Drug Development & Delivery

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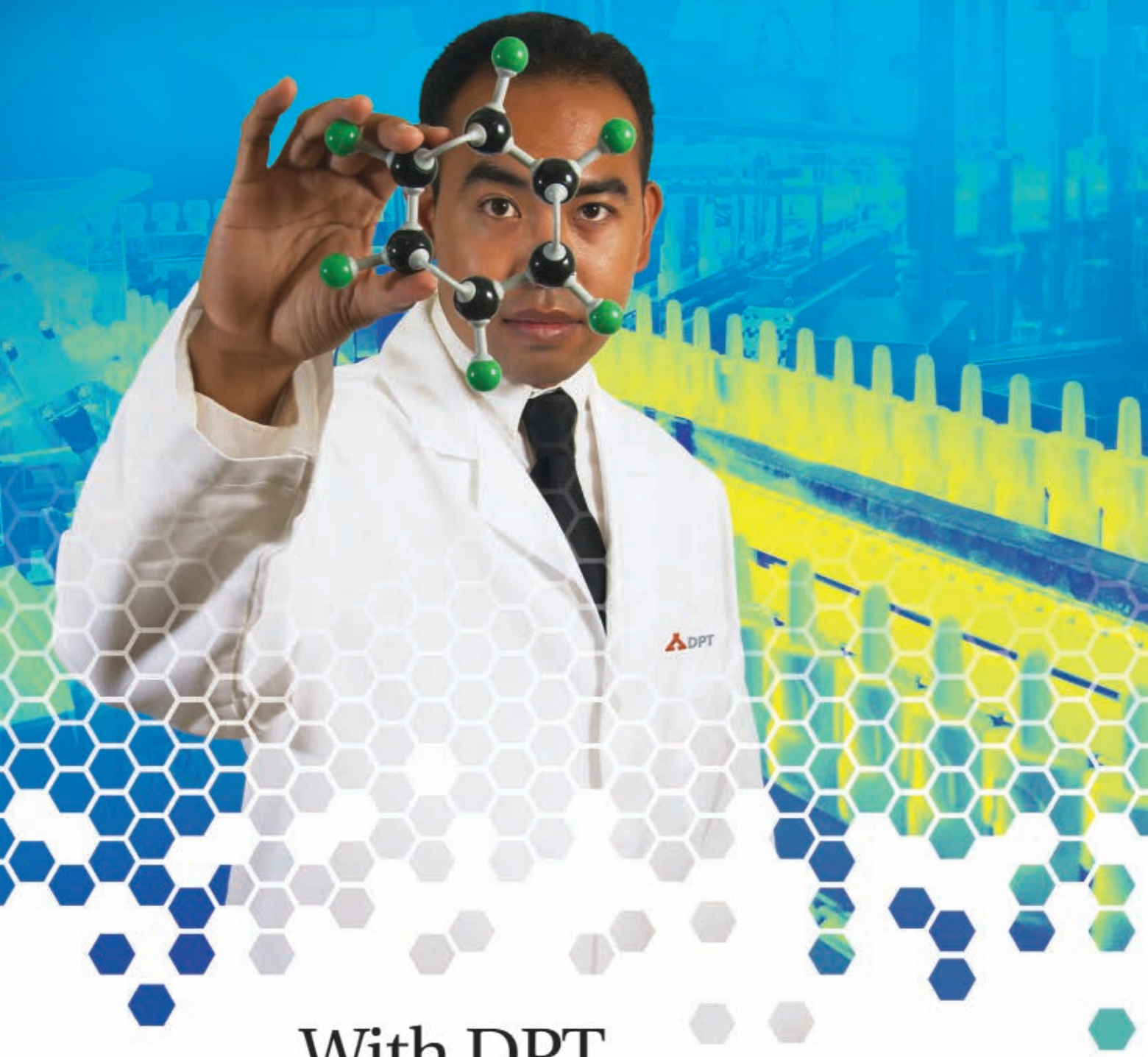

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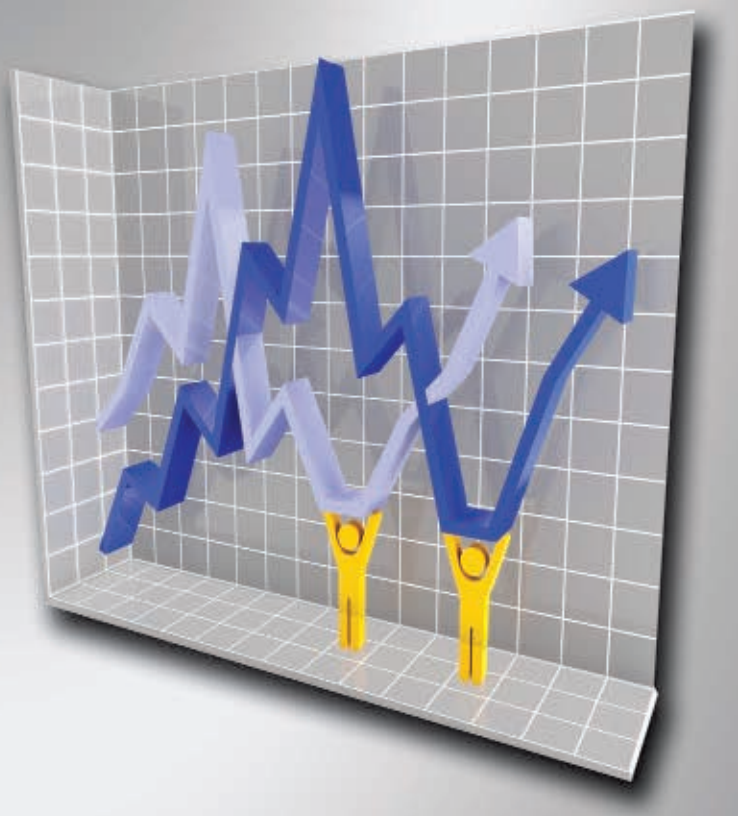

"Yes, contract development and manufacturing organizations (CDMOs) have stepped up to bail out pharma companies that are under pressure to cut costs and get product to market faster, according to a report from Global Industry Analysts Inc. Add to that the decrease in research productivity, the expiry of patents on blockbuster drugs, and budget constraints on procuring extensive equipment, and what you get is an increase in manufacturing and formulation outsourcing."

