing performance, these approaches have derived in the acceleration of nanotechnology to biochips from an archetypal synthesis of top-down and bottom-up developments, constituting the key to the success of microchip technology.

This approach has also revolutionized the technology transfer model from academia and research organizations to industry, strengthening the conjunct efforts among governmental, industry, and university actors.

Life sciences research and biomedical engineering devices constitute the most significant application targets. Experts' opinions agree that in set-up, the major impact of nanofluidics technology, including a fluent commercialization and a wide scale adoption, from 2016, is a continuous and prospective advance toward novel fields of application, involving a synergistic convergence of technology clusters. Indeed, the proliferation of lower cost microfluidics-based genomics tools offering improved capabilities and allowing more access to end-users is expected to drive this technology for pharmaceutical and biomedical research throughout the next 5 years.

Working with micro- and nanoliter quantities of reagents in micro- and nanoscale dimensions, these novel devices allow sample separation and detection with greater sensitivity and specificity. The economic burden of carrying laboratory-scale experiments utilizing expensive equipment is significantly reduced, hence obtaining rapid and reliable results. Moreover, the short footprint of these pieces enables fabrication of portable diagnostic devices, importantly enhancing the access

FIGURE 1



The principal application fields of micro- and nanobiotechnologies. Source: Frost & Sullivan.

of different end-users to medical diagnosis. This fact possesses remarkable importance in developing nations where expensive medical diagnostic facilities are not available to all.

Another remarkable advantage relies on their multiplexing capabilities. Micro- and nanofluidic devices can be used to process multiple samples in parallel, becoming the process substantially more cost and time effective.

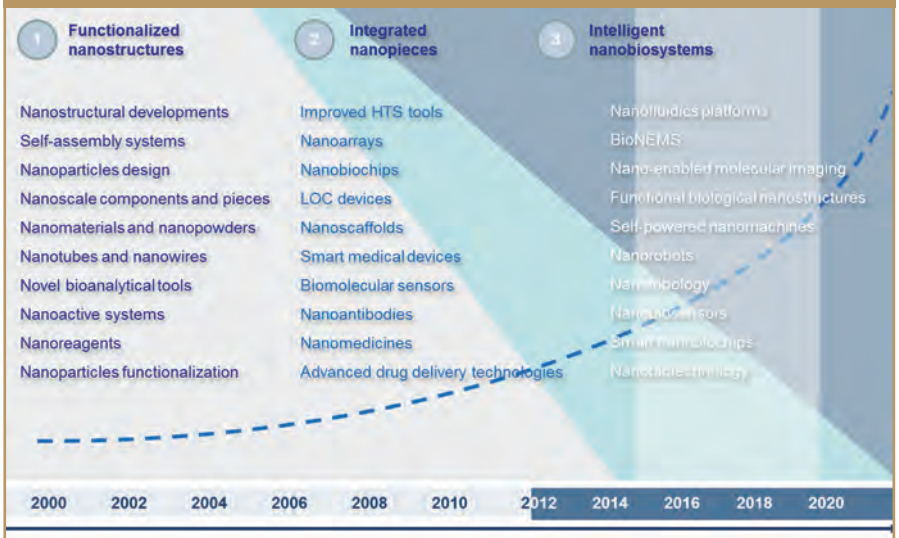
IMPACTING PHARMA, BIOMEDICAL & BIOTECH

Micro- and nanofluidics offer a broad spectrum of novel and potentially valuable developments in several markets, motivating the entrance of new players. Indeed, this technology addresses both the enhancement of existing markets and the creation of new markets. Regarding existing markets, this technology is expected to play a major role in the pharmaceutical industry, singularly optimizing current processes and offering completely new decision supports. New markets, on the other hand, are entering the life sciences research technology cluster, revolutionizing the advance of closely related disciplines.

At this point, the remarkable cross-pollination from other disciplines and sectors, including the electronics, material sciences, and semiconductor industry into the life sciences and biotech arenas, are surprisingly driving the wide field of nanobiotechnologies.

Special impact is observed on the design of novel biochips for HTS and diagnostics applications, on one hand, and lab-on-a-chip (LOC) and POC devices on the other hand.

FIGURE 2



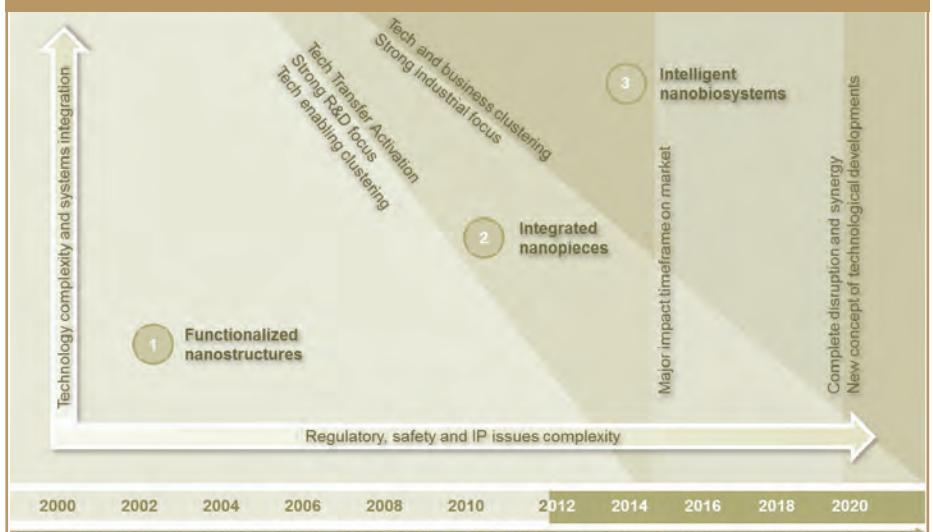
The roadmap of nanobiotechnologies from functionalized nanostructures to intelligent nanobiosensing systems applied to life sciences research and biomedical engineering in terms of technological developments toward 2020. Source: Frost & Sullivan.

CORE TECHNOLOGY APPLICATIONS

Nanomedicines/Nanoenabler Delivery Systems

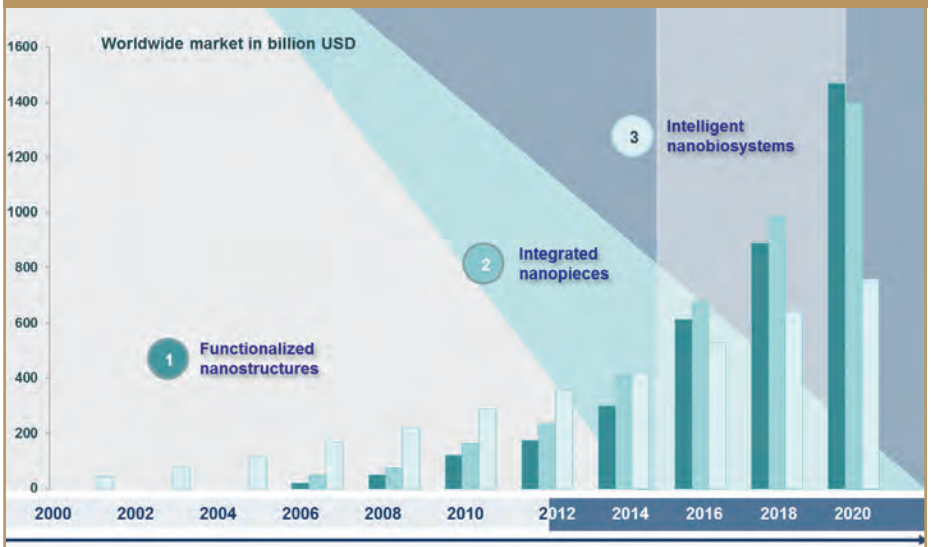
- Molecular nanotechnology (MNT) platforms constitute promising tools due to their ability to conform structures and devices at atomic scale precision and accuracy.
- A more specific target delivery through nanoenabler delivery systems allows using lower doses, avoiding cytotoxicity and minimizing side effects, while improving therapy.

FIGURE 3



The roadmap of nanobiotechnologies from functionalized nanostructures to intelligent nanobiosensing systems applied to life sciences research and biomedical engineering in terms of technology transfer toward 2020. Source: Frost & Sullivan.

FIGURE 4



The market evolution of micro- and nanotechnologies in life sciences research and biomedical engineering toward 2020. Source: Frost & Sullivan.

Cancer Research/Drug Screening Platforms

- Magnetic or antibody-conjugated targeting can guide nanoparticles to a specific body region, and even cells, aiming to improve cancer therapeutics. Nanoparticles are linked to tumor cells, allowing their destruction by different means, such as infrared sources, biochemical agents, etc.
- Nanobio innovations strongly promote the integration of different applications into advanced technology platforms for life sciences research.

Nanobiosensing/Cellular Imaging

- Integrated nanobiosensors indicating the presence of particular molecules or biological structures in microdevices represent important improved capabilities for life sciences and healthcare.
- Cellular imaging represents one of the most promising tools for early diagnostics and personalized medicine. Enhanced imaging technologies by using quantum dots and nanobiomarkers accelerate the pace of future medicine.

Among the most lucrative markets for nanobiotechnologies, medical and life science applications appear first. The advent of nanobiotechniques by hand of LOC devices and nanoenabler drug delivery methods, along with a number of novel experimental medicine and clinical/preclinical studies for early clinical trials, have become micro and nanofluidic techniques as the starring technologies for next-decades developments.

The underlying key of such prosperous development regarding nanobiotech applications comes from the reality that nanoscale particles, including nanoscale devices, are 100 to 10,000 times smaller than human cells. Indeed, nanoparticles are similar in size to large biological molecules, including as enzymes and bioreceptors.

According to this, three principal areas of interest have been mostly related to the promising development of nanofluidics and nanobio devices:

- Disease diagnosis and screening
- Drug delivery systems
- Health monitoring

CORE GROWTH OPPORTUNITIES

Biopharmaceuticals/Next-Generation Biomarkers

- Integrating new technologies into industry value chain at several

FIGURE 5

The participation of North America, Europe, Asia-Pacific, and the rest of the world in nanobiotechnology applied to life sciences research and biomedical engineering. Source: Frost & Sullivan.

levels performing ultrahigh-throughput and parallel analysis at the single-molecule level.

- Accelerating the pace of drug discovery using high-throughput techniques.
- Enhancing target selection, lead identification, preclinical tests, clinical trials, chemical synthesis, formulations studies, and product management.

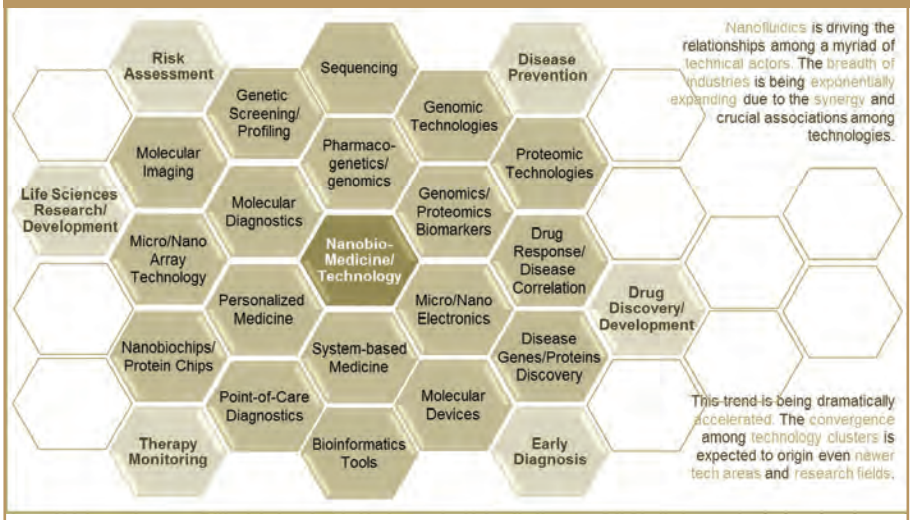
Oncology/Nanoarrays Developments

- Evaluating large number of chemical structures against hundreds of biological targets through novel miniaturization and massively parallel experimentation methods.
- Integrating different functional units for sampling, sample pretreatment, sample transport, biochemical reactions, analyte separation, product isolation, and analysis in a continuous flow manner.

High-Sensitivity & High-Precision Instrumentation

- Developing nano/microfluidic devices with high analytical throughput rates.
- Detecting DNA translocation events through solid-state nanoarray devices as a proof-of-concept that illustrates ultrahigh sensitivity and specificity.
- Interfacing micro/nano and macro-technologies through novel, ease-handling, robust, multiplex, and cost-effective nanobiochips.

FIGURE 6



The principal cross-pollinated disciplines involved in micro- and nanobiotechnologies and their interaction among the different areas of biomedicine. Source: Frost & Sullivan.

MARKET OVERVIEW & PROSPECTIVE LANDSCAPE

Addressing the substantial impact of nanobiotech developments, and especially nanofluidics and bioNEMS on the world's economy, a prospective landscape of market volumes and dynamics constitutes a crucial indicator. Although, the number of industries and the synergistic approaches among a wide range of disciplines, along with the complexity of players in the market, such a quantitative approach represents a matter of great concern.

By screening the investigations and industry breakthroughs evidenced throughout the past decade, the numbers of inventions and innovative ideas, as well as the number of funding programs and human resources involved in the broad spectrum of nanotech-based markets, have all increased by an average annual rate of more than 27%. Indeed, following with the aforementioned defined three levels, that is:

- Functional nanostructures
- Integrated nanopieces
- Smart nanobiosystems

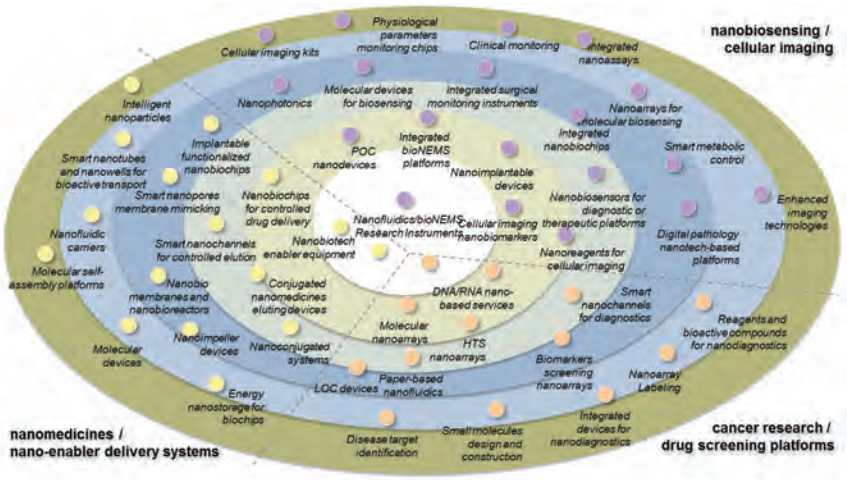
Applied to the life sciences and biotech industry, the total worldwide market reached about $800 billion in 2011, expecting over $1.8 trillion by 2015 and $3.6 trillion by 2020. Interesting, the two last categories have begun to grow as marginal technologies. Nevertheless, their increment throughout the past 5 years, supported by the previous growth of the first category, has resulted in a real breakthrough.

INVESTMENT

Global public and private investments in research and development (R&D) have grown by 40% throughout the past years. Worldwide expenditures have been disaggregated into venture capitals, government grants, regional programs, and private investors. Important differences are being evidenced by regional landscape.

Remarkably, North America

FIGURE 7



The principal products associated with micro- and nanobiotechnologies. In the center are placed those products or kits already in the market, whereas the movement through radial direction exhibits the products under development. Source: Frost & Sullivan.

possesses a strong participation of private sectors, along with government grants, whereas Europe holds a strong position over regional programs. Asia-Pacific region shows the strong involvement of government in R&D decisions, the same as most other regions, such as South America.

Due to fluids exhibiting unique physical behaviors at nanometer scales, different from those present in larger structures, nanofluidic structures have successfully found a broad spectrum of applications. Such variety of technologies range from analytical separations, protein or molecular building, and RNA/DNA manipulation, among many others.