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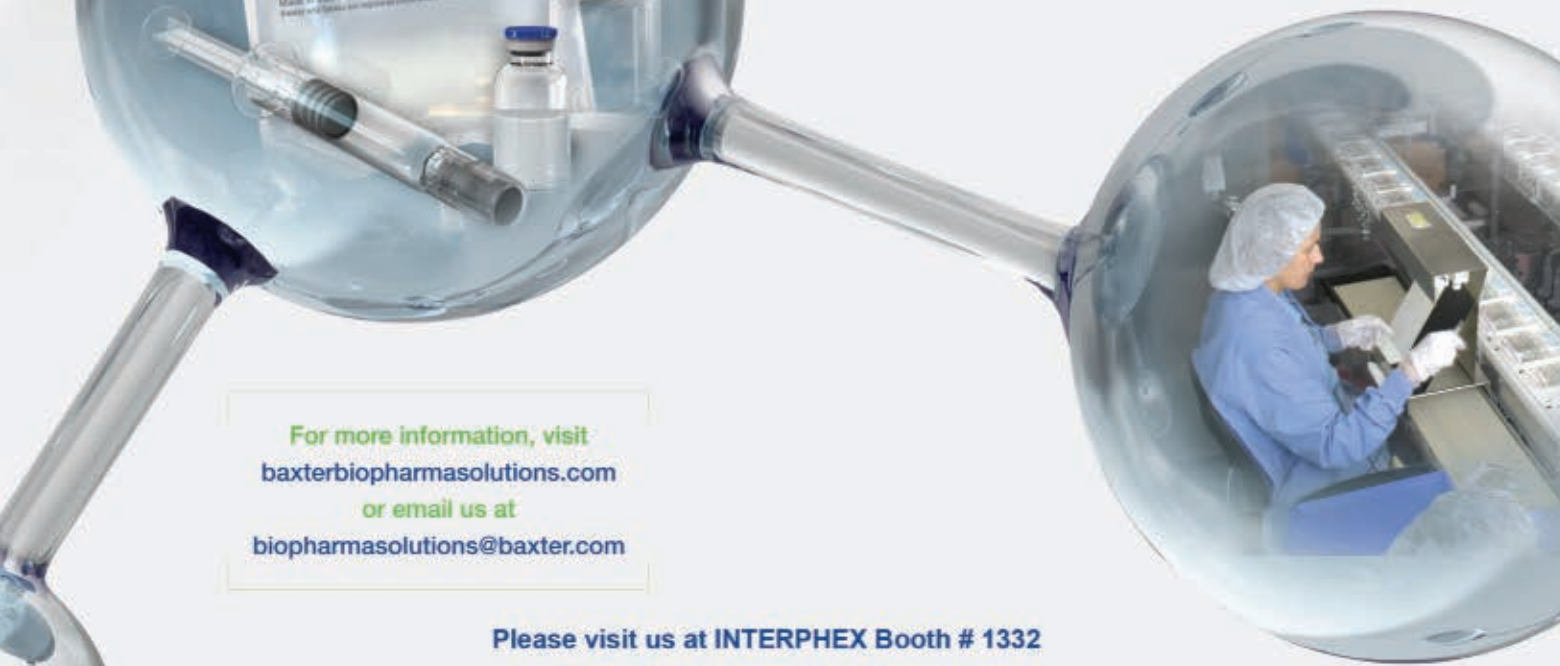

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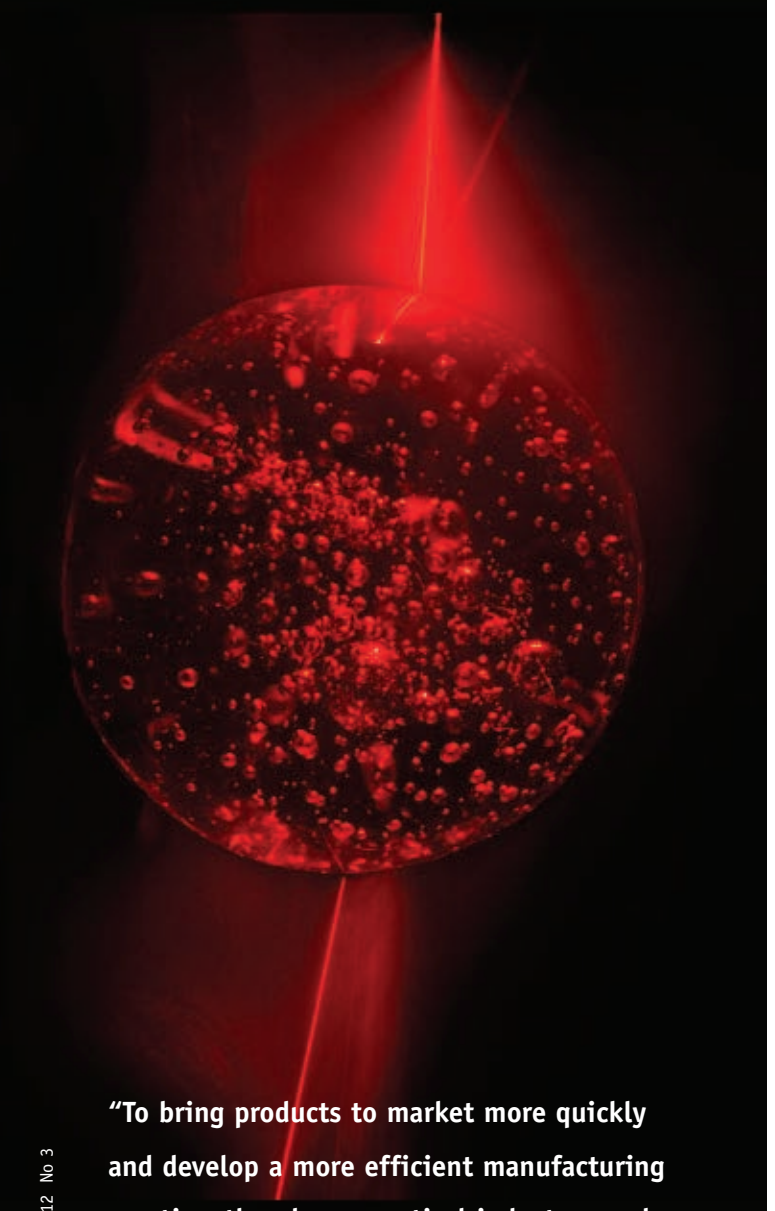

"To bring products to market more quickly and develop a more efficient manufacturing practice, the pharmaceutical industry needs appropriate analytical technology. Laser diffraction is a leading technology for particle size measurement, a major advantage being its ability to support every stage of the development cycle."

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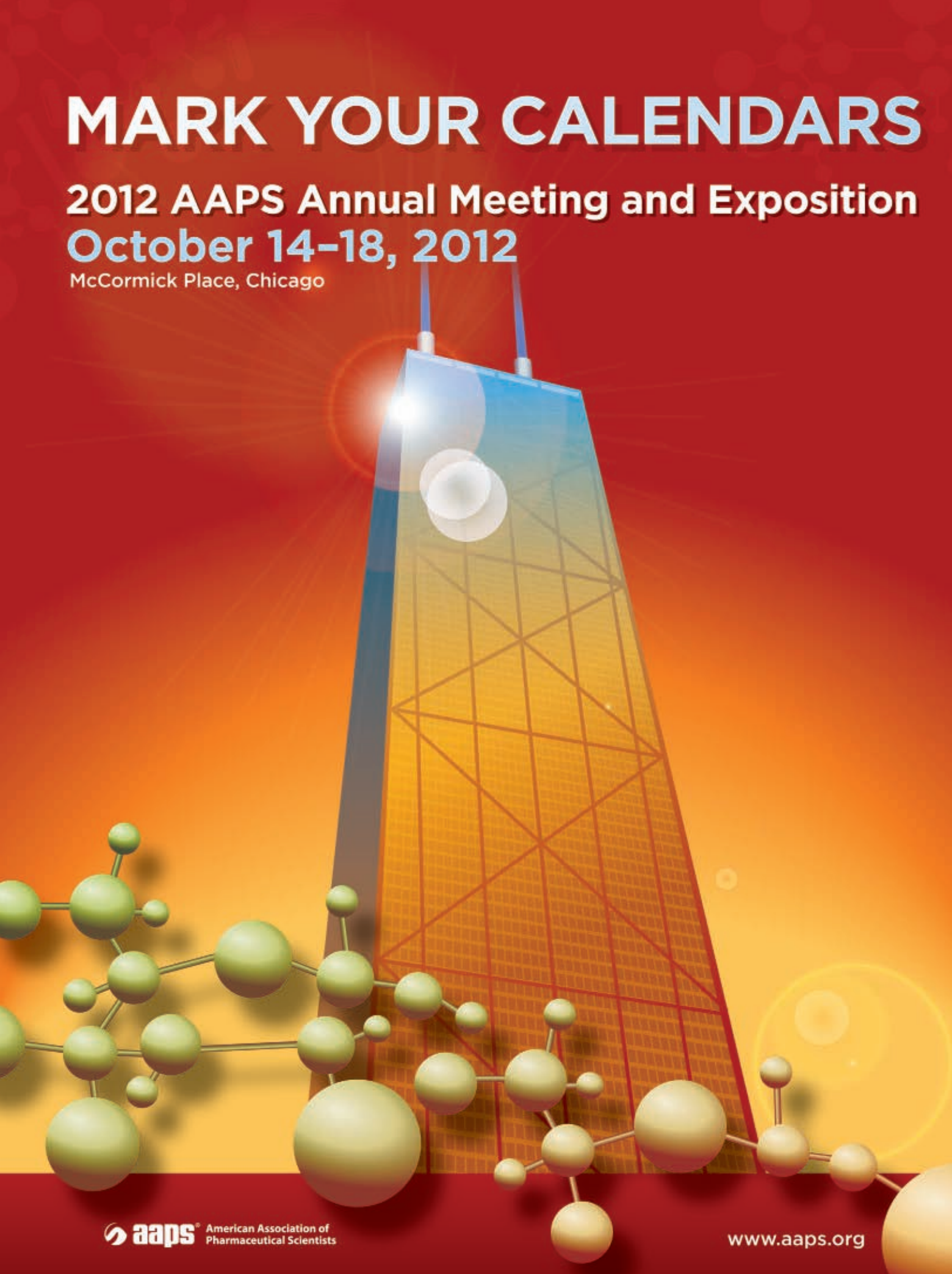

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Market News and Trends

Bend Research Launches New Biotherapeutics Development Initiative

Bend Research Inc. recently announced an initiative to expand its scientific and engineering expertise into biotherapeutics, including offering new technologies and equipment proven to improve biotherapeutic and vaccine production.

In the new initiative, Bend Research will partner with clients to develop and optimize pharmaceutical engineering processes and technologies by coupling fundamental cellular processes with the optimal cell environment for each phase of production.

"The campaign is grounded in science and engineering fundamentals, with a focus on applying macro-engineering approaches to leverage an understanding of complex cell-biology," said Dr. Lisa Graham, Senior Vice President at Bend Research. "We've validated this approach in our small-molecules business, and we're now uniquely positioned to bring this valuable experience to the broader biotherapeutics market."

Bend Research has made a wide range of bioprocessing services and capabilities available to help clients advance biotherapeutic products and processes, capitalizing on the company's extensive experience in process development, analytical sciences, and formulation science. This includes comprehensive development methodologies, individual tools and models, upstream and downstream bioprocessing solutions, computational modeling at multiple scales, and prototype engineering.

The initiative is the outgrowth of Bend Research's more than 35 years of experience in the development of small-molecule pharmaceutical delivery systems, formulations, and processes. It builds upon an exclusive relationship of nearly 7 years, in which Bend Research worked with Pfizer to develop new tools and models to advance candidates in the Pfizer biotherapeutics pipeline. Through those projects, innovative tools were developed that streamline production within existing plants and provide other cost-savings opportunities during the design of new plants.

As part of Bend Research's long-term collaboration with Pfizer, both companies worked on a joint campaign to design the Plant of the Future. The effort was aimed at reducing the capital investment required for new biotherapeutics production facilities by half and reducing conventional plant operating costs by two-thirds. Significant progress and innovations were jointly made toward those goals.

"Pfizer's partnership with Bend Research has focused on developing innovative new technologies in bioprocessing and integrated process analytics," explained John Ludwig, Vice President in BioTherapeutics Pharmaceutical Sciences for Pfizer Worldwide Research and Development. "We are pleased these technologies are supporting advancement of our biotherapeutics and vaccines portfolio."

PharmaForm Announces Manufacturing Agreement

PharmaForm recently announced that Corcept Therapeutics Inc. has chosen them as their primary commercial manufacturer for their newly approved drug product, Korlym. The US FDA approved Corcept's Korlym in February 2012 for patients with endogenous Cushing's syndrome. PharmaForm has worked with Corcept for several years as a contract provider for services in the development, optimization, and validation of the manufacturing process for Corcept's Korlym.

PharmaForm, a wholly owned subsidiary of Akela Pharma, Inc., is a leading specialty contract manufacturer for preclinical, clinical, and commercial products. PharmaForm specializes in the area of pharmaceutical dosage form development, controlled-release, and bioavailability-enhancement technologies, such as hot-melt extrusion, spray-drying, fluid bed processing, and liquid-filled capsules.

PharmaForm's expertise along with its ability to handle certain class potent compounds places PharmaForm as a leader in the field of specialty pharmaceutical dosage formulation and GMP manufacturing. Through its diverse offerings, PharmaForm's solutions help pharmaceutical and biotechnology clients reach their drug development targets, reduce development costs, and accelerate time-to-market for their products.

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Marinomed's Nasal Spray Achieves Positive Clinical Results

Marinomed Biotechnologie GmbH, recently announced that data from a clinical trial for the company's iota-carrageenan nasal spray was presented at the 14th International Symposium on Respiratory Viral Infections (ISRVI) in Istanbul, Turkey. The nasal spray, which contains extracts from red seaweed, proved to be a safe and effective treatment for patients with early symptoms of common cold. The study was conducted by the Medical University of Vienna (MUV), Austria, and was sponsored by Marinomed Biotechnologie. This clinical trial again confirmed the antiviral effectiveness of the company's iota-carrageenan nasal spray.

The study's aim was to investigate the effects of a nasal spray containing iota-carrageenan, a polymer derived from red seaweed that helps create a protective antiviral barrier in the nasal cavity. A total of 203 subjects who had experienced the onset of cold symptoms within 48 hours of the study were administered either a placebo saline nasal spray or iota-carrageenan nasal spray, 3 times a day for a period of 7 days. By keeping track of the symptoms associated with common cold and frequently analyzing nasal lavages for viruses or biomarkers, researchers were able to show that iota-carrageenan nasal spray successfully reduced the viral load in nasal secretions and mediated a reduction of disease duration by about 2 days in virus-infected patients.

"These results show that the statement, a cold comes 3 days, stays 3 days, and leaves 3 days, is finally outdated. By reducing the duration of the disease, iota-carrageenan-containing nasal spray is able to increase the quality of life for numerous people concerned and affected by the high incidence of this illness every year," said Dr. Andreas Grassauer, CEO of Marinomed.

MUV's Dr. Martin Ludwig presented detailed data from the study in a talk titled Carrageenan Nasal Spray Against Common Cold, a Double Blind Placebo Controlled Prospective Trial.

Marinomed Biotechnologie GmbH was founded in 2006 and develops therapies against respiratory diseases based on an innovative antiviral respiratory technology platform. The usability of this safe and effective technology has been proven by its first marketed product, an antiviral nasal spray. The huge potential of the technology is reflected by Marinomed's additional products concentrating on influenza, combination products for asthmatics, and other high-risk patients. In addition, the company develops a novel treatment against type I allergy and autoimmune diseases. Marinomed Biotechnologie GmbH is a spin-off from the Veterinary University Vienna and is located in Vienna.

FDA Clears Expanded Compatibility for Ikaria's Delivery Systems

Ikaria, Inc., recently announced that the Center for Devices and Radiological Health (CDRH) branch of the US FDA has granted 510(k) clearance for compatibility of its INOMAX drug delivery systems with three additional respiratory care devices. The INOMAX DS and the INOMAX DSIR have now been validated with nearly 60 makes of ventilators, anesthesia systems, and other respiratory care devices.

The INOMAX DS and INOMAX DSIR are proprietary drug delivery systems that deliver INOMAX (nitric oxide) for inhalation, the only drug approved by the FDA to treat hypoxic respiratory failure (HRF) associated with pulmonary hypertension in term and near-term infants greater than 34 weeks gestational age. HRF is a serious condition in which blood vessels in the lungs constrict, making it difficult to oxygenate blood. INOMAX selectively relaxes pulmonary blood vessels, improves oxygenation, and treats HRF in this fragile newborn population.

The FDA's clearance of these additional respiratory care devices for use with the INOMAX DS and INOMAX DSIR makes Ikaria's INOMAX drug delivery systems fully compatible with the most commonly used invasive mechanical ventilation methods and non-invasive respiratory strategies in neonatal intensive care units (NICUs), including continuous positive airway pressure (CPAP) and nasal cannulae. This represents Ikaria's ongoing commitment to meet the needs of its customers by providing clinicians with the flexibility to safely deliver INOMAX to critically ill patients using many ventilation strategies.