Naturally, nanofluidics developments not only involve an increasing number of applications emerging but also promote the appearance of a wide variety of innovative fabrication methods and technologies enabling the successful development of these applications. Bio-nano-electromechanical systems (BioNEMS) applications, on the other hand, experience a similar behavior, being even more significant the role of the enabling technologies.

Strong discipline focus is put on life sciences and bioengineering disciplines, expecting a central role of nanofluidics and bioNEMS in future medicine. The complexity of the technology and the access to appropriate equipment, as well as the development of tech enabler technologies, make the advancements of nanofluidics and bioNEMS limited in comparison with microfluidics technologies, for instance.

First-level equipment regarding nanomanufacturing, clean rooms, pumping techniques, and energy need to be set up, which constitutes a limitation for R&D activities. On the other hand, the successful integration of individual components and surfaces for nanofluidics devices and bioNEMS still challenges researchers and scientists.

Despite these limitations, strong evidence set nanofluidics and bioNEMS developments as one of the most promising areas of research worldwide. The relevance of nanobiotech developments is clear when analyzing both governmental and private investment and funding trends in nanosciences related to these particular technologies.

A solid intellectual property (IP) position provides R&D institutions and collaborative actors with a stronger strategy to face business development activities and design new methodologies to transfer the technology to industry sectors through an optimal resolution.

TECHNOLOGY CROSS-POLLINATION

As a physics phenomenon, nanofluidics has been defined several decades ago. However, as a discipline, nanofluidics has emerged only in the past few years with the advent of micro- and nanotechnologies.

Nanofluidic channels range from a random network of pores to well-defined and oriented networks. In this regard, advance manufacturing techniques allowing building nanostructures with the desired properties, practically selected according to the geometry of a device and its application, have begun to play a highly dynamic role.

Beyond the structure, nanofluidic systems and devices constitute powerful tools, applicable not only to study fundamental nanoscale science, but also for practical biochemical and clinical applications.

The convergence of a plethora of technologies suggests the creation of new technology clusters leveraging the synergy among several disciplines. Predictions for 2020 claims for a total restructuration of both tech and business clusters and niches favoring innovation

and technology translation from R&D institutions to industry sectors. This convergence can be strongly evidenced in terms of products.

A direct correlation with business development activities is exhibited by evaluating the evolution and dynamics of business models in the time, taking as a reference research, development, and tech transfer tasks.

FINAL REMARKS

The innovation landscape in nanofluidic devices and nanobiosensors is unlimited. Stakeholders involved in innovation processes, technology transfer, and market incorporation are numerous. Stringent regulations and costly device safety procedures delay the efforts to commercialize MEMS-based medical devices. The timeline from product development to commercialization is long for medical devices than most consumer products. To bring a bioMEMS device to the market, manufacturers need to adhere to various regulations in terms of the manufacturing, safety, and sustainability of the device.

Among the disease diagnosis and screening applications, LOC devices offer a broad spectrum of diagnostic functions, allowing achievable similar results from a complete medical or clinical laboratory, is of the most notable. Similarly, nanobiosensors based on nanotubes, wires, magnetic particles, and semiconductor crystals, including quantum dots, come with remarkable advantages for the near future of medicine and life sciences. Analogously, novel medical imaging techniques can be significantly benefited from the advent of nanobiotechnologies.

Drug delivery systems, also coined as nanoenabler drug delivery systems, include a great variety of nanocapsules, dendrimers, and fullerene-based structures aiming to address a controlled- and sustained drug-release mechanism. Remarkably, the past decade has evidenced a highly focused attention of both portable medical devices for diagnostics and drug delivery systems for therapeutics, not only in developed countries, but also for countries lacking from appropriate drug storage capabilities and distribution networks, such as diverse developing countries.

Health monitoring, on the other hand, could experience a significant change from the appearance of nanobiodevices. The periodic evaluation of physiological variables in a cost- and time-effective manner, also facilitating comfort and building capabilities, through novel POC devices that significantly help to address current issues around healthcare burden like aging population and personalized medicine, among many others.◆

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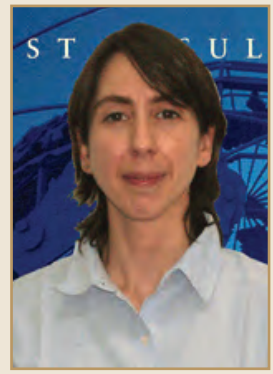
BIOGRAPHY



Cecilia Van Cauwenberghe is a Senior Industry Analyst with Frost & Sullivan's global Technical Insights practice. She has over a decade of professional expertise in chemical and biomedical engineering arenas, which include R&D activities in several well renowned universities and multinational companies. As part of her experience, Cecilia has been involved in a variety of multidisciplinary projects embracing different emerging technologies and establishing strong long-standing working relationships. Cecilia's knowledge base encompasses biopharmaceutical and biochemical modeling, simulation and optimization; microelectronic implantable devices design; and research in metabolic syndrome and cardiovascular diseases applications. Cecilia holds master and doctoral studies in Chemical and Biomedical Engineering. For more information on the Frost & Sullivan's Global Technical Insights or Healthcare practice and offerings, please email: jennifer.carson@frost.com or visit www.frost.com.

DYNAMIC LIGHT SCATTERING

Colloidal Gold: The Gold Standard for Drug Delivery?

By: Stephen Ball

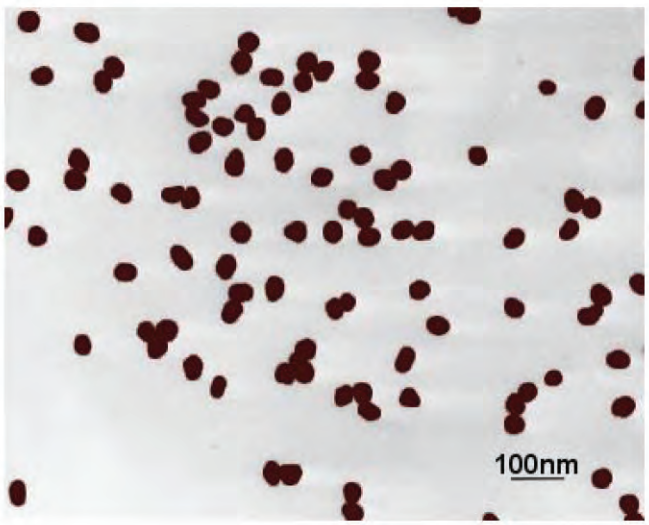
INTRODUCTION

Today, the maturation of a decade's worth of investment into nanotechnology is seeing nanomedical materials steadily emerge into clinical and medical practice. In commercial terms, the result of this carefully fostered research is that by 2015, the market for biomedical nanotechnology is expected to exceed $70 billion.[1] In practical terms, this suggests a potentially transformative shift in the way diseases are targeted and treated.

Nanosized colloidal gold has great potential in multiple therapeutic and biotechnology applications. Taking drug delivery as an example, manipulation of the unique chemical, physical, and electronic properties of colloidal gold enables researchers to develop drug-nanoparticle conjugates for targeted drug delivery, improving a drug's biodistribution and pharmacokinetics within specific biological targets, such as diseased tissue or cancerous cells. In this way, gold nanoparticles are set to play an important role as a platform for novel intracellular delivery vehicles and controlling nanoparticle size throughout the formulation process, which is crucial to defining this functionality.

This article explores the importance of particle size in biomedical nanotechnology. Experimental data are presented to illustrate how advanced Dynamic Light Scattering (DLS) techniques deliver these measurements for colloidal gold in the nanosized and sub-nanosized ranges.

FIGURE 1



Relying on number-based particle size distribution measurements with electron microscopy alone may be a statistically poor approach during the study of nanoparticle homogeneity and aggregation.

ALL THAT GLITTERS: A BRIEF HISTORY OF GOLD THERAPY

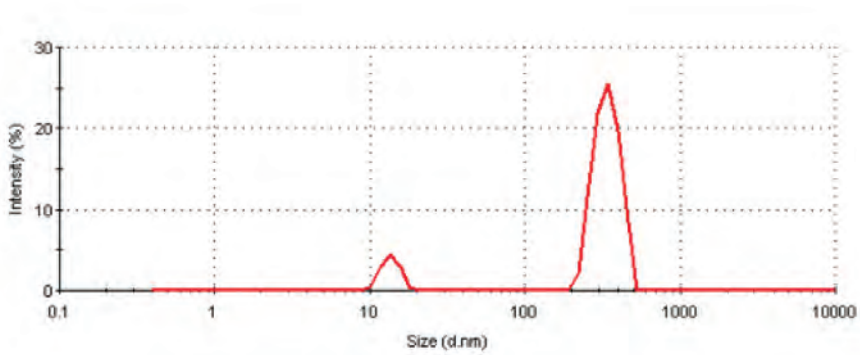
Belief in the therapeutic properties of gold can be traced back to ancient times. However, it wasn't until the 18th century that the antibacterial properties of gold cyano salts were discovered. Fast forward another 100 years, and gold salts are now routinely administered for the treatment and management of rheumatic arthritis. Beyond these conventional therapies,

modern interest in gold lies in its colloidal form.

A number of properties of colloidal gold make it well-suited for nanomaterial-based clinical applications. Its chemical and physical inertness ensure the material is toxicologically safe in vivo, while its fine size allows particles to cross a cell membrane without harming the cell. Furthermore, gold nanoparticles suspended within aqueous media form negatively charged ions that have a strong affinity for biological macromolecules, such as proteins and antibodies, which form biological ligands around the ion. These unique physical properties are currently being exploited for a variety of biomedical applications, including their use as imaging probes, diagnostic agents, and for advanced drug delivery. In this last area, gold nanoparticles are being developed to provide sophisticated delivery mechanisms for a range of conventional and novel treatments, from oral insulin administration to targeted cancer drugs and DNA conjugates for advanced gene therapies.

As with all particulate therapeutics, the pharmacokinetic properties of colloidal gold conjugates, such as bioavailability and clinical efficacy, are strongly influenced by particle size. Controlling the particle size of colloidal gold is therefore of great importance to ensure treatments meet performance and safety criteria in vivo. Particle characterization forms an important aspect of nanoparticle R&D and QC in which routine analysis is performed during intermediary and endpoint formulation stages to ensure particles are homogenous in diameter and there are no aggregates present in the dispersion.

FIGURE 2



A bimodal intensity size distribution for colloidal gold samples indicates the presence of agglomerates within the sample.

This calls for a powerful analytical technique that combines the robust and reliable characterization of particles within the entire sample with the efficiency demanded of routine analysis. Dynamic Light Scattering (DLS) is emerging as a highly effective technique to meet these industrial needs.

INTRODUCING DYNAMIC LIGHT SCATTERING

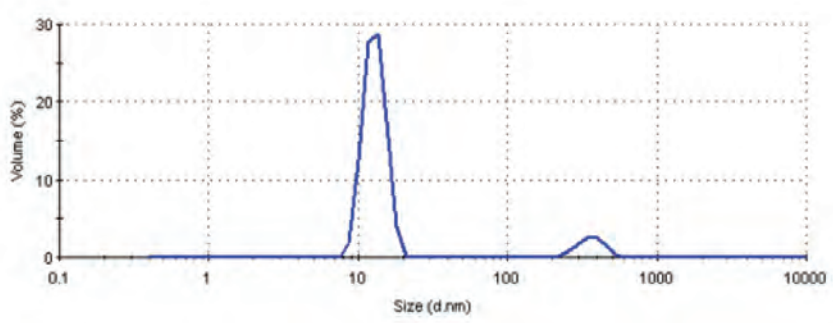
Several particle characterization techniques are used routinely within nanoparticle development. Particle visualization with electron microscopy is widely applied to deliver detailed insight into the structure and morphology of individual particles within the system (Figure 1). However, the technique has several limitations that restrict its practical application for routine analysis.

Electron microscopy only measures a small sample distribution and derives a number-based mean particle size measurement. Colloidal gold products consist of tens of thousands of particles, and so deducing overall product homogeneity or aggregate concentration from this data may be a statistically poor approach. As the presence of even low level aggregates can impact clinical efficacy, and are often indicative of processing or formulation issues, electron microscopy alone cannot be relied upon for QC. Moreover, electron microscopy often requires lengthy and intensive analysis, both in terms of cost and operator effort. A complementary ensemble technique that determines a volume- or mass-based size distribution of the particles in relation to the entire dispersion is therefore desirable to identify out-of-specification aggregates.

Dynamic Light Scattering (DLS) is a non-invasive technique that is used routinely for the analysis of dispersed particles and colloidal nanoparticles.[2] DLS measures the time-dependent fluctuations in the intensity of scattered light from a suspension of particles undergoing random Brownian motion. Analysis of these intensity fluctuations allows determination of the diffusion coefficients, which in turn yield the particle size through the Stokes-Einstein equation.[3]

Several advances in DLS technology over recent years have improved the sensitivity and resolution of DLS measurements within the nanosize region.

FIGURE 3



The volume size distribution for a colloidal gold sample analyzed with DLS reveals over 90% of the sample consists of small particle around 13 nm.

For instance, patented non-invasive backscattering (NIBS) optics now enables particle size measurements across a dynamic size range, from 0.3 nm to 10 microns in diameter within solutions from 0.1 ppm to 40%w/v in concentration.[4] Rapid data acquisition and non-destructive sample recovery means DLS can be efficiently employed for both "peace-of-mind" studies as well as more formal QC.

The following case study explores the benefits of using DLS for nanoparticle characterization. Experimental data using colloidal gold highlights the differences in the results that might be obtained with DLS compared to electron microscopy and how this can be used to gain a better understanding of the nanoparticle system.

CASE STUDY: CHARACTERIZATION OF COLLOIDAL GOLD USING DLS

An experiment was carried out using an advanced DLS system (Zetasizer Nano S, Malvern Instruments, UK) to measure a sample of colloidal gold. All measurements were performed at 25 degrees C with the DLS system operating at 633 nm with an avalanche photodiode (APD) detector. The scattered light was detected at an angle of 173 degrees.[2]

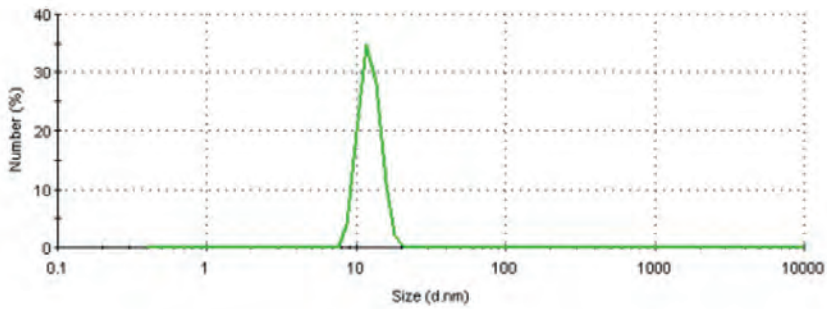
Figure 2 shows the intensity particle size distribution obtained for the colloidal gold sample. The plot shows the relative percentage of light scattering by the particle against various size classes. The two distinct peaks at 13.6 nm and 339 nm indicate a bimodal distribution and imply the presence of aggregates within the samples.

From the relative intensities of the size distribution peaks, it first appears that there is a high number of aggregates within the sample. However, when this is converted to a volume-based distribution, as shown in Figure 3, it becomes clear that, in reality, the concentration of aggregates is relatively low. This transformation is performed by smart instrument software using the Mie theory of light scattering and particle refractive index and absorption. The volume size distribution shows that, on a mass basis, the majority of the sample consists of small particles around 13 nm and indicates a 9:1 ratio of primary particles to aggregates.

Comparing volume- or intensity-based particle sizing to number-based techniques reveals the value of supplementing conventional nanoparticle analysis with DLS. Conversion of the volume-based distribution into a number-based distribution is shown in Figure 4. As the sample contains very few aggregates, the number distribution is monomodal with a peak mean at 12.4 and considers only the primary particles. The result suggests that if this sample were to be characterized using a technique, such as electron microscopy, the vast majority of particles present would be small ones, making it very difficult to accurately extrapolate the overall concentration of aggregates.