The INOMAX drug delivery systems are now compatible with the Fisher & Paykel Healthcare Bubble CPAP System and the Hamilton-C2 and Hamilton-G5 ventilators.

The INOMAX DS and INOMAX DSIR drug delivery systems are part of a comprehensive offering known as the INOMAX therapy package. In addition to use of Ikaria's proprietary, FDA-cleared drug delivery systems, the INOMAX therapy package includes INOMAX (nitric oxide) for inhalation, distribution, emergency delivery, technical and clinical assistance, quality maintenance, on-site hospital training, 24/7/365 customer service, and all related disposable items.

Nektar Therapeutics Moving 30 Research Jobs

Nektar Therapeutics recently announced it is consolidating its US-based research scientists at the company's existing San Francisco state-of-the-art R&D center, which is located adjacent to the UCSF research and medical campus in Mission Bay. With the consolidation, research scientists from Nektar's Huntsville, AL, research site will be relocating to San Francisco. Nektar's San Francisco R&D Center at Mission Bay opened in November 2010 and includes 102,000 square feet of biology and chemistry lab space, as well as Nektar's corporate headquarters. Under a 10-year sublease with Pfizer signed in March 2010, Nektar received free rent through July of 2014 for the newly constructed biopharmaceutical lab space.

"Bringing our highly productive US research team together in San Francisco will greatly increase our efficiency and further enhance critical interaction between research, clinical, and product strategy teams as we continue to generate new drug candidates," said Howard W. Robin, President and Chief Executive Officer of Nektar Therapeutics. "Nektar's R&D Center in Mission Bay is located in the heart of a growing hub of leading biopharmaceutical companies and surrounded by world-renowned scientific research institutes and medical facilities."

Nektar will continue to operate its 105,000-square-foot manufacturing and process development facility in Huntsville that manufactures proprietary PEGylation compounds for its own clinical pipeline, as well as Nektar's pharmaceutical partners. The facility supplies polymers for UCB's Cimzia, Roche's PEGASYS, Pfizer's SOMAVERT, Amgen's NEULASTA, and Affymax's peginesatide, among others.

Particle Sciences & Pernix Therapeutics Enter Development Agreement

Particle Sciences, Inc. recently announced it is developing with Pernix Therapeutics a new topical dermatology product for the pediatric market.

“There are multiple treatments for many pediatric skin conditions,” said Mark Mitchnick, CEO of Particle Sciences. “The unmet need is in the delivery of these agents via a more convenient, and improved vehicle. Particle Sciences is applying advanced drug delivery and formulation technologies to an established pediatric product category. For parents, this product is designed to be a potentially better and easier-to-use product.”

“We are enthusiastic about working with Particle Sciences for this product candidate, which may be another opportunity to further expand our pediatric product line,” added Cooper Collins, Pernix Therapeutics’ President and CEO.

Particle Sciences is an integrated provider of drug development services focusing on emulsions, gels, micro and nano-particulates, drug/device combination products and highly potent compounds across all dosage forms. Through a full range of formulation, analytic, and manufacturing services, Particle Sciences provides pharmaceutical companies with a complete and seamless development solution that minimizes the time and risk between discovery and the clinic.

Bioniche Life Sciences Secures $20 Million

Bioniche Life Sciences Inc. recently announced it has accepted an offer of a $20 million financing from investment funds managed by US-based Capital Royalty L.P. Capital Royalty has agreed to provide a 5-year term loan to Bioniche Life Sciences Inc. to facilitate the company's corporate growth and support its capital requirements. The terms include a 15% interest rate, with a portion deferred and capitalized for the first 3 years of the term of the loan. An additional royalty interest of 2% will be paid to Capital Royalty on all product sales revenues for the term of the loan. Principal repayments of eight equal installments begin in June, 2015. The transaction is expected to close April 2012.

"We are very pleased that Capital Royalty has expressed its confidence in the company through this strategic investment," said Mr. Graeme McRae, Chairman, President, and CEO of Bioniche Life Sciences Inc. "Through the due diligence process, Capital Royalty has demonstrated an excellent understanding of our business and commercialization program. It is particularly gratifying to be able to receive such an investment with no dilution of our equity shareholders."

"We welcome the opportunity to develop and fund customized financing structures for innovative life science companies like Bioniche," said Charles Tate, Chairman & Founder of Capital Royalty L.P. "The company has a diverse base of existing revenue in addition to exciting opportunities for future growth."

Bioniche Life Sciences Inc. is a research-based, technology-driven Canadian biopharmaceutical company focused on the discovery, development, manufacturing, and marketing of proprietary and innovative products for human and animal health markets worldwide. The fully integrated company employs more than 200 skilled personnel and has three operating divisions: Human Health, Animal Health, and Food Safety. The company's primary goal is to develop and commercialize products that advance human or animal health and increase shareholder value.

ThromboGenics Enters Commercialization Agreement With Alcon

ThromboGenics NV recently announced it has entered into an agreement with Alcon (a division of Novartis), the global leader in eye care, for the commercialization of ocriplasmin in all markets outside the US. As a result of this important strategic deal, ThromboGenics will concentrate on commercializing ocriplasmin in the US, where it plans to build its commercial and medical organization to support the product's anticipated launch within the next 12 months.

Under the terms of the agreement with Alcon, ThromboGenics will receive an up-front payment of $98 million. The company is also entitled to a further $118 million in potential near-term milestone payments. Additional milestones bring the potential total of up-fronts and milestones to $491 million.

In addition, ThromboGenics will receive royalties on net sales of ocriplasmin that are commensurate with a product that has successfully completed Phase III development and that has been filed for regulatory approval.

Under the agreement, ThromboGenics will have a strategic and focused operational role in the commercialization of ocriplasmin in the five largest European markets, enabling it to build the foundation for an expanding ophthalmology franchise.

In addition to the commercial introduction of ocriplasmin in markets outside the US, the agreement specifies that Alcon and ThromboGenics will work together, and share the costs, to further develop new clinical applications of the product that the companies will introduce in their respective territories.

ThromboGenics has completed an extensive clinical development program, including two successful Phase III studies that have shown that ocriplasmin could play an important role in treating symptomatic VMA, including macular hole. Symptomatic VMA is an increasingly recognized sight-threatening disease of the vitreoretinal interface. VMA may lead to symptoms such as distorted vision, decreased visual acuity, and central visual field defects. VMA can cause traction resulting in anatomical damage, including formation of a macular hole, which may lead to severe visual consequences and central blindness.