Dynamic light scattering is a low resolution technique, capable of producing discrete distributions for materials that differ in size by more than a factor of 3. However, through smart data interpretation the technique can still deliver insight into systems with very narrow size distributions. For instance, a mixture of single particles and aggregates made of 2, 3, or 4 particles would be expected to give a broad single peak. As the larger particles scatter the majority of the light, aggregate species have greater influence over the peak than primary particles. The z-average diameter and polydispersity index values are sensitive to the presence of aggregates and are a good indication of their presence within the samples. The z-average diameter is the mean intensity-weighted hydrodynamic diameter and the polydispersity index is an estimate of the width of the distribution. Both of these parameters are calculated by the system in accordance to the International Standard on dynamic light scattering ISO22412.[5]

FIGURE 4



Measuring particle size by number distribution produces a single monomodel distribution for the primary particles.

SEEING THE LIGHT

Dynamic Light Scattering provides a solution to the need within nanoparticle development and formulation for quick and reliable quality control analysis that encompasses the entire sample. By generating a particle size distribution for the whole dispersion, DLS enables users to quickly identify the presence of aggregates or, out of specification, particles that may otherwise be overlooked with number-based particle sizing techniques alone. Today, the availability of this high-end technology within commercial DLS systems is delivering the high sensitivity, accuracy, and resolution required for homogeneity and aggregation studies of nanoparticles within advanced biomedical applications. ◆

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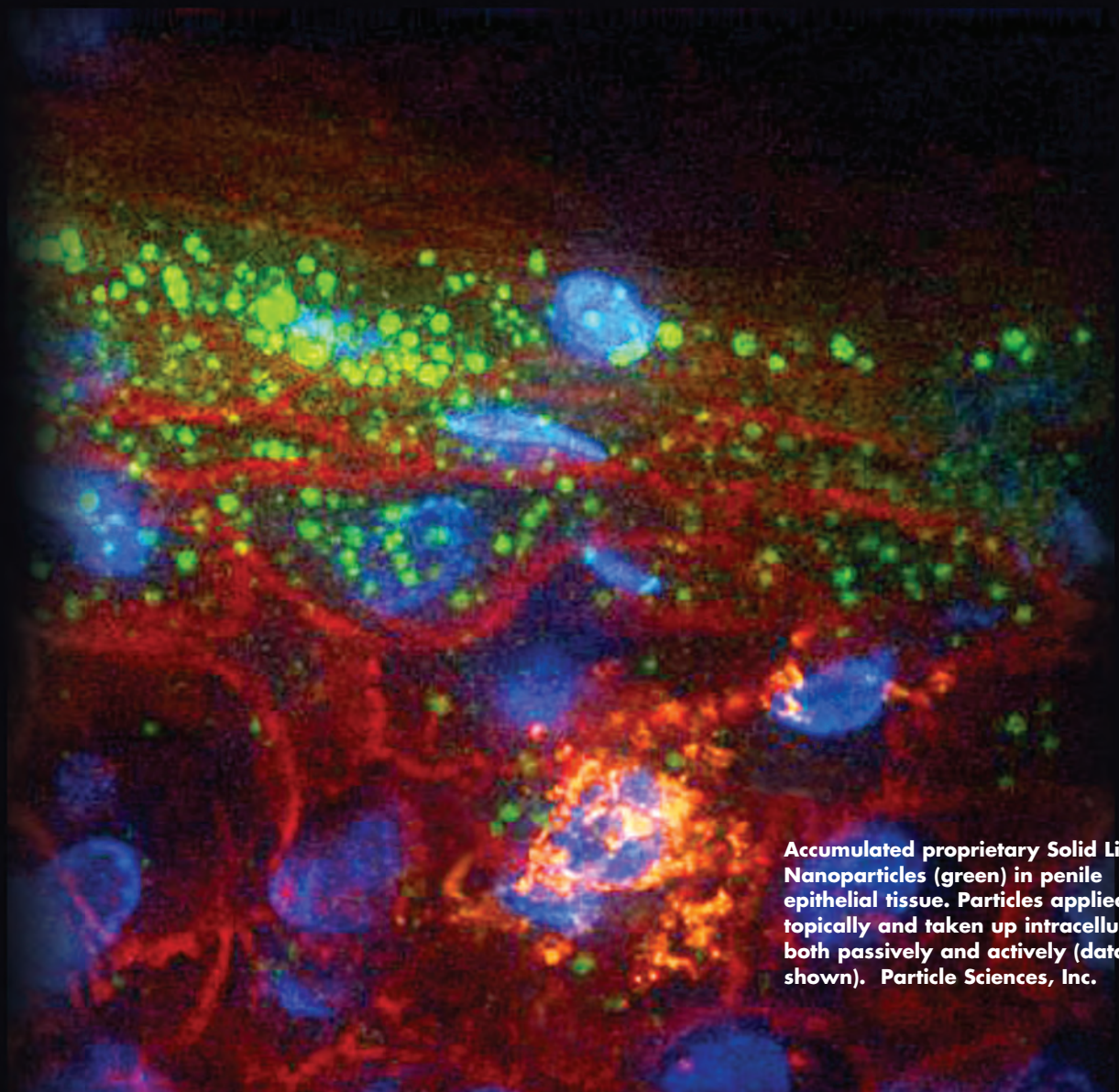
BIOGRAPHY

Stephen Ball is Product Marketing Manager, Nanoparticle and Molecular Characterization, at Malvern Instruments. He earned a degree in Computer Aided Chemistry from the University of Surrey, UK, which included a year in industry working as a Research Chemist for the Dow Chemical Company in Horgen, Switzerland. Before joining Malvern Instruments, he worked for Polymer Laboratories as an Applications Chemist, then took on a marketing position as a Product Manager for light scattering instrumentation at Agilent Technologies.

Special Feature

Bioavailability & Solubility: A Demand for Enhanced Technologies & Materials Is Spurring Innovation

By: Cindy H. Dubin, Contributor



Accumulated proprietary Solid Lipid Nanoparticles (green) in penile epithelial tissue. Particles applied topically and taken up intracellular both passively and actively (data not shown). Particle Sciences, Inc.

Poor bioavailability is a major reason for compounds to fail in preclinical development. Due to the complex nature of a multitude of existing as well as newly discovered active ingredients, solubility and bioavailability problems are inherent in the pharmaceutical industry causing major delays in drug development. Fortuitously, several novel technologies can now be deployed to address solubility and bioavailability issues. These include solid dispersion, hot melt extrusion, nanotechnology, lipids-based approaches, micronization, and advances in solubilization platforms.

A new report identifies 30 poorly soluble drugs with low bioavailability recently launched in the US that represent a huge business opportunity for specialty pharmaceutical, drug delivery, as well as generic companies using these technologies.[1] In fact, the authors of the report believe that poorly soluble and poorly permeable drugs are valued at $145 billion. Thus, demand for novel technologies and materials to improve solubility and permeability of drugs is only going to rapidly increase over time.

In addition to technological advancements, excipients continue to play a key role in bioavailability and solubility. The industry is building relationships with CROs/CMOs and excipients manufacturers to expedite excipient selection and identify the desired technologies to shorten the overall development time line, explains Shaukat Ali, Technical Support Manager at BASF. Furthermore, rising expectations from regulatory agencies to meet the desired safety profile of dosage formulations forces industry to take the necessary steps and take the appropriate measures to mitigate toxicity and alleviate the side effects of drug candidates. As a consequence, the excipient manufacturers are in the midst of assessing their portfolios, and designing, developing, and launching new and innovative ingredients to meet the solubility and bioavailability challenges.

This report will highlight some of the ways that CROs and CMOs are overcoming issues of poor solubility and bioavailability—from matching APIs to formulations to choosing the best excipients.

Agere Pharmaceuticals, Inc.—Analyzing Best-Fit Technology

There are numerous technologies and approaches available to overcome poor solubility, but this wasn't always the case. The number of solubilization service providers has grown significantly from six in the 1970s to approximately 75 today.[2] The emerging preponderance of BCS Type II/IV molecules combined with the advances in solubilization platforms – and the specialized expertise required to fully exploit them – makes it economically viable, and even essential to engage external experts in solubility at the earliest stages of development. Agere specializes in amorphous solid dispersions, which is growing in popularity with now 35% of companies in this solubilization service segment offering this technology.

Agere offers clients full-service from formulation through cGMP. Its solubilization formulation platform, Quadrant 2™, is used to analyze the best-fit technology for each API and client business objectives, and then to explore a range of excipient candidates and enhancing additives as required for an optimal formulation, explains Casey Jones, Vice President Corporate Development, Agere. The platform performs rigorous modeling of the drug and polymer molecular properties and analyses to obtain a fundamental understanding of drug-polymer interactions. Included are an assessment of the single crystal structure, full-scale molecular modeling, and advanced thermodynamic analyses.

An example of results using Agere's Quadrant 2 platform is evidenced in a Phase I pharmacokinetic (PK) study of relative bioavailability, comparing a client's prior formulation with one enhanced by Agere. The process started by identifying and modeling five lead amorphous dispersion polymer candidates, and then selecting the top two to progress as amorphous dispersion formulations. After formulation optimization and solid dosage form development, clinical

"The emerging preponderance of BCS Type II/IV molecules combined with the advances in solubilization platforms – and the specialized expertise required to fully exploit them – makes it economically viable, and even essential to engage external experts in solubility at the earliest stages of development."

trial materials (CTM) were manufactured and dosed in a Phase I human clinical study. The PK data from the study showed substantial improvement in exposure levels with the amorphous solid dispersion formulation that delivered a 9-fold improvement in Cmax, and a 5-fold increase in AUC.

Ashland—Understanding Solid-Dispersion Technology

Over the last decade, Ashland has made significant investments in the understanding and development of solid-dispersion technology, believing the technology has tremendous potential to increase bioavailability and absorption for active pharmaceutical ingredients (API) with poor solubility. Although the technology requires some specialized manufacturing equipment, early development can be accomplished relatively quickly and at a reasonable cost.

A key component of a solid dispersion is the polymer system. Some scientists will choose a carrier that has limited or no history of use in solid-dispersion technology. Still others will select known polymer systems, but make the mistake of limiting their evaluation to one type or what seems to be the most popular at the time, explains Dean Ross, Sr. Business Manager, Solubilization. Over the years, Ashland has developed and characterized hundreds of solid-dispersion prototype APIs. In more than 90% of the studies, a prototype with good stability and increased solubility was achieved. "We have learned that no one polymer system is a solution for all APIs," says Mr. Ross.

Mr. Ross points out that Ashland can provide know-how and expertise to support R&D programs focused on improving solubility. Ashland can help with advice and guidance on polymer selection and if a facility is needed to outsource solid-dispersion studies. It all starts with feasibility or proof-of-concept studies to determine if solid-dispersion technology is the right approach for increasing API solubility. Initial studies can be conducted with small amounts of API (~10 g) for development of several formulations to select an effective combination of drug and dispersant system. The study can then be expanded to a comprehensive set of experiments to optimize the drug load and dispersant system. Once the optimum formulation is selected, Ashland's scientists can continue the drug development program by providing scale-up, process development, final dosage form development, and non-GMP manufacturing services for animal toxicology or additional studies.

As an example, a pharmaceutical innovator approached Ashland with a poorly soluble API, for which an exceptionally large dosage was required to achieve therapeutic benefits. The company planned clinical trials within the next three months, and requested Ashland's scientists to design a program that included development of a solid-dispersion formulation; a film-coated modified-release tablet formulation, and a scaled-up manufacturing process for spray drying, tableting, and coating. The resulting tablet formulation had significantly better drug solubility and bioavailability with excellent shelf stability. "Most important, the dosage was reduced from 18 capsules per day to two tablets," Mr. Ross says.

The PharmaCircle Drug Delivery and Formulation Newsletter and Blog

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

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

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

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

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

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

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

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BASF—Excipients & Polymers Enhance Solubility

More than 70% of new chemical entities (NCEs) are poorly soluble and the drug industry is at a crossroad to find the desired solutions by identifying the appropriate formulation technologies for those molecules. Those solubility challenges stem from inherent highly crystalline (melting temperature), lipophilicity, and/or hydrophobicity of drug candidates. The conventional formulation approaches of micronization/milling, pH modification/salt formation, and/or pro-drug approaches, all bode well for designing and developing low-dose drugs, but for those requiring medium to high doses the choices of using physical modifications of NCEs are often limited. Therefore, the non-conventional formulations technologies such as amorphous solid dispersions (ASD) and lipid based self-emulsifying drug delivery systems (SEDDS) have been the subject of continued interest to overcome these challenges to design better and smarter pills that improve solubility and enhance bioavailability and meet the requirements of regulatory agencies for patient compliance.

BASF Pharma marketing platforms include solubilization, instant and modified release, skin delivery, and soft gels technologies to meet formulation challenges. Each of the market platforms covers a range of high functional excipients for multifunction applications in solid and/or liquid dosage formulation development. For instance, BASF's expertise in hot melt extrusion and a range of polymers, such as Kollidon® VA64, Soluplus®, Kollidon® (12PF, 17PF, 25, 30 and 90F), Kollidon® SR, Kollicoat® IR, Kollicoat® MAE100P, and others, provide boundless opportunities to find the desired solutions for drug candidates being pursued either in the early or late stage of development process, explains Shaukat Ali, PhD, Technical Support Manager at BASF. In addition, with a wide solubilizers portfolio ranging from low molecular weight polyethylene glycols (PEGs) to surfactant-based solubilizers such as Kolliphor® grades possessing an array of hydrophilic lipophilic balance (HLB) values, offer the additional choices to formulators working with insoluble drug candidates.

Recent trends in poorly soluble drug candidates will continue to rise. BASF is addressing these challenges in solubilization by offering a broad product portfolio to meet industry needs. "Building partnerships and working closely with drug manufacturers, CROs and CMOs and equipment manufacturers, BASF will design and introduce new and innovative polymers and ingredients to address the solubility and bioavailability and other areas of formulation development," says Dr. Ali.

Gattefossé—Drug Development Options With the End in Mind

Bioavailability is the rate and extent to which the active drug molecule reaches the systemic circulation or a specific site of action. Attaining the right dose at the desired rate however is a daunting challenge for drug delivery scientists. Currently, a vast majority of molecules out of drug discovery have poor solubility/dissolution properties. Further complicating the task are the biological barriers to absorption like poor intestinal permeability often coupled with pre-systemic degradation found with a significant percentage of new API's.

Among the possible solutions, and of increasing interest to scientists, are lipid-based drug delivery (LBDD) systems that help solubilize/disperse the drug molecule, notably in the gut milieu by micellization, thus preventing the active drug from falling out of solution; ameliorate the drug affinity for the aqueous monolayer; and crossing the intestinal wall due to enhanced membrane fluidity. Additionally, certain classes of lipid excipients can improve drug permeability by inhibiting/saturating the enterocyte-based transporters; or may increase bioavailability by promoting lymphatic absorption of highly lipophilic drugs that would otherwise be eliminated pre-systemically.

Achieving adequate bioavailability may be challenging but remains the ultimate goal of every

therapy. "Our company recognizes the importance of expanding the drug development toolbox by providing new products and new approaches much needed for the development of new and effective dosage forms," says Jasmine Musakhanian, Scientific & Marketing Director, Pharmaceutical Division of Gattefossé USA.

"Lipid excipients and LBDD systems are core specialties of Gattefossé. "As such, we provide guidance documents for excipient selection and formulation design for preclinical as well as late development stages," she continues. "To meet the bioavailability challenge, we have worked hard developing new excipients. This has meant extensive investments in creation and characterization; conducting safety studies; guaranteeing quality and consistency of supply; and seeing that the new products have global regulatory acceptance. In the past decade, Gattefossé was responsible for more than 25 new excipient monographs."

Metrics Contract Services—Optimizing Formulations for Site-Specific Delivery Improves Bioavailability

Many new drugs have either poor bioavailability or solubility and are in limited quantity. Some of the quickest and easiest ways of trying to improve solubility is to change the physical properties of the drug molecule itself. This would include reducing particle size by various forms of milling. Milling can be performed on a limited quantity of API and is a continuous process that is easily scalable.