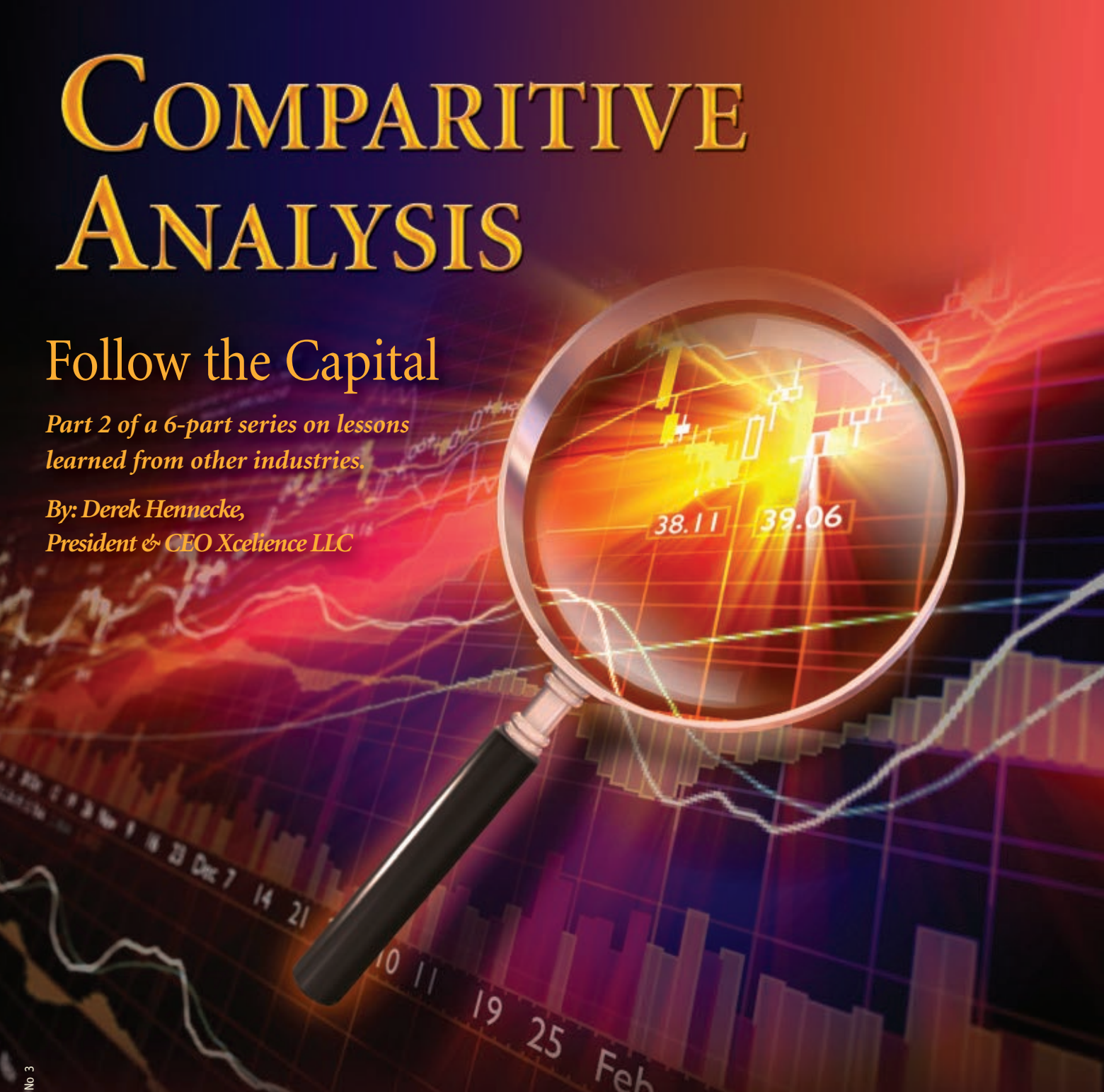
Members of the international retina community have already shown great interest in ocriplasmin, as it could for the first time provide them with a pharmacological option to treat patients with symptomatic VMA, including macular hole. The availability of ocriplasmin may also enable retina specialists to treat patients earlier than they do with surgery. This could address a significant unmet need as earlier intervention has been shown to limit the progress of the disease and its related complications. ThromboGenics is confident that ocriplasmin has significant commercial potential, given estimates that more than 300,000 patients in Europe alone could potentially benefit from this novel treatment.

Comparitive Analysis

Follow the Capital

Part 2 of a 6-part series on lessons learned from other industries.

By: Derek Hennecke, President & CEO Xcelience LLC



When IBM CEO Sam Palmisano stepped down at the end of last year, legendary investor Warren Buffett lamented the loss of a man he said had, "delivered big-time." His words were hardly idle praise - Buffet recently announced that his company, Berkshire Hathaway, owns $10.7 billion in IBM stock, making it IBM's largest shareholder at 5.4%.

Mr. Palmisano is credited with many attributes, but the one that stands out in my mind is his knack for execution. You'd be surprised how many CEOs get to where they are without becoming adept with money. Too many corporate chiefs will throw huge sums of money at acquisitions in an effort to pump up earnings per share. Think Sears purchase of Kmart, Mercedes Benz buying Chrysler, or AOL buying Time Warner.

Mr. Palmisano was all about the capital. He took capital out of businesses that didn't produce, and put it into businesses that did. I can only imagine the board room discussion when he decided to sell IBMs money-losing hard drives business to Hitachi. Hard drives had been a part of the lifeblood of this once great hardware company. But hard drives had become a commodity; a good bought and sold on price with little differentiation. He said he would rather buy a commodity than to sell one. In fact, through more

than a hundred similar transactions, he completely reprogrammed the legendary hardware maker, reinventing IBM as a key provider in the lucrative businesses of software and services.

A FLOOD OF VENTURE CAPITAL INVESTMENT IN R&D

I've been thinking about Mr. Palmisano a great deal of late as I watch a different kind of re-programming taking place in our own industry. There is no CEO overseeing this change. It's being led by venture capitalists who know better than anyone how to follow the capital. I'm talking about a shift of capital from late-stage development back into R&D.

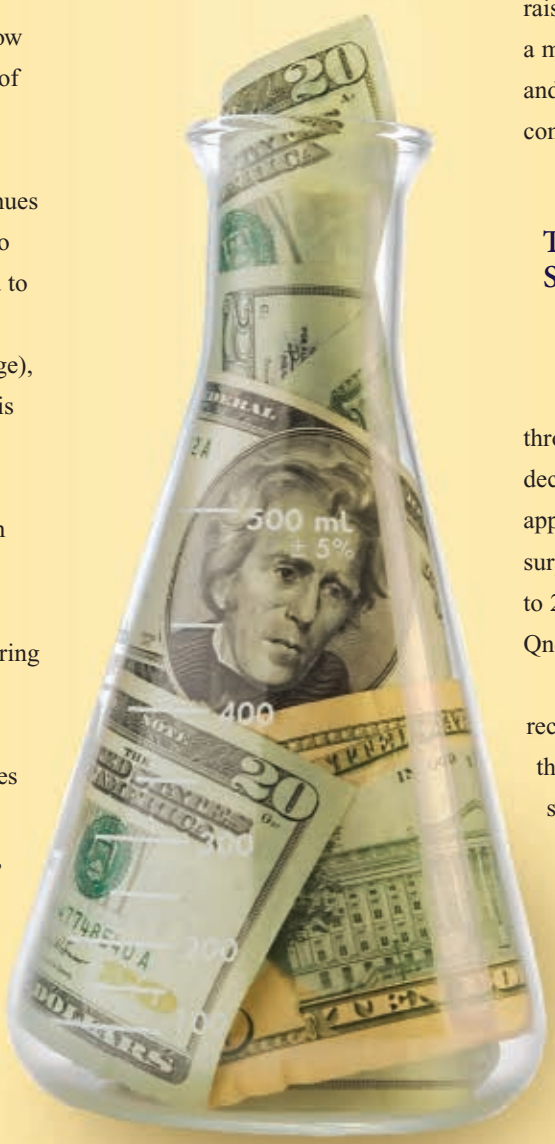
While large-scale pharma continues to neglect early stage development, to invest in late-stage development, and to layoff and cutback throughout the industry (see side bar on the next page), venture capital knows that Phase III is tapped out. Every penny has been squeezed from it in the recessionary years. The higher returns today are in Series A investments, and venture capital has quietly but confidently opened the spigot, and money is pouring into R&D.

The fourth quarter of 2011 witnessed the largest number of Series A financings in 15 quarters of data tracking by OnBioVC trend analysis, including 37 first-time institutional financings, which raised $483.4 million. The total amount of investment quadrupled investment in the same quarter of 2010.

This expansion is nothing short of stunning, and was experienced in every region except the southwest. The largest infusion of cash went to the west, with a total of $561.2 million in fourth quarter investment, more than double the previous year's $268 million.

But something really exciting is brewing in the northeast, where investment exploded from $153.5 million in the last quarter of 2010 to $528.3 million in the same quarter of 2011. The northeast, now only $30 million behind the west, is nipping at California's status as the biotech hub.

Nevermind what's going on in Europe: All the investment in biotech outside of the US only totaled $349 million in the fourth quarter. Sure, that's up from $224 million the previous year, but even when you pool it all together, all the investment that's going on in the rest of the world doesn't even come close to what's going on just in the northeast, much less California. We live, without question, in the most exciting center of biotech in the world, and that reality shows no sign of abating anytime soon.