Another way of improving solubility is to make a salt form of the drug to utilize ionizable groups. Generally, manufacturing a salt form of a drug is performed during the API synthesis and not at the formulation stage. From a formulation perspective, a scientist can change the crystalline drug molecule to an amorphous form. This can be achieved using spray drying or hot melt extrusion — techniques common to solid oral dosage forms.

Metrics offers several formulation approaches to increase solubility or bioavailability. "For drugs formulated as a solution, we optimize the pH of the solution to maximize ionization of the drug molecule. We also can incorporate other excipients — such as surfactants, alcohols, etc. — to help increase solubility," explains Michael DeHart, PhD, Developmental Scientist II at Metrics Contract Services. "In the case of solid oral dosage, we can micronize the drug molecule to increase the surface area of the drug to help solubility."

Metrics also has the ability to generate amorphous material via spray drying. Spray dried material is generally amorphous in material that has significantly higher solubility when compared to the crystalline form. Both micronization and spray drying allows the powder to be further processed into a capsule or tablet — two dosage forms that Metrics manufactures on a regular basis.

"The pharma industry is always looking for ways to improve the solubility or bioavailability of a drug molecule. Conventional methods, such as micronization, spray drying and hot melt extrusion, are used on a regular basis. However, something that seems to be common in the work being performed at Metrics is optimizing a formulation to provide site-specific drug delivery, or modified-release profiles, to increase bioavailability," says Dr. DeHart. One of the most common methods is enterically coating multi-particulates, or tablets, to optimize drug delivery in the small intestine. In the small intestine, the pH helps deliver molecules that are susceptible to acid degradation or may have increased solubility in slightly basic conditions.

Nanocopoeia—Nano-Enabled Particle Design

Pharmaceutical companies continually search for better, faster, scalable ways to improve drug performance. Common problems include poor solubility, low bioavailability, impractical dosage regimens, and need for alternatives to injection. Nanoformulation is an emerging tool for addressing these challenges, but only a limited number of processes for producing nanoparticle formulations have been scaled for commercial production

needs. The ability to get a BCS class II or IV compound into a solubilizable form is what guides most decisions to use solubilization technologies, explains Robert Hoerr MD, PhD, Co-Founder, CSO, Nanocopoeia..

Nanocopoeia is a therapeutic particle engineering company providing nano-enabled particle design, services, and equipment to the pharmaceutical industry. Specific to ElectroNanospray™ (ENS) nanoformulation, the most important API considerations are solubility in organic solvents, the need to reduce or eliminate problematic excipients, and the desire to protect, stabilize, and/or control the release of the API at the point of delivery.

Nanocopoeia's ENS process creates complex, homogeneous nanoparticles in a single processing step. First, by using electrospray in a stable cone-jet mode, ENS provides exquisite control over particle size (from a few nanometers to micrometers) and composition at ambient conditions. "Second, our patented D-series co-axial spray nozzle allows us to create complex composite nanoscale particles from a range of compounds, boosting throughput 30-60x vs. single-capillary nozzle ES processes," says Dr. Hoerr.

Because ENS is a non-destructive process, particles' chemical or biological properties can be preserved without degradation from heat or mechanical stresses. Thus, ENS can provide the enhanced drug solubility pharmaceutical manufacturers seek by producing consistently sized nanoparticles and enabling scale-up ES capabilities.

"Nanocopoeia is targeting commercial activity in drug discovery and development as a formulation resource for industry and academic researchers," says Jane Nichols, Director of Business Development, Nanocopoeia. "Nanocopoeia can work with those researchers to create an efficient and effective way to leverage existing libraries of compounds with known solubility issues but potentially great commercial potential. A particular advantage of the ElectroNanospray process is the ability to work with very small quantities of expensive research grade materials that the compounding pharmacists can make of these materials. A further advantage of ENS-produced drug nano-formulations is our ability to rapidly turnaround fully characterized material for preclinical testing."

Particle Sciences—An Array of Services for Successful Execution

Bioavailability is the ultimate determinant of efficacy for any therapeutic, and solubility along with permeability, are the drivers of bioavailability. Both solubility and permeability are inherent properties of a given molecule and can't be altered. However, permeation can be maximized by high local concentrations of drugs and the rate of solubilization is critical for it is the kinetics that dictate local concentration, explains Robert W. Lee, PhD, Particle Sciences (PSI). Therefore, solubility rate is one of the key physicochemical parameters a formulator needs to manipulate to develop viable formulations.

Active Pharmaceutical Ingredients (APIs) of interest are often sparingly water-soluble with a majority of New Chemical Entities (NCEs) belonging to the BCS Class II. "At PSI, we have a number of solubilization approaches ranging from *in silico* design to nanoparticles to solid solutions to lipid-based systems, such as LyoCells® (PSI proprietary reverse cubic and hexagonal phase nanoparticulate delivery system)," says Dr. Mark Mitchnick of PSI. "For long-term delivery, our drug-eluting device work is frequently the solution."

A well-informed formulation effort starts with preformulation data, including extensive solubility data. PSI uses DOSE™, a proprietary solubility evaluation approach based on Hansen Solubility Parameters. "This data helps guide our selection of excipients and matrix components in the case of emulsions, solid lipid nanoparticles, polymeric micro/nanoparticles, and solid solution approaches," says Dr. Lee. "Based on the physicochemical characteristics of the API, we assess what drug delivery approaches will provide the biological performance and match the desired target product profile."

PSI has assembled a range of technologies aimed at getting past the

Solumerized trans-Resveratrol product in tablets form (Solubest Ltd.).

common bioavailability barriers. "Key to our clients' success is PSI's ability to work with their molecules, even if highly potent or DEA controlled substances and importantly, to quickly bring them into the clinic with our cGMP production of both sterile and non-sterile products," says Dr. Mitchnick.

Dr. Lee adds: "It is becoming increasingly accepted that bioavailability can be impacted in a predictable way. If one studies the currently available, scalable technologies, it is clear that there have been only incremental technical advances, but the real improvements have come from better execution. There are only a handful of unique drug delivery approaches – particle size reduction, amorphous forms, permeation enhancers – but each has different flavors. It is in excellent execution and having access to a full array of approaches that the best products are developed."

Solubest Ltd.—Increasing Solubility & Drug Absorption

Most molecular interactions within the body occur in solution or colloid, but around 50% of known pharmaceutical and natural bioactive compounds, as well as drug candidates under discovery, have poor aqueous solubility properties and/or poor permeability. Such low solubility in body fluids is translated to inadequate bioavailability and, thereby, insufficient bio-performance.

Most known drug delivery systems that aim to improve bioperformance essentially interfere with this basic physico-chemical parameter. Solubest lets clients leverage its proprietary particle engineering R&D and drug development expertise to overcome formulation challenges of hydrophobic, poor permeable, instable bioactive ingredients for multiple applications.

In addition to its leading technology, Solumer™, Solubest offers a diverse array of drug delivery approaches tailored to client needs. The proprietary solid dispersion of liphophilic APIs in polymer matrix is produced by a spray drying technique. Once in the body, Solumer solid-dispersions disintegrate into colloids, increasing drug solubility and bio-absorption. "It's important to note that particle size minimization is not the only parameter that enhances solubility," points out Dr. Galia Temtsin Krayz, Solubest COO and Vice President, R&D. There are additional essential Solumer characteristics that result in the enhanced prolonged super-saturation in relevant biological fluids. These include physico-chemical characteristics where the solubilized drug homogeneously disperses in disordered crystalline form that is interwoven into dual polymer matrix; thermodynamic features, such as depressed melting temperature and enthalpy of fusion; and surface-to-volume characteristics, the spontaneous formation of nano-colloidal dispersions upon contact with aqueous media.

Solumer technology has been used to generate a new solubilized formulation of natural antioxidant resveratrol with improved solubility. Solu-Resveratrol needs 4-5 times less dose to get the same bioavailability as not improved resveratrol products.

Xcelience—Balancing Solubility & Bioavailability

The pharmacokinetics of an active pharmaceutical ingredient can be a laborious scientific endeavor in the early stages of drug product development. As these newly synthesized compounds show significant advantage or promise in animal models, many pharmaceutical companies look toward preformulation to provide the foundation of the program's design space. Many contract pharmaceutical development companies (CDMOs) are challenged with high level details of getting as much of the API into a single dosage form, physically and chemically stable, tolerable for human ingestion, all in an expedient timeframe by using a limited amount of material at a low cost. Thus, any specific measures on to gain scientific confidence on how the API will likely "behave" when orally administered becomes critical at an early stage. The API solubility profile and how solubility can be improved usually leads the charge.

Combinatorial chemistry and high throughput screening techniques are used in drug research for their efficiency that compares favorably with rational drug design. However, oral activity of these compounds is dependent on the ability to dissolve in the GI fluids for absorption

"At Xcelience, we understand the delicate balance of solubility as it relates to bioavailability versus the need to keep it simple for early-phase development without compromising quality," says Parag Ved, PhD, Team Leader, Formulation Development, Xcelience. "We use a systematic approach towards improving solubility starting with the conventional pH solubility profile. For instance, a simple titration experiment with a dispersion of the drug at desired concentration and the use of GRAS excipients such as citric acid or sodium bicarbonate can be performed to visually confirm solubility."

The same acid or base can be incorporated in the formulation at the desired concentration to assist with the dissolution. Certain compounds may show preferentially higher solubility in presence of a specific buffer system in solution at a given pH as compared to other salts under the same condition. "We also have the ability to measure pH solubility with the aid of instrumentation," says Mark Cappucci, Team Leader, Preformulation & Formulation Development, Xcelience. "The use of automated systems at Xcelience can help determine the kinetic, equilibrium and intrinsic solubility using significantly lower amounts of API as compared to the conventional titration methods."

Cyclodextrins are cyclic oligosaccharides consisting of 6, 7, 8 or more glucopyranose units linked by α- (1,4) bonds that have been used at Xcelience to formulate orally active formulations of poorly soluble compounds. "These provide a micro heterogeneous environment that is hydrophilic outside and dissolve in water, and a hydrophobic cavity that can form inclusion complex with compounds to keep them solubilized," explains Dr. Ved.

"It is a never-ending battle of solubility versus bioavailability; enhancements to increase a poorly soluble compound sometimes lead to a decrease in the compound's ability to reach the intended target area," says Mr. Cappucci. "At Xcelience we understand the concerns and utilize several approaches, whether chemical or physical to drive the compound into a successful life cycle that includes a commercial product."◆

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1. Technology Catalysts International, Poorly Soluble and Poorly Permeable Drugs, Seventh Edition, 2014.
2. Agere Pharmaceuticals, Inc. analysis, January 2015.

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Jingjun (Jim) Huang, PhD
CEO & Founder
Ascendia

Ascendia Pharmaceuticals: Sophisticated Formulations for Poorly Soluble Drugs

Many NCEs and repurposed drugs in early development are challenging to formulate in an adequately bioavailable form due to their poor solubility in water. To overcome these challenges, many formulation approaches have been developed by the drug delivery industry. Among the most successful technologies have been particle size reduction to nanometer-size drug crystals with greater surface area for dissolution, production of amorphous solid dispersions for reducing the energy required for dissolution, nanoparticle systems for dissolving/dispersing a hydrophobic drug in either a lipid or polymer material, and the use of nanoemulsions to dissolve a drug in an oil phase of an oil-in-water system. Ascendia was established to provide pharmaceutical companies with a contract research partner that can provide all of these technologies in order to efficiently determine which approach is most suitable for a given molecule. Drug Development & Delivery recently interviewed Jingjun (Jim) Huang, PhD, CEO and Founder of Ascendia, to discuss the company's unique vision and strategy.

Q: Why did you decide to establish a new company in the drug delivery field?

A: After 15 years of big pharma experience as a pharmaceutical scientist in the field of formulation development, I strongly believed there were unmet needs in drug delivery of poorly water-soluble compounds - both in discovery and in life cycle management.

More than 50% of NCEs and drug products approved by the FDA fall in the category of BCS II or IV, and delivery of these compounds in a soluble form is required for many reasons. For example, adequate solubility is needed to provide sufficient drug loading for parenteral products, to establish a sufficient concentration gradient for oral absorption through the GI tract, and for a

high influx for topical and ocular dosage forms. Many early stage compounds are abandoned due to poor biopharmaceutical properties, such as low solubility or permeability. In addition, in a race to be the first one to market, many sub-optimized formulations of poorly soluble drugs are rushed through development - this creates an opportunity to reformulate these medicines to enhance their safety and efficacy.

The main mission of Ascendia is to capture the current unmet needs in formulation science by utilizing our drug development expertise and advanced formulation technologies to provide sophisticated formulation solutions for poorly water-soluble compounds. We want to bring out "a new life" for difficult-to-formulate compounds or existing medicines that will eventually help patients prevail over their disease and enhance their quality of life.

Q: What is the company's current strategy?

A: We focus on three fast-growing market segments: 1) development of novel 505 b(2) formulations of existing medicines, especially niche hospital drugs and injectable pharmaceuticals; 2) development of ANDA dosage forms for drugs with solubility and/or stability challenges; and 3) offering contract product development services to other leading biotech and emerging pharmaceutical companies. In all of these segments, we leverage our in-house drug delivery platforms: EmulSol for nano-emulsions, NanoSol for nano-particles, and AmorSol for amorphous solid dispersions. Our technologies are suitable for oral, parenteral, and topical products, so we have a broad capability to develop novel products for ourselves and our partners.

Q: What technologies does Ascendia offer to its partners, and what makes the company unique?

A: We have a suite of nanoparticle technologies - nanoemulsions, amorphous nanodispersions, and lipid/polymer based nanoparticles - so we can assess the feasibility of a broad array of formulation options to improve a drug's bioavailability and create formulation solutions with enhanced biopharmaceutical properties suitable for clinical scale-up. We execute rapid, comprehensive, and cost-effective programs for difficult compounds, and provide both development and analytical testing services. We partner with emerging, discovery-stage pharmaceutical companies to provide early stage formulations, with generic companies that seek enabling technology, and with specialty pharmaceutical companies that need development of a product for clinical testing.

The unique feature that makes our company stand out in the crowded CRO field is our sophisticated and thorough drug development programs, in combination with our advanced nanoparticle-based formulation technologies. We ensure the successful translation of a drug program from discovery to a marketable dosage form. Our team of scientists has decades of big pharma experience in discovery pharmaceutics, formulation approaches, and clinical development. We understand the essential properties of compounds and the finished dosage forms required for successful early and late-stage development. For our discovery-stage partners, we provide a tailored formulation solution for compounds that have promising efficacy in an animal/human model, but yet have some deficiency in their biopharmaceutical properties, such as poor water solubility. Often our formulation solutions provide our partner with new intellectual property for their products.

Q: How do your nanoemulsion and nanoparticle technologies improve a drug's bioavailability?

A: Nanoemulsions have droplet sizes in the range of 50 to 500 nanometers. Ascendia produces nanoemulsions using a high-shear process called EmulSol. After a suitable oil phase is chosen, a mixture of the oil, water, and the drug substance is processed through the homogenizer, creating a suspension of the oil droplets in a water phase. As the drug substance is significantly more soluble in the oil phase than in the water phase, the vast majority of the drug is solubilized within the interior of the oil droplets. Thus, when the nanoemulsion is delivered to the body, the drug substance is more readily bioavailable. Ascendia's nanoemulsion process is novel in that it uses no organic co-solvents, and a minimal amount of

"We have a suite of nanoparticle technologies - nanoemulsions, amorphous nanodispersions, and lipid/polymer based nanoparticles - so we can assess the feasibility of a broad array of formulation options to improve a drug's bioavailability and create formulation solutions with enhanced biopharmaceutical properties suitable for clinical scale-up. We execute rapid, comprehensive, and cost-effective programs for difficult compounds, and provide both development and analytical testing services."

surfactants. By minimizing surfactants and eliminating solvents, Ascendia's nanoemulsions are much more suitable for pharmaceutical applications. A nanoemulsion can be used to deliver a poorly palatable drug in liquid form for a pediatric development program, significantly reduce the irritation and injection site pain for a parenterally delivered product, or be used to develop a topical formulation with superior clarity and bioavailability properties. In addition, nanoemulsions can be dehydrated and incorporated into solid oral dosage forms.

Nanoparticles produced by our NanoSol technology normally have a size range below 400 nm, and the drug contained in the particle is either in crystalline or amorphous form. Formulation of a drug in a nanoparticle form significantly increases the surface area available for dissolution - a 10 to 20-fold increase in surface area can result from reducing particle size from a micronized drug substance to a nanonized drug substance. As surface area increases, the rate of dissolution increases, and bioavailability improvements may result. If a solid dosage form is desired, the nanoparticles are stabilized by adsorption onto polymer carriers - a process conducted by fluid bed coating. Alternatively, the nanoparticles can be prepared as a suspension and administered orally or by injection. Ascendia can produce nanoparticles using a wide variety of processes - bead-milling, high-pressure homogenization, microfluidics, or solvent evaporation. We can investigate the impact of nanonization with less than a gram of drug substance. Ascendia's nano-particle technologies can enable pharmaceutical products with enhanced bioavailability, reduced food-effect, and more rapid onset-of-action.

Q: How does Ascendia work with its clients? What is the business model?

A: Business development at Ascendia is focused on our clients' needs. You will find us responsive, thorough, and easy to work with. After gaining a solid understanding of a project's requirements, we provide a client with a customized proposal.

Our goal is consistent with your goal - provide quality service, exceptional insight, timely output, and fair pricing. Currently, Ascendia operates under a hybrid model: developing proprietary products for out-licensing, and offering state-of-the-art contract research for difficult formulation development projects. Our contract research projects are designed to quickly determine the viability of a technical approach, and are conducted in stages that allow us to modify a work plan as needed. Our goal is to produce an optimal product formulation for our client by understanding the compound's properties, route of administration, and bioavailability goals. Our contract research programs are done on a fee-for-service basis, and we avoid encumbering an early stage project with intellectual property licenses; in fact, we seek to add value to our clients' projects with new patentable formulations.

Q: Does Ascendia have current partners, and what kinds of projects is the company involved with?

A: Ascendia is currently working with several partners on confidential development programs, including an emerging biotech company, a specialty pharma company, a virtual, early stage discovery company, and a mid-cap pharma company. Typically, we have three kinds of projects. First, working with an NCE at the discovery stage, collaborating with our partner to provide a CMC solution to bring the compound from discovery to the clinic using one of our technologies. Second, we reformulate existing medicines for a new route of administration, or to an enhanced version, to address an unmet medical need. Such products are available for co-development and out-licensing. Third, is the application of our technology platforms for the development of a generic equivalent product. Typically, those compounds chosen for an ANDA project have either a solubility, bioavailability, or stability issue that our technologies can address.

Q: So you are developing your own products? On your website, Ascendia is positioned as a specialty pharma company.

A: Yes, we are creating "innovative" specialty pharmaceutical products; however, we do not intend to market our products ourselves, but instead seek commercialization partners. Our business model is to identify products that our technology and expertise can improve the safety or efficacy of. We then conduct preclinical development, proof-of-concept studies in animals, secure IP protection for the product, and then license out to a partner for further clinical development. One such product is ASD-002 - an injectable form of clopidogrel. This important anti-thrombotic drug is only available as an oral dosage form today due to its challenging biopharmaceutical properties. Ascendia has created a parenteral form with adequate solubility and stability to be used in an acute, emergency setting - this addresses an unmet medical need. In addition to partnering our pipeline, we are actively looking for collaboration opportunities with specialty pharma or generic companies to develop sponsored pharmaceutical products.

Q: What is your vision for the company, and what are the critical success factors?

A: We are striving to position our company as a world-class leader in drug delivery for poorly soluble compounds. We plan to achieve this vision by expanding our expertise in nanoparticle technologies, developing an innovative drug pipeline for out-licensing, growing our team of scientists, building up a GLP/GMP manufacturing capability, and exploring new opportunities to serve emerging markets outside of the US, such as China. ◆

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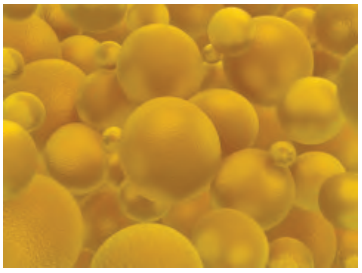
Nanoemulsion Formulations



Ascendia Pharmaceuticals offers services for contract formulation development of poorly soluble drugs. Our formulation approaches include nanoemulsions, amorphous solid dispersions, and nanoparticles. These technologies are suitable for oral or injectable delivery of drugs that are challenging to formulate. EmulSol is our technology for production of oil-in-water nanoemulsions, with droplet sizes in the range of 50-500 nanometers. Ascendia's process is novel in that it uses no organic co-solvents, and minimal surfactants. Our nanoemulsions use a high-shear homogenization process to create a suspension of the oil droplets in a water phase, with the drug solubilized within the interior of the oil droplets. Thus, when the nanoemulsion is delivered to the body, the drug is more readily bioavailable. For more information, contact Ascendia at (732) 640-0058 or visit **www.ascendiapharma.com.**

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US-Manufactured Tromethamine

BioSpectra's cGMP, US-manufactured ICH Q7-based Tromethamine, for use as an API, will be produced in its new FDA-registered facility in Bangor, PA, in Q4 2014. Regulatory Packets, Validation Reports, and Type II Drug Master File Authorization are scheduled for contract customers of Bio Active Tromethamine during Q2 2015. Bio Active Grade Tromethamine, Product Code TR22, will be manufactured in a qualified, validated ICH Q7-compliant API manufacturing suite as a highly purified crystal with optimum solubility, purity, and traceability. Future versions of will include liquid and spray-dried forms, both of which are currently scheduled for release in Q3 2015. This product will be added to the current portfolio, which already includes BioSpectra's Bio Excipient Grade Tromethamine, Product Code TR32, which is an ICH Q7-compliant Excipient supported by a Type IV Drug Master File. For more information, contact BioSpectra at (877) 982-8333 or visit **www.biospectra.us.**

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Platform Technology

CAPTISOL®

Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 7 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.com.**

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Catalent Pharma Solutions has invested in its Somerset, NJ, facility to create a Center of Excellence for potent handling across the company's portfolio of oral solid dose forms. The investment included an expansion of facility and engineering controls for high-potency tableting to supplement existing capabilities, giving additional capabilities to handle potent compounds for large-scale blending, fluid bed processing, and high-shear granulation. Catalent's acquisition of Micron Technologies allows the company to undertake particle size engineering of potent compounds, complementing handling and manufacturing facilities at Somerset. Investment was announced in 2014 at Catalent's Kansas City, MO, facility to increase highly potent and cytotoxic clinical drug packaging capabilities. Catalent offers end-to-end solutions for development, analysis, and clinical and commercial manufacturing for oral solid manufacturing of potent compounds. For more information, contact Catalent at (888) SOLUTION or visit **www.catalent.com.**

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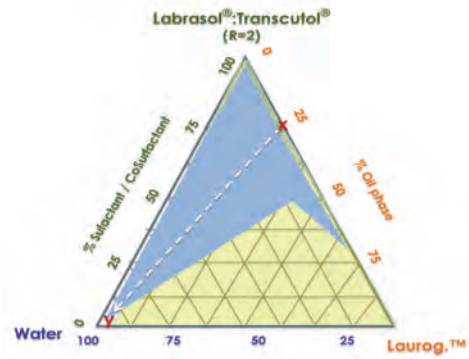
Showcase

Formulation Development



Ternary diagramming is an indispensable tool for developing microemulsions and SMEDDS for topical or oral delivery of poorly soluble drugs. In this example, the blue zone represents unlimited number of formulations possible by simply varying combinations of three excipients. Point "X" for instance is SMEDDS containing 25% Lauroglycol™ +75% mixture of Labrasol®: Transcutol® (2:1). Continuously adding water to formulation "X", we would be following the dilution path along the white arrow. In other words, the formulation "X" may be diluted with no risk of phase separation as it will remain a nano-dispersion even at a very diluted state. Designing SMEDDS and Microemulsions binary and ternary diagramming is a Gattefossé expertise. For more information, please contact **jmusakhanian@gattefossecorp.com**

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Analytical Tools for Drug Delivery

Malvern

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Innovative Dosage Forms

With four industrial sites, one R&D center, and commercial offices in Paris, the UNITHER group is the world leader in manufacture of dosage forms for pharmaceutical laboratories and generic manufacturers in Europe, with strong experience in the manufacture of products as stick-packs and effervescent tablets, as well as in pharmaceutical development. Created in 1993 with the purchase of a manufacturing plant from the Sanofi group, UNITHER developed in sterile unit dose manufacture. UNITHER acquired a second manufacturing site in 2002 for its traditional activity of sterile unit dose manufacture, and then diversified its activity by entering the areas of effervescent products and pharmaceutical development on taking over the Créapharm group in 2005. In 2009, UNITHER purchased the Colomiers site from Sanofi-Aventis, gaining a competitive platform for the production of liquid stick packs. For more information, visit Unither at **www.unither-pharma.com.**

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STANDARDIZATION TECHNOLOGY

Innovative Temperature Standardization Technology Supports Cell Therapy Clinical Trials

By: Rolf O. Ehrhardt, MD, PhD, and Maria Thompson, PhD

INTRODUCTION

Cell-based therapies are primed to transform biological medicinal products in the pharmaceutical industry. The past 2 decades have seen biologics pave the way for a broad range of new treatments, from small molecules to synthetic hormones and antibody-based drugs. Now the use of human and microbial cells as therapeutic entities is challenging the very concept of what constitutes a drug product. There are currently more than 300 cell therapies in late-stage development, and almost 40 more already in commercial distribution.[1,2] With this field burgeoning so rapidly, regulatory agencies are striving to introduce new guidelines for manufacturing, storing, and transporting cell therapy drug products.

Cells have therapeutic capabilities distinct from previous classes of biologics. They are naturally programmed to perform therapeutic tasks, such as when T-cells act to mediate or regulate immune response. They can be used to provide new, functional tissue to replace tissue lost to damage or disease. Their method of action is inherently more complex than that of a small biologic because a cell can sense changes in its environment, and mediate its response in a tissue-specific or cell-type-specific manner. Cells are capable of more than one function, including activating diverse signaling pathways, expressing a variety of peptides and proteins, and even migrating to different sites in the body.

NEED FOR STANDARDIZATION

The promise of cell-based therapies is evident in the profusion of drug discovery research dedicated to unlocking its potential. The very complexity that gives cells such promise, however, has led to regulatory concerns about safety and efficacy. Cells are fragile and highly sensitive to even minute changes in their environment. Without proper handling, cells are capable of genetic drift and transformation. This is evident when over-passaged cells no longer express biomarkers specific to their parental cell type, or when stem cells mature into committed progenitor cells that may have lost most or all of their pluripotency. In order to obtain FDA approval, small molecule therapeutics are subject to standards of due diligence. These same standards must be applied to cell therapy, albeit in a manner appropriate to this new technology.

Cell, tissue, and gene therapy products are so functionally and biologically diverse that the US FDA acknowledges "unique scientific challenges in terms of regulatory review." In 2007, the European Medicines Agency saw fit to establish an entirely new set of guidelines based on these treatments, which are classified as "advanced therapy medical products."[3,4] To ensure quality products, the natural variability of cell therapies must be met with meticulous standards of reproducibility. The key to reproducibility is standardization of common laboratory or manufacturing practices, in particular, protocols for cell culture, cryopreservation, and storage. Cellular viability is highly dependent on cold chain management during transport, handling, and storage. BioCision, a private company founded

FIGURE 1

The CoolCell® freezing container is a passive freezing device made of highly insulative, closed-cell polyethylene. Radially symmetric distribution of serum vials and ampules ensures identical heat removal from each vial, and a solid alloy thermal core fine tunes the freezing profile.

in 2007 in Larkspur, CA, has developed unique proprietary temperature standardization technology that is practical for all stages of cell processing and handling.[5] This technology is supporting a Phase IIb clinical trial conducted by TxCell, a French company specializing in cell-based therapies for chronic inflammatory diseases. The trial is investigating the efficacy of Ovasave®, an immunotherapy treatment for patients with moderate-to-severe refractory Crohn's disease.

REGULATORY T-CELL THERAPY

Regulatory T-cells (Tregs) are a sub-population of T-cells that modulate immune response through interaction with other lymphocytes at the molecular level. Tregs can inhibit immune cell activation and unwanted inflammatory response to foreign antigens that are normally tolerated, such as dietary, bacterial flora, or inhaled antigens. They can also suppress pathological immune responses, like those involved in auto-immune disorders. Ovasave is an autologous, antigen-specific Treg (Ag-Treg) that targets the diet antigen ovalbumin. It has been shown to be a well-tolerated, effective treatment for Crohn's disease in Phase I/IIa clinical trials.[6]

Tregs are extremely sensitive to variations in temperature, which can affect viability, recovery, and functionality.[7] Consequently, temperature control is a critical aspect of Treg sample handling. The cryopreservation process figures large in any cell-related study, and is of particular importance in the Ovasave study because the same blood sample is used to make multiple doses over several years of patient treatment. Successful cryopreservation depends on a tightly controlled rate of temperature decrease during freezing, specifically -1°C/min.[8]

DEVELOPING A NEW CELL-FREEZING CONTAINER

Current methods of cryopreservation include freezing cells in isopropanol-filled devices, which necessitates long equilibration times and can introduce variability depending on vial position, or the use of programmable freezers. The latter are documented to have highly reproducible freeze rates, but are also costly, difficult to maintain, susceptible to malfunction, and require a large footprint in terms of space and energy use.

BioCision's CoolCell® cell-freezing containers (Figure 1) are passive freezing devices that deliver a consistent -1°C/minute freeze rate to all cryogenic vials when placed in a -80°C freezer. This is achieved through the unique design of the CoolCell container, which is made of a highly insulative closed-cell polyethylene foam material. Cryogenic vials are placed in a radially symmetric manner around a solid alloy thermal core that ensures identical heat removal profiles for each vial. This combination of insulative and thermally conductive materials ensures high thermal control and reproducibility. The simple, single-block base design makes the CoolCell container extremely durable and maintenance free, while a small footprint permits use across multiple study sites. CoolCell cell freezing containers may be used with cryogenic vials or closed-system injectable ampules or vials.

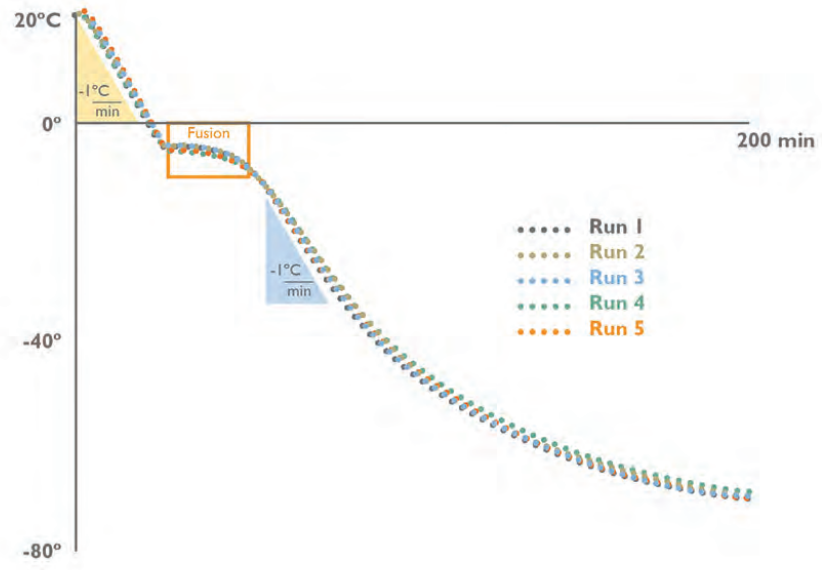
The device has been used successfully in the preservation, storage, and recovery of human stem cells, and is recommended for use by ATCC®, the world's leading provider of authenticated biological material, in their current stem cell handling guide.