Any way you slice it, biotech will begin to feel the action. Even compared to other industries. Overall, biotechs raised $3.5 billion last year, compared to a mere $1.9 billion for device makers and a paltry $482 for diagnostic companies.

THE WIND IN BIOTECH'S SAILS: UNEXPECTED FDA APPROVALS

Are the winds of change sweeping through the FDA? For more than a decade, not a single diet drug has been approved by the FDA. Then, in a surprise move, an FDA panel voted 20 to 2 in favor of recommending the Qnexa diet pill developed by Vivus.

Some are saying the recommendation for approval is a sign the FDA is trying to relax its stringent standards. Balancing safety concerns against medicinal benefits is a tough act, and many have argued the pendulum has been on the side of caution for some time.

The recommendation and likely approval means the FDA will give the go-ahead to the drug despite significant concerns. Qnexa contains phentermine, which is half of

the now rejected fen-phen cocktail, and topiramate, the active ingredient in the Topamax seizure med. FDA reviewers have shown concern about cardiovascular and teratogenic risks - specifically, cleft palates, which led the agency to reject the drug in 2010. Perhaps the FDA recognized the benefits of a drug that showed a remarkable 10% weight loss in clinical trials, and decided the benefits outweighed the risks. After all, obesity is, in and of itself, a risk for numerous health complications.

The FDA vote is encouragement for Arena Pharmaceuticals, which hopes to sell its Lorcess pill, and Orexigen Therapeutics, which seeks FDA approval for Contrave.

The FDA's new attitude was also witnessed by Chelsea Pharmaceuticals in seeking approval for Northera, a drug for treating neurogenic orthostatic hypertension - a rare disorder that causes a sudden drop in blood pressure when someone stands after lying down.

The agency initially released a review pointing out several safety concerns for the drug, and spooking investors who assumed an imminent non-approval. Shortly thereafter, in a courtroom drama worthy of Perry Mason, Mr. Bob Temple, the Director of the FDA's Office of Drug Evaluation 1, made an unexpected appearance at a panel meeting and persuasively disagreed with the agency's own reviewers about some central points. The outcome was a reversal of fortunes, and the expectation now, judging from a 66% increase in the stock price, is that the recommendation from the PDUFA will be favorable.

THE RISING COST OF LOW QUALITY

While the outcomes of an FDA approval can be hard to predict, sometimes drugmakers make decisions knowing full well the FDA won't like them, such as when a company chooses to reduce quality to save money and consciously accepts the risks of an FDA fine. Until recently, the worst that company could expect was a fine. But the costs for lower quality could become much, much higher in the near future.

A group of patients whose medication ran out are suing the US Department of Health and Human Services, the FDA, and the National Institutes of Health, saying the federal government has a duty to take adequate enforcement actions against the drugmakers who failed to maintain their supply, and to allow for alternative means to protect supplies.

The patients contend the drug companies in question should have their FDA licenses invalidated and their patents declared unenforceable. Essentially, the company's intellectual property would be forfeit. Further, they expect the government to assume responsibility for protecting the flow of drugs and to enter into contract manufacturing to maintain availability, in the way that the HHS does for pandemic flu vaccines.

The drug companies at the heart of the issue are Genzyme, which produces Fabrazyme to treat Fabry disease, a rare life-threatening genetic disease, and Hospira, which produces Aquasol A to treat vitamin A deficiency. Aquasol A is often taken by Fabry pateints. Both companies have suffered several long-term manufacturing problems.

While these two companies are taking the heat for the shortages, many more companies could be affected by any

SIDEBAR

Industry Outlook: Big Pharma Job Worries

Big Pharma may be excused for failing to bubble over with enthusiasm for biotech's recent good fortune. In fact, 44% of big pharma employees said they feared for their jobs over the next 12 months, according to a poll by Pharma IQ of 535 industry employees conducted in the last weeks of 2011. This less-than-rosy outlook was in fact gleaned in better times, prior to the 4,071 pharma layoffs in January, and before word spread that AstraZeneca will be cutting thousands more jobs. Big pharma had the third highest rate of layoffs in the US in January, trailing retail and the financial sector. Survey respondents generally agreed that the R&D preclinical sector was hardest hit by the recession. Some pharma companies proved significantly better than others at managing their R&D budget. Amgen proved the most adapt with an R&D spend of $33.2 billion on nine drugs for a total of $3.7 billion per drug adjusted for inflation, according to a recent article in Forbes Magazine, using data from InnoThink Center for Research In Biomedical Innovation and Thomson Reuters Fundamentals via FactSet Research Systems. AstraZeneca during the same period spent $59 billion on R&D, earning five FDA approvals for a total of $11.8 billion per approval.

resulting policy changes. The US is struggling with shortages of hundreds of other medications, including life-saving cancer drugs and drugs to treat children with attention deficit hyperactivity. Congressional hearings and legislative efforts have been launched to bolster FDA authority and give the agency more teeth.

The FDA finds itself in a most uncomfortable squeeze. On the one side, it's under pressure to crack down on manufacturing violations since the Heparin safety scandal. On the other, drug makers say the increased agency scrutiny has in itself contributed to the shortages. Still, others say the true cause of the shortages is not the FDA, but lack of profitability. If a drug fails to contribute to the bottom line, drug makers have little incentive to try to maintain supply and quality; yet patients still need it.

One way or another, high quality has to be maintained across the industry. Industry has to accomplish this without radically increasing the scope of government in our industry, particularly in the area of manufacturing. While I respect the FDA's role in maintaining supply and quality, the idea of the government entering into manufacturing in the way that it has entered into mortgages and insurance strikes me as a frightening and radically industry-changing prospect. It is up to us.

AND NOW FOR SOMETHING COMPLETELY DIFFERENT.....

What if the FDA just tested drugs for safety? What if it skipped the Phase II and III efficacy studies, unleashing the drugs on the market untested, and relying on post-market studies to determine whether or not the drugs actually do what they're supposed to do? This is an idea being proposed by former FDA commissioner Andy von Eschenbach in an editorial in The Wall Street Journal. Mr. von Eschenbach proposes a pilot program in which patients would be entered in registries, and the FDA and drug makers would later decide if the medicine was working as intended.

"Take regenerative medicine," Mr. von Eschenbach writes. "If a company can grow cells that repair the retina in a lab, patients who've been blinded by macular degeneration shouldn't have to wait years while the FDA asks the company to complete laborious clinical trials proving efficacy. Instead, after proof-of-concept and safety testing, the product could be approved for marketing with every eligible patient entered in a registry so the company and the FDA can establish efficacy through post-market studies."

As appealing as it is to get certain drugs out there faster, what he is suggesting amounts to a return to the snake oil days. Any company could produce any drug, prove concept, safety, and get it out on the market. As long as it's safe, they can sell it. By dumping double-blind randomized clinical trials and relying instead on epidemiological studies, we could never neutralize the placebo affect. Then, once those cash registers start ringing, companies would be incentivized to drag their heels as long as they possible to avoid having to publicly accept the fact that a given drug doesn't work.

The healthcare lawyers must be salivating over this one. Consider the group of patients we just discussed who are suing because of supply shortages. What would that same group do if they had treated a condition (for the sake of argument, le's make it a life-threatening one) spent thousands of dollars, and then discovered they or their loved one had foregone other forms of treatment in favor of a medication that proved no more effective than a Skittle? That leaves a sour taste in my mouth. ◆

BIOGRAPHY

Derek G. Hennecke is a Founding Member, CEO, and President of Xcelience. He has a long history of growing strong businesses around the world. Blending a scientific and business background, he has nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner, having launched a management buy-out from MDS Pharma Services in 2006. The newly-formed company immediately embarked on a robust pattern of growth. Before founding Xcelience, Mr. Hennecke spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250-staff Biologics plant for more than 2 years. In Cairo, Egypt, as GM, he oversaw a turn-around in an anti-infectives plant that had been slated for closure. He spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke has a BSc in Microbiology from the University of Alberta and an MBA from the Erasmus University in The Netherlands.