Consequently, TxCell decided to investigate whether to incorporate the use of CoolCell in its ongoing Ovasave clinical trials, in place of programmable freezers.[9]

CLINICAL TRIAL METHODS

In order to isolate clinical grade Ova-Treg products, peripheral blood mononuclear cells (PBMCs) were first collected from healthy donors, isolated

FIGURE 2



Freezing profiles of cells in a CoolCell freezing container (with 12 wells holding 2-mL cryovials) demonstrate consistent freezing conditions in five consecutive freeze runs. Freezing with the CoolCell container in a -80°C freezer yields reproducible freezing profiles with optimal controlled-rate freezing (-1°C/min).

via a Ficoll gradient, and then cultured in the presence of ovalbumin to expand ova-specific T-cells. Following a week in culture, T-cells were cloned and selected based on ovalbumin-specific IL-10 production. Both PBMCs and Ova-Treg cells were aliquoted into 2-ml closed-system glass ampules containing appropriate cryopreservation media in preparation for freezing, and then frozen at varying dosage. Cell viability was determined before and after freezing, via propidium iodide staining combined with flow cytometry.

In accordance with European Union Good Manufacturing Practice (GMP) cleanroom guidelines, CoolCell cell-freezing containers must be sanitized with two surface cleaning and disinfectant solutions.[10] The effectiveness of the cleaning procedure was assessed by measuring the particle emission profile on a particle counter, and measuring microbial counts on gelose plates. Cells were then frozen using the CoolCell cell-freezing container placed in a -80°C freezer.

STUDY RESULTS

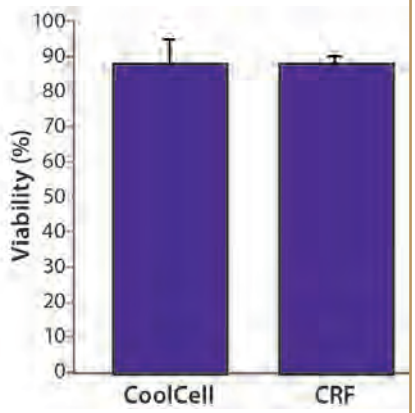
The researchers first tested the performance of the CoolCell cell-freezing container in five back-to-back runs. Because the device requires no isopropanol or other fluids, it is possible to maintain a mere 5- to 10-minute wait period between runs. The five consecutive runs yielded tightly reproducible freezing profiles, with each of the 12 cryovials having a freezing rate of -1°C/min (Figure 2). This rate is considered optimal for post-thaw cell viability, and is the same as that obtained with a programmable freezer.

Cell viability was assessed next for both PBMCs and Ova-Treg cells. Pre-freezing cell viability for PBMCs was consistently over 95%. Viability was assayed for PBMCs frozen either in a controlled-rate programmable freezer, or using the CoolCell cell-freezing container. In both protocols, cells were frozen and maintained at -80°C, then stored at -150°C for 5 days. Post-thawing, PBMC viability was analyzed on a flow cytometer using propidium iodide; a stain which is excluded from living cells. Analysis showed there was no significant difference in viability rates between cells frozen using a programmable freezer or those frozen in a CoolCell container (Figure 3).

Researchers then measured viability using a similar experimental set up in target cells, the Ova-Tregs that are used for the Ovasave clinical trials. FDA guidelines require cell viabilities for cell therapies to be over 70%.11 In this study, pre-freezing viability for all cells was consistently over 90%. Once again, no significant difference in post-thaw cell viability was observed between controlled-rate freezers (91.7% ± 4.0%) and cells frozen using the CoolCell container (91.7% ± 3.7%) (Figure 4). Similarly, there was no significant difference in cell yield using either the CoolCell cell-freezing container or a programmable freezer.

Because all ex-vivo cell handling and cryopreservation procedures for cell therapy manufacturing must be performed in adherence to EU GMP cleanroom regulations, researchers also needed to assess whether the CoolCell cell-freezing container met these regulatory requirements.[9] After subjecting CoolCell containers to standard cleanroom procedures, particle-release profiles and microbial contamination assays were performed. Three different CoolCell cell-freezing containers were tested three different times. In each case,

FIGURE 3



Freezing peripheral blood mononuclear cells (PBMCs) in a CoolCell container or a controlled-rate programmable freezer results in comparable post-thaw viability. Healthy donors' PBMCs were frozen at a concentration of 30 × 106 cells/mL, either using a CoolCell freezing device (n=17) or a controlled-rate freezer (CRF, -1°C/min, n=7). Post-thaw PBMC viability was evaluated by flow cytometry using propidium iodide.

CoolCell container profiles were well below the acceptable particle-release level (Figure 5). Decontamination procedures were also effective in containing microbial contamination to a level suitable for a class B cleanroom. In light of the results obtained in these proof-of-principle studies, the researchers elected to incorporate the CoolCell cell-freezing container into their clinical trials going forward.

IMPACT ON FUTURE CELL THERAPY CLINICAL TRIALS

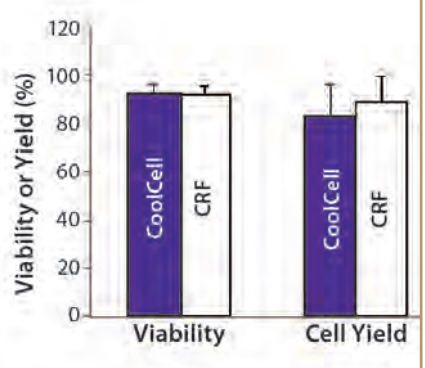
The results demonstrate that the CoolCell cell-freezing container is a suitable alternative to a controlled-rate freezer for clinical studies. The TxCell Phase IIb clinical trial is of particular interest in that it resulted in the decision to switch to the CoolCell container despite the fact that controlled-rate programmable freezers had been used in the primary stages of the trials. This implies that the new device represents not simply an alternative to other freezing methods, but in fact is preferable in that it offers several very significant advantages in comparison to conventional methods.

One of the most obvious drawbacks with conventional methods, especially for multi-site clinical trials, is the high cost of a dedicated controlled-rate freezer. This will affect preclinical development as well as clinical, and the cost consideration will only be magnified going forward because many successful drug candidates will have to be scaled up for commercial development and manufacturing. The CoolCell cell-freezing container is designed for use with a -80°C freezer, which is standard equipment even in academic labs. Furthermore, due to the small size and portability of the CoolCell container, the freezer it resides in need not be dedicated to cell freezing, an important point for most researchers in the R&D stages of development, when the cells in question generally represent one of many drug candidates. Cost of maintenance must also be considered. Set up and maintenance of an instrument as large and sophisticated as a programmable freezer isn't trivial, and precious samples could be lost if a malfunction were to occur. The simple one-piece design of the CoolCell cell-freezing container requires no maintenance, and virtually no training, giving the device the additional advantage of eliminating variability in how it is employed from researcher to researcher, or from site to site.

The use of a portable, passive freezing device will also have a positive impact on scalability, being easier and less expensive to employ at multiple clinical sites. For future scale up of Ovasave manufacturing, larger capacity CoolCell units may be used, or multiple devices might be used in parallel. The CoolCell container can be used in combination with other BioCision temperature standardization products. TxCell, for example, is also deploying the CoolRack modules and CoolBox ice-free cooling systems to minimize temperature variation and lower the risk of contamination during its cell handling and preparation stage.

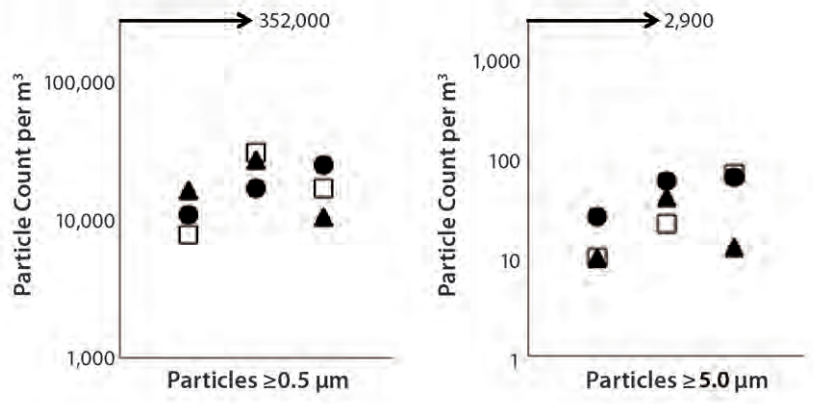
Cell therapy carries an intrinsic variability, for the simple reason that each person is different. Not every blood sample drawn from a healthy donor will contain an identical number of target cells with the same potency from cell to cell. Not every patient will respond to therapy in the same manner. For cell therapies to succeed in the clinic, standardized protocols for cell culture, handling, and freezing should be instituted to guarantee the highest possible standards in reproducibility.

FIGURE 4



Effects of freezing on antigen-specific Treg (Ag-Treg) cell therapy products; Ag-Tregs (n=6) were frozen at a concentration of 1 to 10 × 106 cells/mL using the CoolCell freezing container or controlled-rate freezer (CRF, freezing rate of -1°C/min). Viability and absolute viable cell count of thawed Ag-Treg cell therapy products were evaluated by flow cytometry.

FIGURE 5



Particle-release performance was tested three times on three different CoolCell freezing containers (nine measurements). Upper line on each graph indicates maximum acceptable particle count for each particle size measured. The CoolCell device is suitable for use in an active class B cleanroom.

We need to identify those steps at which variation can be eliminated. Years of intense cell therapy research have made it clear that even a slight variation in temperature at any point during sample handling can potentially affect the efficacy or potency of the final therapeutic product.

Cryopreservation protocols are of singular importance to the entire drug development process, because while fail-safes, such as screening assays, may be employed at earlier steps, once a cellular product is frozen for cryopreservation, its next intended use is for patient treatment. As is the case for the TxCell Ovasave clinical trial, a single blood sample may represent years of patient treatment once target cells are expanded. Steps taken to ensure maximum quality and reproducibility of cell samples will no doubt carry over into non-clinical areas as well. Basic biomedical research, preclinical studies, and biobanking all stand to gain from standardization of sample handling. The development and use of temperature standardization technologies that is cost-effective, maintenance free, and easy to use is an important step in the right direction.◆

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BIOGRAPHIES

Dr. Rolf Ehrhardt is the President and CEO of BioCision. Prior to this, he was responsible for the early (Phase 1a) clinical development of a novel HCV protease inhibitor at Intermune. Before that, he was the Vice President of Preclinical Development at Corgentech and Founding President of BioSeek. Dr. Ehrhardt was a Deutsche Forschungsgemeinschaft (DFG: German Research Foundation) and Fogarty Fellow at the NIH, where his focus was on mucosal immunology and inflammatory bowel disease. Dr. Ehrhardt earned his medical and doctoral degrees with distinction from the Technical University of Munich, Germany.

Dr. Maria Thompson is the VP Scientific Affairs with BioCision. She has a background in molecular genetics and over 16 years of experience in pharmaceutical and diagnostics research and development. She has held a variety of roles, including Head of Genome Wide Screening for type 2 diabetes, Six Sigma Black Belt, Principal Consultant, and Head of Scientific Affairs, as well as running APEX Think, a private scientific writing and marketing consultancy. Dr. Thompson earned her BSc in Genetics and her PhD in Molecular and Cellular Biochemistry from the Royal London School of Medicine, UK.

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DISSOLUTION ENHANCEMENT

Dissolution Enhancement Through Factorally Designed Porous Solid Dispersions

By: Balwan Singh and Harish Dureja, PhD

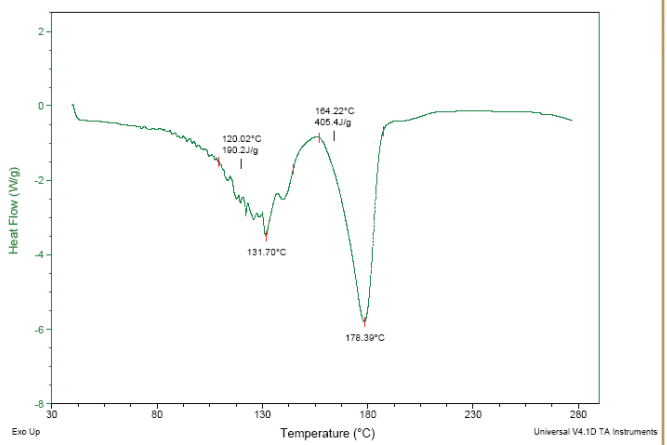
ABSTRACT

An amalgamation of hot-melt technology and effervescence has been employed to yield porous solid dispersions (PSDs) for dissolution enhancement using glimepiride as a model drug. Citric acid was used as a hydrophilic carrier, and sodium bicarbonate as an effervescence-causing agent. Factorial design was applied to study the effect of amount of glimepiride and amount of citric acid on the in vitro dissolution profile of glimepiride. DSC, FTIR spectroscopy, and powder X-Ray diffraction studies were employed to characterize PSDs. The in vitro dissolution rate of PSD (batch F3) was found to be much faster and higher than the corresponding conventional solid dispersion and pure drug. ANOVA was applied on cumulative percentage of glimepiride release. The mathematical models developed in the present study can be used to predict cumulative percentage of glimepiride from PSDs. These models can be utilized to formulate PSDs with desired glimepiride release.

INTRODUCTION

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the challenging aspects of drug development.[1] Techniques that have commonly been used to improve the dissolution and bioavailability of poorly water-soluble drugs include micronization, salt formation, solubilization, and formation of solid dispersions.[2,3] Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent, melting-solvent method.[4]

FIGURE 1



DSC scan of porous solid dispersion (batch F3).

The term solid dispersion was initially used by Sekiguchi and Obi (1961) and has grown to become one of the most active ideas in the pharmaceutical field.[5] Chiou and Reigelman outlined six types of drug-carrier interactions in solid state dispersions: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates, and compound or complex formation.[4] The mechanism by which the solubility and dissolution rate of the drug is increased includes: firstly, the particle size of a drug is reduced at submicron size or to a molecular size in the case in which the solid solution is obtained, the particle size reduction by micronization or nanonization can enhance the dissolution rate; secondly, the drug is changed from crystalline to

amorphous form, with excess thermodynamic properties and lower energy barrier that can offer solubility benefits; finally, the wettability of the drug particle is improved by the dissolution carrier.[6-9] The additional mechanism for enhancing dissolution rate in porous solid dispersion is due to capillary action wherein liquid can be drawn into the capillaries instantaneously.

In the present study, porous solid dispersions were prepared using a hot-melt method coupled with effervescence. Glimepiride was chosen as a model candidate because of its low dissolution rate and solubility-limited bioavailability. Citric acid was used as a hydrophilic carrier and sodium bicarbonate as an effervescence-causing agent. The objective behind the work was to quantify the role of critical variables of PSDs using statistical experimental design.

MATERIALS

The active ingredient, glimepiride, was procured ex-gratis form M/s Cadila Pharmaceuticals, India. Citric acid and sodium bicarbonate were purchased from M/s Loba Chemicals, India. All other chemicals were of analytical grade.

METHODS

Preparation of Porous Solid Dispersions & Solid Dispersions

The porous solid dispersions (PSDs) of glimepiride were prepared employing amalgamation of a hot-melt method and effervescence. The calculated amount of the carrier, ie, citric acid (1 to 5 g) was melted over a thermostatically controlled magnetic stirrer, and the drug (100 to 400 mg) was incorporated into the molten carrier. The blend was heated at the corresponding temperature for 5 mins followed by the addition of sodium bicarbonate (1.2 to 6.0 g). The mixture was cooled on an ice-bath. The dispersions were subsequently desiccated under vacuum for 48 hrs and sieved (300 microns). The conventional solid dispersion of the drug with citric acid alone was also prepared using the aformentioned method followed by sieving (300 microns).

TABLE 1

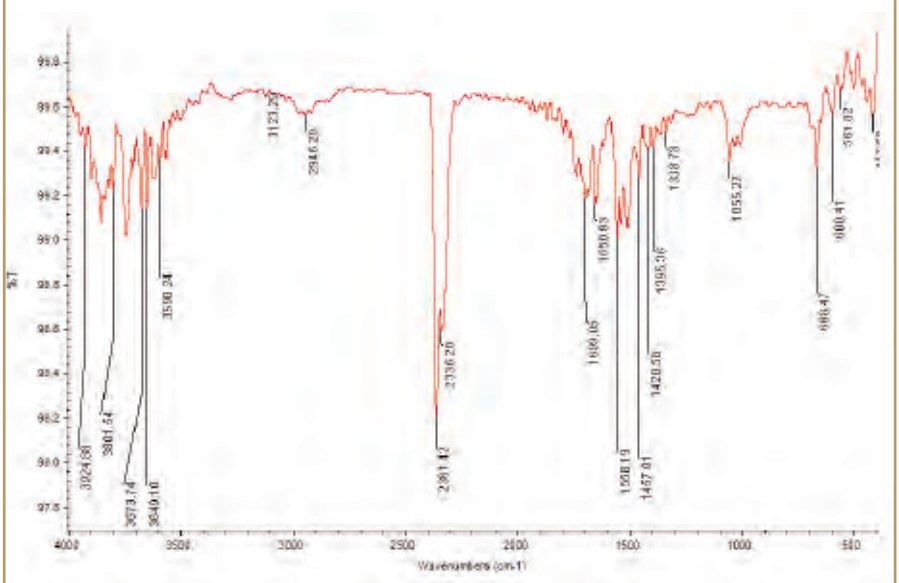
Formulation Code	Amount of Drug (X_1) mg	Amount of Carrier (X_2) gm	Cumulative % of Drug Release (%) ±SD
F1	400 (+1)	5 (+1)	88.93±0.82
F2	400 (+1)	1 (-1)	85.13±0.94
F3	100 (-1)	5 (+1)	98.99±0.77
F4	100 (-1)	1 (-1)	87.15±1.02

Formulation of porous solid dispersions

Experimental Design

A 2^2 full factorial design was used in order to investigate the influence of two variables. In this design, two factors were evaluated, each at two levels, and the experiments were performed at all four combinations. The composition of all four batches is shown in Table 1. The amount of the drug (X_1) and the amount of citric acid (X_2) were selected as independent variables. The cumulative percentage of drug release was selected as a dependent variable. ANOVA was applied on the cumulative amount of drug release to study the fitting and significance of the model.

FIGURE 2



FT-IR scan of porous solid dispersion (batch F3).

TABLE 2

	Degree of Freedom	Sum of Square	Mean Square	F
Total	3	113.7944	-	3.021
Regression	2	97.634	48.817	
Residual	1	16.1604	16.16.04	

ANOVA of regression (cumulative percentage of glimepiride release).

Differential Scanning Calorimeteric (DSC) Studies

Differential scanning calorimetric analyses of the drug, carrier, physical mixture, solid dispersion, and porous solid dispersion (PSD) were carried out using DSC-Q10 (Waters, V9.0 Build 275). Samples (2 to 5 mg) were heated under nitrogen atmosphere in an aluminum pan at a rate of 10°C /min over the temperature range of 40°C to 250°C. The instrument was calibrated using a high-purity indium standard.

Fourier Transform Infrared Spectroscopy Studies

Fourier transform infrared (FT-IR) spectroscopy was employed to further characterize the possible interaction between the drug and carrier in the solid state on an FT-IR spectrophotometer (Perkin Elmer Paragon 1000 IR, UK) by the conventional KBr pellet method. The spectra were scanned over a frequency range of 4000 to 400 cm^{-1}.

Powder X-ray Diffraction Studies

Powder x-ray diffraction patterns were traced employing x-ray diffractometer (X'Pert PRO, Panalyical, Netherland) for the samples using Ni-filtered (0.154 nm wavelength) Cuk-alpha radiation, a voltage of 45 kV, a current of 40 mA, and receiving slit of 0.2 inches. The samples were analyzed over 2θ range of 5° to 50° at a scan rate of 1.5°/min.

In Vitro Dissolution Studies

Dissolution experiments of the drug in the porous solid dispersions were carried out in triplicate using United States Pharmacopoeia dissolution apparatus I (basket-type) employing 900 ml of phosphate buffer (pH 6.8) at a temperature of 37°C ± 0.5°C and at a rotation speed of 75 rpm. Dissolution studies were performed on the pure drug (4 mg), solid dispersion, and porous solid dispersions, each containing an equivalent amount of drug. At predetermined intervals (5, 10, 15, 20, and 30 mins), samples were withdrawn and replenished by an equal volume of fresh phosphate buffer (pH 6.8). The samples were filtered and analyzed spectrophotometrically at 226 nm using a spectrophotometer (Systronics 2201, India).

Content Uniformity Studies

Ten samples of porous solid dispersion equivalent to 4 mg of drug were dissolved in 100 ml of phosphate buffer (pH 6.8). A 2.5-ml aliquot was pipetted out, and the volume was made up to 10 ml with phosphate buffer (pH 6.8). The absorbance was measured spectrophotometrically at 226 nm using a spectrophotometer (Systronics 2201, India).

RESULTS & DISCUSSION

In order to investigate the factors systematically, a factorial design was employed. The amount of drug (glimepiride, X_1) and amount of carrier (citric acid, X_2) were chosen as independent variables in a 2^2 full factorial design. Preliminary studies revealed that the ratio of 1:1.2 of citric acid and sodium bicarbonate produced good effervescence. The real values of factors were transformed to facilitate orthogonality and ease in calculations.

The developed model can be used to draw conclusions after considering the magnitude of coefficients and mathematical sign it carries (positive or negative). The results of multilinear regression (MLR) showed that the coefficient b_1 = -3.02 and b_2 = 3.91. Therefore, an increase in the amount of drug results in a decrease in the cumulative percentage of drug release. When a high amount of citric acid is used, the cumulative percentage of drug release was increased in PSDs as indicated by coefficient b_2. The statistical model developed from MLR for estimating cumulative percentage of drug release from PSD can be represented mathematically as: $Y= 90.05-3.02.X_1+3.91.X_2$.

Where X_1 is the amount of drug present in PSD, and X_2 is the amount of citric acid present in PSD. Table 2 shows the results of analysis of variance (ANOVA), which was performed to study the fitting and significance of the model. F-test was carried out to compare the regression mean square with residual mean square. The ratio F = 3.021 for PSD showed the regression to be significant.

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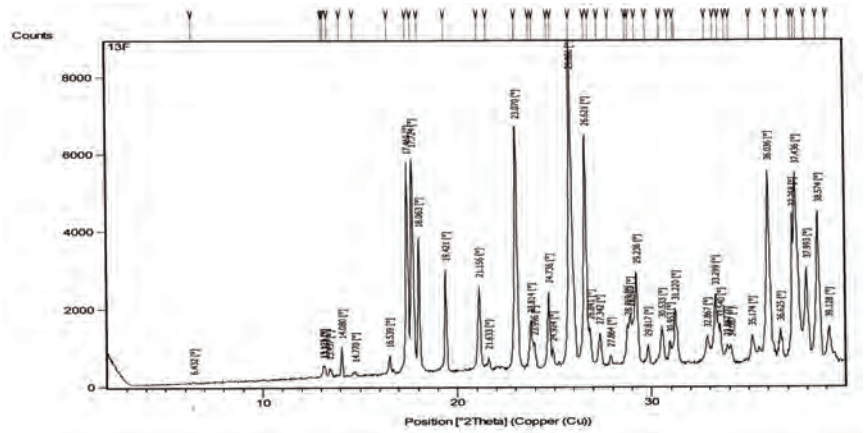
The differential scanning thermograms of glimepiride exhibited a sharp endothermic peak at 207°C, corresponding to its melting point. Similarly the melting peaks of citric acid and sodium bicarbonate were observed at 157°C and 167°C, respectively. The DSC scan of PSD (batch F3) lacks endotherm at 207°C, indicating the presence of drug in an amorphous form (Figure 1). The thermogram of PSD (batch F3) exhibited peaks at 178°C, indicating the melting point of sodium citrate.

The infrared spectrum of PSD exhibited significant difference in the intensities of the absorption peaks (batch F3). Broadening of various absorption peaks with a slight shift in the position of lower wavelength was observed, which may be attributed to the absence of the intermolecular hydrogen bonding in the glimepiride present in PSD (Figure 2).

The x-ray diffractogram of glimepiride showed numerous distinctive peaks that indicated crystallinity. The PSD (batch F3) exhibited lesser and broader peaks, confirming the amorphous form of the drug and negligible crystallinity in PSD (Figure 3).

The primary aim of formulating poorly soluble drug in porous solid dispersion is to enhance the dissolution rate. Figure 4 shows in vitro dissolution profile of glimepiride from solid dispersion, porous solid dispersions, and pure drug. The result showed that drug in PSD (batch F3) has a higher dissolution rate than the corresponding conventional solid dispersion and pure drug. The performance of PSD is outstanding: more than 98% of drug is dissolved with in 30 mins. This may be attributed to the presence of the amorphous form of drug.

FIGURE 3



X-RD scan of porous solid dispersion (batch F3).

This may also be credited to a more intimate drug-carrier interaction (glimepiride with citric acid) in the molten state during formulation of PSD. The dissolution enhancement of citric acid in solid dispersion has been reported to be due to the formation of glass dispersions associated with high dissolution rates.[10,11] Increased dissolution could be ascribed to wetting of the hydrophobic particles and augmentation of its solubility by the effervescence mechanism. The increased porosity of PSD resulted in greater surface area, which leads to rapid dissolution in contact with the dissolution medium and encourages penetration and circulation of dissolution fluid into the porous solid dispersion owing to capillary action.

The results obtained from content uniformity studies revealed that the porous solid dispersion (batch F3) passes the I.P. limits.

CONCLUSION

Porous solid dispersions provide a practical means of enhancing the drug dissolution employing amalgamation of a hot-melt technique and an effervescent approach. Glimepiride served as a model candidate for the formulation of PSD (batch F3). It can be concluded that significant enhancement of drug dissolution was achieved through PSD in comparison to conventional solid dispersion and pure drug. Application of factorial design revealed that a high level of citric acid increases the cumulative percentage of drug release. A proposed mathematical model can be used for predicting cumulative percentage release of glimepiride from PSD. The said model possesses immense potential for designing PSDs with desired glimepiride- release characteristics.


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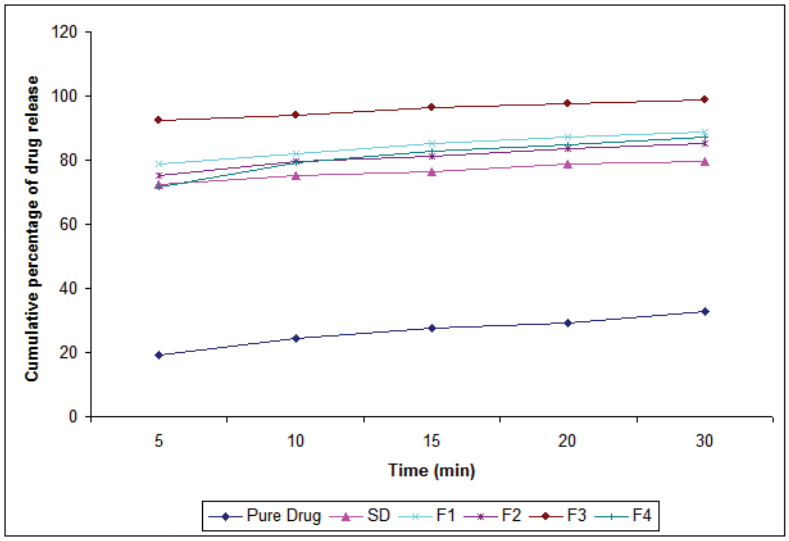
FIGURE 4



In vitro dissolution profile of pure drug, conventional solid dispersion (SD) and porous solid dispersions (F1-F4).

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BIOGRAPHIES

Balwan Singh is an alumnus of MD University Rohtak. Currently, he is working as an Assistant Professor at HIMT College of Pharmacy Greater Noida Uttar Pradesh, India. He has more than 6 year experience in academics and has several publications to his credit in various journals of repute, and presented papers in various seminars/conferences. He is the author of a book Pharmaceutics-IV (Unit Operations-II) published by Thakur Publisher Lucknow. He is a life member of APTI. His areas of interest are nanotechnology, solid dispersion, NDDS, validation, and quality assurance.

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REGULATORY GUIDANCE

Staying on Top of FDA Guidance for Industry - Training Webinars Foster Transparency & Collaboration

By: Frost & Sullivan

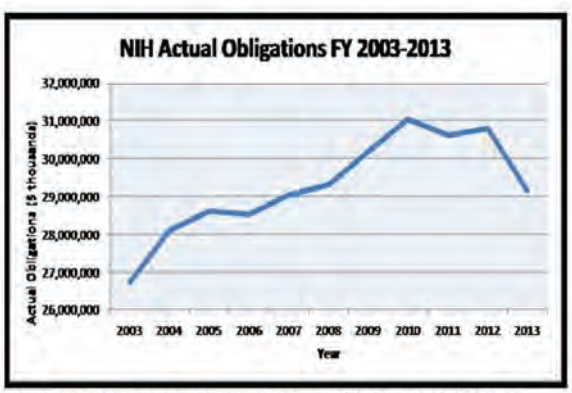
INTRODUCTION

The US FDA periodically releases new guidance documents for industry (GFI) or revised versions of previously released guidance in order to keep pace with medical advancements, such as developments in therapeutics that alter the natural history of disease conditions and/or new knowledge of underlying pathologies. These guidance documents are intended to reflect the agency's current thinking on specific topics and to provide industry sponsors with recommendations for the development of new therapeutics. Accordingly, careful attention to these recommendations will help increase approvability of new drugs, although there is, of course, still no guarantee. Oftentimes, the draft guidance is presented in a webinar format in order to foster communication with industry and encourage comments while still in draft form. Webinars are interactive with attendees who are encouraged to pose questions or comments at the end of the presentation. Frost & Sullivan recently tuned in to three of these webinars presented in the past few months that were considered to be particularly relevant to current hot topics and therapy areas. Read on to discover background on the current trends and needs behind each new or revised guidance document and key insights for potential sponsors.

REVISED DRAFT GUIDANCE FOR DRUG DEVELOPMENT FOR RHEUMATOID ARTHRITIS

Drug development for rheumatoid arthritis (RA) has been one of the most active and highly competitive therapy areas of the last couple decades. At the time of the publication of last RA guidance document in February 1999, biologic therapy for this condition was still very new, with only the first of several tumor necrosis factor (TNF) blockers approved for the treatment of RA. In February 1998, Enbrel (etanercept), a TNF blocker developed by Amgen, was the first biologic agent approved for RA. The approval of Enbrel was followed shortly in November 1999 by Remicade (infliximab), developed by

FIGURE 1



Source: http://officeofbudget.od.nih.gov/spending_hist.html; FY2013 Operating Plan Note: Excludes American Recovery and Reinvestment Act

Centocor, now part of Johnson & Johnson. Several additional TNF inhibitors followed over the next several years, including Abbvie's Humira (adalimumab) in 2002, UCB's Cimzia (certolizumab) in 2008, and Johnson & Johnson's Simponi (golimumab) in 2009. A few novel biologics have also arrived to this market, such as: Orencia (abatacept), a T cell costimulation modulator marketed by Bristol-Myers Squibb (BMS); Actemra (tocilizumab), an interleukin-6 (IL-6) inhibitor marketed by Roche; and Rituxan (rituxumab), an anti-CD20 antibody marketed by Roche/Biogen Idec. The breakthrough efficacy of biologic therapy has revolutionized the treatment of RA and, as a result, the bar has been raised for the development of the next generation of drugs, hence the need for revised guidance for industry.

On July 25, 2013, the FDA held a webinar to discuss and summarize the revised draft guidance for industry for development of drugs for RA. The agency felt the time was right to update their recommendations for industry to account for these changes, as well as address some concerns of the regulatory and rheumatology communities. Draft guidance was published May 31, 2013, and public commentary was open until July 31, 2013.