Marketing Matters

Current Outlook on Marketing & Economics

A multiple part series on effective messaging and communications in the life science industry.

By: David F. Scelba, Partner, LifeSciencePR

Drug Development & Delivery asked me to write this column because they believe many of its readers who are running and working in small to mid-size companies would find it very insightful, just like the annual positive response the publication receives from its Attorney Review and External Delivery columns. After all, these companies have to deal with business, legal, and marketing and communication matters just like their big brothers, no? In addition, it's certainly in my opinion a nice little break from living and breathing pharmaceutical science every day.

If you're a marketing or communications professional, especially in the life science industry, you're facing new budgetary challenges each and every day. Senior management can't prepare strategic plans and are afraid to invest back into the businesses simply because they have no idea what's going to happen next. In fact, every time we think things can't get any worse, we're proven wrong, because they do.

For the purposes of this column, we will briefly discuss strategic investment in an integrated Public Relations and Social Media strategy that can reach virtually millions of people 24/7/365. As a complement to your existing advertising initiatives, an integrated PR and Social Media program will produce additional effective and economical avenues to brand your emerging innovations, technologies, and services, and if the content is well-developed and engaging, will educate your targeted audience in a two-way interactive communication.

Many life science companies have already recognized the need to start participating in the social media phenomenon; however, too many are still just making a token effort and aren't truly committed to this communication tactic. Without a coordinated and comprehensive strategy, the execution and implementation is typically amateurish at best and can have a negative effect on a company's reputation.

Even in these difficult and fragile economic times, life science companies must continue to communicate with their potential investors and development partners to proactively drive their message. And with budgets being slashed to the bare bone, they can't afford to make even the smallest marketing and communication mistake.

I don't know anyone who isn't facing this economic dilemma and being forced to produce more with much less. But while you may have no control over this budgetary situation, you do have control over your marketing and communication strategies and tactics. Even with a total annual budget of only $50,000 you can still implement a program that effectively and efficiently communicates with your existing partners/customers, promotes to new sales prospects, maintains your brand and message, and generates measurable ROI reports.

Don't make a mistake and dilute your precious marketing and communication investment. Speak to a PR professional about developing a coordinated and comprehensive public relations and social media strategy.

If you do, I'm confident you'll weather this economic storm we're all experiencing and be way ahead of your competition when the sun starts shining again. ◆

BIOGRAPHY

David F. Scelba is Founder and Chairman of SGW Integrated Marketing & Communications and presides over the Board of Directors of LifeSciencePR, responsible for the development of new products and services. He is also involved in researching and investigating all acquisition opportunities and for initiating all negotiations on behalf of the company. He is directly responsible for the day-to-day management of the accounting, financial, legal, Web, IT, Co-op, and fulfillment departments, and plays a key role as senior strategist in the development of clients' interactive integrated marketing communications programs. His diversified B2B, consumer, and retail experience encompasses industries such as: automotive; biochemical; broadcast; education (K-12-colleges/universities); healthcare; hospitals; microwave; pharmaceutical (research/drug delivery); political; professional video/audio; medical; telecommunications; and many more. David develops and maintains relationships at the business, corporate, community, county, and state levels, and frequently speaks on the subject of utilizing technologically innovative tools to implement integrated marketing communications strategies. He earned his BA and MA in Education.

Scaling Up a Pharmaceutical Film-Coating Process

By: Thorsten Cech and Maureen Mistry

Film-coating is a well-established process in the pharmaceutical industry. Though processing experience is abundant in this field, the difference in batch size and process parameters of the different equipment increases the variables that make the scale-up procedure complex. The typical challenge is to expose the cores to the same amount of humidity and temperature at all scales. This ensures the results obtained in stability testing for products produced in one scale would apply for the same product in another scale.

The aim of this work was to develop a scale-up strategy, which is easy to apply and independent of difficult mathematical and thermodynamic calculations. The procedure works with a wide range of drum-coating equipment (eg, side-vented pan coaters and solid wall coaters among others) as well as functional or non-functional coatings. Finally, an easy-to-use method is suggested that takes into consideration the relationship between inlet air quantity and spray rate. It will be shown that the inlet air quantity, because of its velocity, has a significant impact on the drying of the tablets throughout the coating process by influencing the thermodynamic heat transfer coefficient. Furthermore, ascertaining the fastest applicable spray rate, in ratio to the inlet air quantity, is the ideal starting point for scale-up considerations.

PHYSICAL BACKGROUND

Drying of the cores is a critical step in film coating. As a basic requirement for stability test results, the moisture exposure of the cores should be the same in all scales. This is especially relevant when considering moisture-sensitive active pharmaceutical ingredients (APIs). For the same reason, thermolabile APIs need to have the same energy exposures at different scales; energy flux is the parameter by which all up-scaling considerations are based.

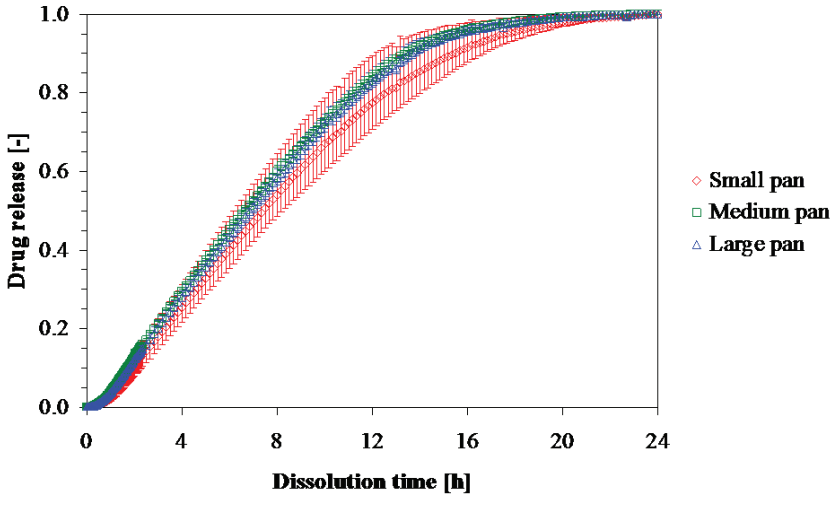
The Coating Pan as a Thermodynamic System

The coating pan can be regarded as a thermodynamic system. During the steady state of the film-coating process, there is no change in the amount of energy in the process as the energy brought in by the inlet air and film-coating dispersion is equal to the energy content of the exhaust air. Most importantly, the energy delivered by the dispersion distinctively influences the coating processes.[1]

The General Drying Process

In the coating process, the evaporation of the liquid is a rate-limiting step. In an

FIGURE 1



Dissolution profiles of the round-shaped tablets coated in different scales.

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TABLE 1

Trial	No. of Nozzles	Batch Size [kg]	Inlet Air Quantity [m3/h]	Inlet Air Temperature [°C]	Spray Rate [g/min]
1	4	136	3,500	65	400
2	3	136	2,625	65	300
3	3	75	2,625	65	300
4	2	75	1,750	65	200
5	2	35	1,750	65	200

Tested parameters at constant spray rate per nozzle and pan speed.

ideal set-up, the cores are sprayed in the upper third of the tablet bed, where their speed is highest. Before they immerse again at the lower end of the tablet bed, they should be completely dry to prevent defects. One can only spray as fast as the cores can dry, which depends on the efficiency of the drying process.