One of the main concerns for RA trials is the use of placebo. While the agency acknowledges that comparison to placebo is sometimes necessary, it recommends that exposure to placebo be limited to 12 weeks maximum. Ethical concerns about keeping patients with uncontrolled disease on either placebo or an ineffective therapy have arisen, and the FDA recommends that trial designs need to incorporate provisions for escape to rescue therapy without compromising the integrity of the data. This suggests that measurement of primary and some secondary endpoints will coincide with conversion to rescue therapy.

FIGURE 2

FY2013 Funding Strategies for Select NIH ICs

Institute	Non-Competing Grants Reduction	Competing Grants Strategy
National Center for Advancing Translational Sciences	6.0-8.0%	Appropriate levels based on programmatic recommendations
National Cancer Institute	6.0%	Discretionary based on peer review evaluation
National Human Genome Research Institute	4.5%	Discretionary based on institute priorities
National Heart, Lung, and Blood Institute	4.8%	Reducing grants or direct costs by 4.8%, eliminating inflationary increases, adjusting grant durations to 4 years
National Institute of Allergy and Infectious Diseases	6.0%	Reducing competing grants by 6% (excludes certain mechanisms), reducing competing initiatives 20%
National Institute of General Medical Sciences	3.5%	Overall average costs will remain at FY2012, no inflationary increases
National Center for Advancing Translational Sciences	6.0-8.0%	Appropriate levels based on programmatic recommendations

Source: FY2013 Funding Strategies; Frost & Sullivan

Measurement of efficacy was also an issue. The minimum expectation is that efficacy needs to be demonstrated for both clinical response (eg, ACR 20) and physical function with 12-week data for both points. The agency noted that additional relevant secondary endpoints, such as radiographic evidence of disease progression are becoming increasingly difficult to measure, and that other methods of evaluating disease progression need to be validated to enable shorter trials. Pursuit of clinical remission as an endpoint, which was unrealistic at the time of the last guidance, is highly encouraged by the FDA. However, it was noted that a Disease Activity Score (DAS) 28 of less than 2.6, which is considered by many to define clinical remission, will be considered by the FDA as low disease activity but not remission. The agency states that remission is indicated with scores between zero and less than 2.6. In regard to durable remission, the FDA would consider these claims on a case-by-case basis. It was also noted that an acceptable timeframe for remission would be highly dependent on the risk/benefit profile of the drug. In other words, a longer duration of remission would be needed for more toxic drugs, but shorter durations would be acceptable for more benign drugs. Sponsors should plan to discuss this endpoint with the FDA.

Issues regarding drug dosing were also noted. The agency recommends that evaluation of dose selection extend beyond a single dose ranging trial and be fully explored in preclinical and early clinical work, as well as into Phase III confirmatory studies with at least two doses tested in late development. It was noted that dose finding studies are often of shorter duration and size and not really adequate for fully assessing the

safety of each dose. The FDA would like to see solid data for the minimum effective dose as well as the efficacy plateau. The use of drug-device combination products has also become a new issue since the last guidance due to the numerous biologics introduced to the market since. The FDA recommends that the combination product be used in the Phase III confirmatory studies. Finally, safety of RA drugs is becoming a critical issue, in light of the inherent risks of chronic immune-suppressive therapy and the latency period of safety issues, such as opportunistic infections and malignancy. The minimum requirement for a safety database is 1,000 to 1,500 patients with at least 1 year of data.

DRAFT GUIDANCE FOR INDUSTRY ON STREAMLINED DEVELOPMENT PROGRAM FOR ANTIBACTERIAL DRUGS

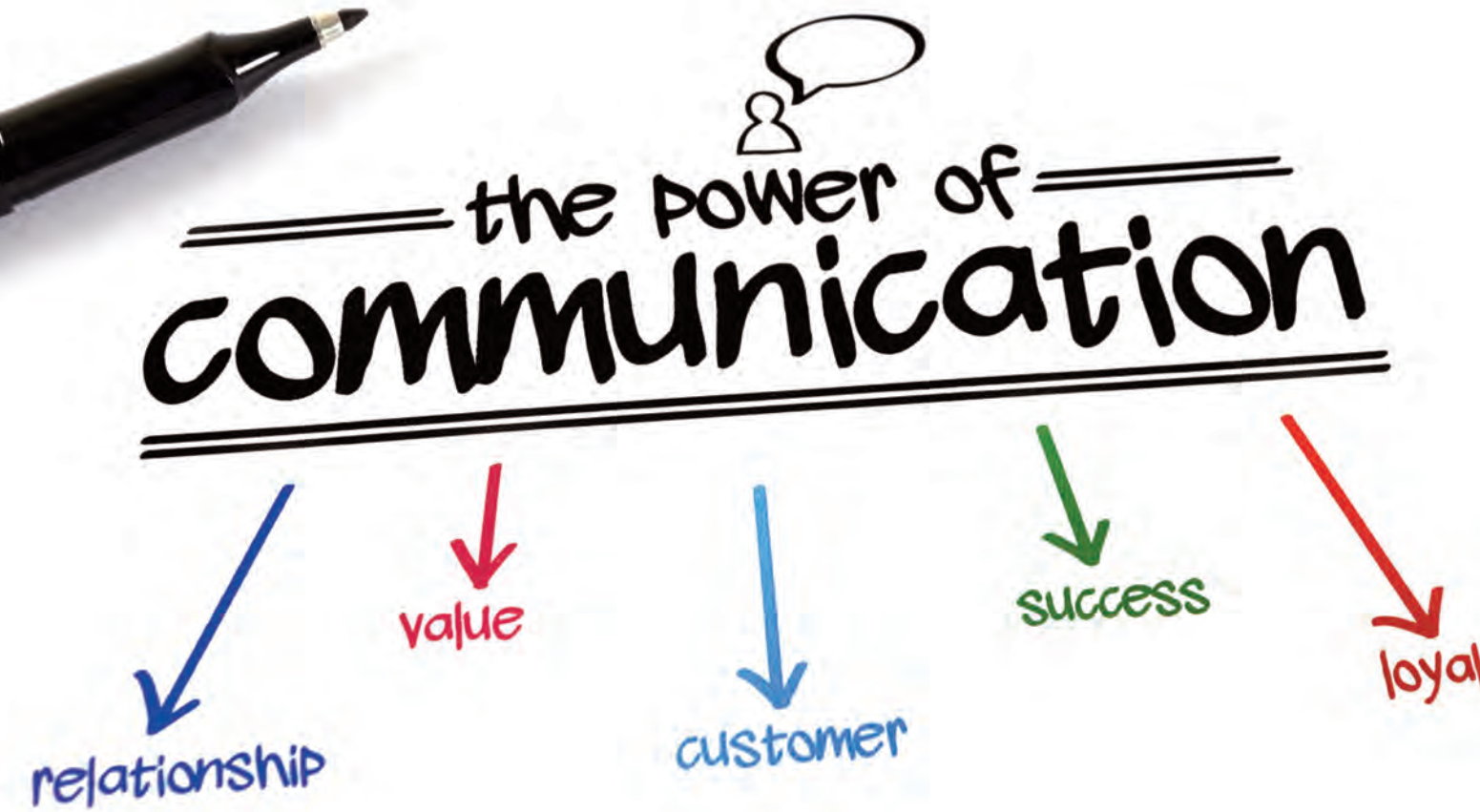
Drug development for serious bacterial infections is an area in dire need of innovation and drug development activity. The GAIN (Generating Antibiotic Incentives Now) act, which was signed into law in July of last year, authorized a streamlined development process for antibacterial drugs meeting certain criteria. Such initiatives have been undertaken in response to the lagging development of antibacterial drugs, which is no longer keeping pace with the development of drug resistance, spurning a concerning increase in unmet medical need. Among several factors hindering antibacterial drug development, challenges with conducting proper clinical trials is among the most important due to issues, such as the urgent need to initiate standard antibacterial therapy that can obscure the effect of the investigational drug, diagnostic uncertainties, and difficulty getting consent from patients with serious infections due to impaired cognitive abilities, among others.

In response to the urgent need for effective treatments for serious infections and to address these issues and concerns, the Division of Anti-Infective Products in the FDA's Center for Drug Evaluation and Research (CDER) has drafted new guidance for industry for the development of antibacterials for serious diseases, which includes an accelerated development program in order to expedite access to these critically needed drugs. The draft guidance covers topics, such as drug types suitable for the streamlined development program, possible development approaches, clinical trial design, non-clinical requirements, and marketing issues, such as companion diagnostics. A webinar was presented by the FDA on Sept. 27, 2013, outlining this program.

The streamlined program is for drugs for the treatment of serious bacterial infections in which there are few or no treatment options and thus, unmet need. Potential candidates are expected to be drugs with a novel mechanism of action (MOA) or alterations of existing MOAs that address resistance and can include drugs targeting a specific genus and species. The modification of an existing drug for other purposes, such as to reduce hospital stay or dosing frequency would only be considered if the sponsor could justify the meeting of an unmet need.

Trial design is one of the most challenging aspects of this therapy area and, as such, was discussed in depth. Superiority trials are a definite possibility if the treatment effect is expected to be large enough, and in this case, the sample sizes can be much smaller as opposed to non-inferiority trials. Alternatively, a non-inferiority trial might identify a sub-population in which a superiority trial could be conducted. In light of the challenge of recruiting larger numbers of patients per trial site, it was noted that trial centers can be randomized, as opposed to patients, facilitating trial conduct. Adaptive trial designs, such as Bayesian and other approaches, can be used. Use of a historical control is acceptable if the untreated morbidity is high and the treatment effect is expected to be high. However, randomization of even a few patients to active control, such as ratios of 3-to-1, 4-to-1, or even 5-to-1 randomization, would yield valuable information. Selection of optimal endpoints can be challenging and should be discussed with the FDA. Accelerated approval based on surrogate endpoints may be appropriate and should be discussed with the FDA as well, and the agency particularly welcomed comments and suggestions on this aspect of the draft guidance.

Safety is, of course, always a concern for any new drug but must be considered relative to the benefits of the therapy along with the nature of its use - chronic versus acute setting. In the case of serious bacterial infections, a pre-market safety database of at least 300 patients is considered adequate with the rationale that this would rule out a 1% or greater risk of a serious or unexpected adverse event/s in the post-market setting.



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The non-clinical development program is just as critical, if not more so, in light of the abbreviated clinical program, and cannot be streamlined. It will be important for sponsors to provide comprehensive data on the MOA, dosing, and frequency, pharmacokinetic/pharmacodynamic (PK/PD) profiles, and tissue distribution. Also, the agency notes that the "Animal Rule," which allows for approval of drugs that have only undergone animal testing when human studies are not ethical or feasible, does not apply in this scenario because it is possible to ethically conduct clinical trials.

Development of a companion rapid diagnostic would be very useful, and in the setting of a pathogen-focused antibacterial, could be crucial and/or essential. Multiple drugs per pathogen can be approved, and robust development programs are encouraged in the event of unexpected side effects of one drug or better response of a certain sub-population to one drug, as well as in the event of a drug shortage or emerging public health threat.

NEW DRAFT GUIDANCE FOR INDUSTRY ON BREAKTHROUGH THERAPY DESIGNATION & ACCELERATED APPROVAL

The pharmaceutical industry has had its share of "me too" drugs introduced to the market, due to the relatively low risk of this approach. Follow-on drugs using the same or similar mechanism as proven therapies usually have no surprises with regard to safety signals, and physicians are comfortable with their profiles and how to use them, leaving differentiation from existing therapies the only real marketing concern. However, oftentimes, this risk-averse approach leaves significant gaps in medical advancements for serious diseases with a high degree of morbidity/mortality. In order to encourage the development of novel therapies that represent important medical advancements with the promise of addressing the unmet needs of serious diseases, the FDA provides incentives to industry in the form of expedited approval programs.

The FDA hosted a live webinar to present the new draft guidance for industry for Fast Track designation, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review Designation. This is the first such guidance published by the FDA on the new Breakthrough Therapy Designation and Accelerated Approval. The intent of these programs is to encourage drug development to address unmet needs for serious conditions. Breakthrough Therapy Designation can be given to a new drug or biologic that demonstrates "substantial" improvement over available therapies for a serious condition, and it is the term "substantial improvement" that largely differentiates Breakthrough Therapy from Fast Track Designation.

According to the presentation, the FDA would consider "substantial" to be a clear benefit with regard to both the magnitude and importance of the effect. Particularly valuable would be demonstration of treating the underlying disease rather than just treating the symptoms. A new drug with similar efficacy but one that avoids a serious toxicity or a side effect would also be considered as well. Add-on therapies would be considered as long as they meet the criteria. Breakthrough Therapy Designation gives the sponsor all of the benefits of Fast Track status plus more intensive guidance from the FDA. Accelerated Approval could be granted to a new drug that demonstrates efficacy on a surrogate endpoint that is likely to predict an important long-term or an intermediate clinical endpoint. In these cases, the sponsor will usually be required to demonstrate post-marketing that the drug does indeed provide the predicted long-term clinical benefit. The FDA encourages sponsors to submit an application for potential Breakthrough Therapy Designation early in the development process, as soon as there is sufficient evidence of the clinical benefit of the drug. The FDA is not liberally giving out Breakthrough Designations, however. Since May 31, 2013, the FDA has received 59 requests for Breakthrough Designation, of which 20 have been granted and 20 denied.

FDA training webinars are an easy way for industry sponsors and other key stakeholders to keep abreast of some of the agency's latest important developments. The interactive forum provides simplification of the lengthy and detailed documents while emphasizing the key take home messages, and attending a webinar gives viewers a more personal view of the FDA's thought processes behind the development of these valuable resources for industry. u

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External Delivery

Crisis Management

By: John A. Bermingham

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

The saying, "when the going gets tough, the tough get going," always comes to mind when I hear about the challenges facing many companies, particularly when the issue a company is facing turns out to be a full blown crisis.

Crisis management is not risk management. Risk management has to do with planning for certain situations that may occur in the future. Crisis management is reacting to an event once it has occurred.

If you are a CEO, this is not the time to go it alone in an effort to resolve the crisis. There is so much to do simultaneously that no one person can be effective trying to resolve the crisis on his/her own.

Obviously, you want to take immediate control of the situation and not let the crisis spin out of control. The natural reaction is to communicate externally to customers, vendors, the trade and consumer press, and others. There are plenty of companies that specialize in crisis management and external communications, and you should seriously consider retaining one as the good ones are worth every cent that you pay them.

Even with a crisis in full bloom, you still have a company to run. So as a CEO or senior manager, you must also focus internally. This is because the company crisis is also an employee crisis, and internal communications are equally important to the external communications.

If you have a Board of Directors, you must communicate with them first. You never want the directors of your company to be out of the loop on what you are planning. In addition, if you have a competent Board, they can be excellent advisors and sounding boards (no pun intended). You should also keep in mind that directors of a company, public or private, have a fiduciary responsibility to the investors, and the investors will want to know what is being done to save the company and their investment. Keeping directors out of the information loop can be a disaster for you.

Just as importantly, you must communicate internally to the people in your company to keep the rumor mill under control and the "hysteria factor" to a minimum. You will never be 100% in control of the rumor mill, but you can exert control over it through constant communication.

You should also consider holding weekly staff and town hall meetings to ensure that accurate information flows throughout the company. You should also maintain an open door policy so that employees can ask you questions directly, especially from those who are suffering from the "hysteria factor."

Many of the people in your company will be living paycheck to paycheck, and the thought of losing their jobs and incomes due to a company crisis is something that will keep a person awake all night. The last thing you want to do is not let people know where everything stands on a frequent, honest, and open basis.

Otherwise you may develop a bailout scenario in your company, and losing valuable people can rapidly exacerbate an already difficult situation. So in one word, you must exercise CONTROL.

It must be positive control but control nonetheless. Your people will be looking to you for strong leadership during this time. They will be depending on you to save the company and their jobs.

Never forget, "when the going gets tough, the tough get going," and communicate, communicate, communicate. ◆

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