The Drying of the Dispersion on the Core Surface

Another aspect, which is directly attributed to the drying process, is the heat transmission on the core surface. As the heat is transferred by the fluid, the general equation of convection applies. The equation explains that the quantity of heat is directly proportional to the surface area and the temperature gradient. Furthermore, heat transmission rate depends on the heat transfer coefficient (α).[2] The heat transfer coefficient is a performance indicator describing the efficiency of the drying process. It is influenced by process air velocity because higher air flow leads to a higher amount of energy available for utilization. For this reason, higher inlet air volumes result in better drying conditions even when the relative exhaust air humidity is at low levels.[3]

THEORETICAL CONSIDERATIONS

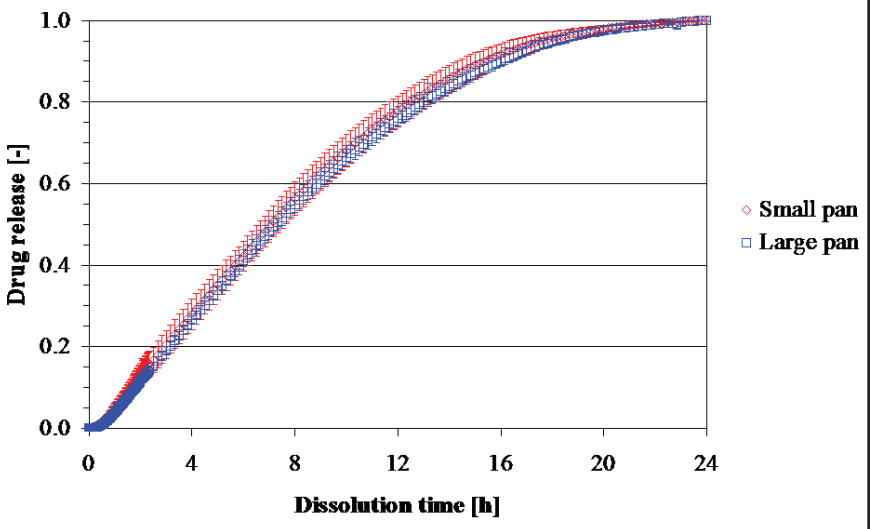
Influence of the Air Quantity on the Drying Efficiency

Increasing the air volume leads to a higher air velocity, and this influences the heat transfer coefficient (α) and supports the drying process. Therefore, the contribution of elevated air quantities to the drying efficiency is minimal.

Influence of the Spray Rate on the Coating Efficiency

Over wetting should be minimized or avoided completely to ensure an optimally coated tablet surface. Coating with a fast spray rate is often responsible for over wetting. During coating, when the tablet passes the spray pattern, it takes up the film-coating dispersion, the amount of which depends on the spray rate and the speed of the tablet. Over wetting results when the liquid carrier on the core surface does not evaporate before the core re-immerses into the core bed. It should be noted that the quantity of coating dispersion that can be applied on the surface depends on the product (formulation of core and dispersion), the inlet air temperature, and the air velocity (inlet air quantity). The amount of dispersion applied onto a single core when it passes the spray pattern can be calculated. To achieve this, one needs to know the tablet's velocity on the surface of the core

FIGURE 2



Dissolution profiles of the oblong-shaped tablets coated in different scales.

bed. As this is difficult to measure, an easier approach is to use the drum speed as an indicator of the tablet speed. By keeping the circumferential speed of the drum constant, identical tablet speeds can be achieved in all scales.[4] Additionally, using the same type of nozzle and nozzle to core bed distance in all batches ensures scale ups can be performed easily. In summary, the coating result in pilot and production scale is the same when (1) the circumferential speed of the drum is constant; (2) the spray rate of a single nozzle is constant; and (3) the ratio of process air and spray rate is constant.

PRACTICAL APPROACH

Instant Release Coating in Perforated Drum Coater

In contrast to other types of equipment, the position of the shark fin baffles on the perforated wall of the Perfima 200 (IMA S.p.A., Bologna, Italy) allows for variations in batch size, using the same drum coater. This means a tablet batch from 35 to 136 kg can be coated in the same coater without changing the drum. Given the same drum size and a constant circumferential speed, it can be assumed the tablet speed in the spray pattern is constant and independent of the batch size. Therefore, the same drum speed can be used in all trials. The number of nozzles however should be adapted to the drum and batch size. Because the drying efficiency depends on the ratio between overall spray rate and amount of process air, for our trials, we kept the inlet air quantity per nozzle constant (Table 1).[3] To show this criterion can be used in up-scaling of film-coating processes, the trials were started using the optimal coating conditions (short and robust process) in large scale.

TABLE 2

Number of Nozzles	Batch Size [kg]	Spray Rate [g/min]	Inlet Air Quantity [m³/h]	Process Time [minutes]
2	35	200	1,750	31
2	75	200	1,750	66
3	75	300	2,625	44
3	136	300	2,625	79
4	136	400	3,500	60

Scale-up process calculated on 3.5% weight gain using a constant drum speed.

For the batch size of 136 kg, an optimal inlet air quantity of 875 m³/h per nozzle (overall 3,500 m³/h with four nozzles) and a spray rate of 100 g/minute per nozzle (overall 400 g/minute). Reducing the batch size and the number of assembled nozzles, the trials shown in Table 1 were conducted. The coated cores were visually appraised and were the same for all batches. Over wetting was not observed. In addition, parameters like exhaust air humidity showed comparable values.[3] With the results of the aforementioned trials, the following scale-up scheme for the Perfima 200 was developed. Kollicoat® Protect formulation was the dispersion used (Table 2).

As a first step in scale-up processes, it is recommended that the shortest process time (highest applicable spray rate per nozzle) in lab scale be determined. After which further scale up steps can be easily calculated.

In pilot scale, the process time was made short to simulate the final coating process in production scale, and though a homogeneous coating might not be achieved within such a short time, nevertheless, for scale-up purposes, the shortest process time (ie, fastest possible spray rate with sufficient drying) is of interest, irrespective of the homogeneity of the applied coating.

As the coating quality depends more on the dwell time of the core in the spray pattern than on the batch size, the scale-up approach detailed in this article should be applicable for all scale-up processes using the same type of technology (eg, side vented coating technology with completely perforated pan).3

Instant Release Coating in Small & Large Perforated & Solid Wall Drum Coaters

The maximum spray rates in small scale for both types of equipment (perforated drum

TABLE 3

	Optimal Settings Perfima Lab	Calculated Settings Perfima 200	Optimal Settings GS HP 25	Calculated Settings GS 300
Batch size	40 kg	140 kg	22 kg	202 kg
Number of nozzles	2	4	1	4
Drum speed	7 rpm	5 rpm	8 rpm	4 rpm
Circumferential speed	361 mm/s	349 mm/s	335 mm/s	329 mm/s
Inlet air temperature	50°C	50°C	60°C	60°C
Inlet air quantity	1,060 m³/h	2,120 m³/h	350 m³/h	1,400 m³/h
Maximum spray rate	150 g/min	300 g/min	48 g/min	192 g/min

Settings for the side-vented and solid wall pan coating processes.

coater Perfima Lab and solid wall drum coater GS HP 25) were determined to be used for the scale-up approach. One of the important factors in finding the maximum spray rate is the surface quality of the coated core, which requires visual inspection of the coated cores while gradually increasing the spray rate. The obvious sign of surface roughness is taken to suggest that the maximum spray rate has been exceeded, due to increased pump speed. As was noted, the highest applicable spray rate was established. Based on the results, the coating parameters for large scale were calculated.

SIDE-VENTED PAN COATER: The process settings for the large-scale coating process in the Perfima 200 were determined according to the theoretical scale-up approach (Table 3). Independent of the batch size and the type of coater, a smooth and shiny surface was achieved. The coating processes for both scale-up batches were comparable with regard to moisture exposure to the cores during the coating process. The drying efficiency was kept in a similar range by only adjusting the inlet air quantity in large scale without changing the inlet air temperature. From the product quality point of view, the resulting cores appeared the same with regard to their stability toward moisture and temperature.

SOLID WALL COATER: For these trials, oblong-shaped caffeine tablets were used. The process settings for the GS HP 25 lab-scale coater were determined as already described for the side-vented pan coater. The process settings for the GS 300 were determined based on these values (Table 3).

TABLE 4

	Round			Oblong	
	Small	Medium	Large	Small	Large
Batch size	10.9 kg	21.8 kg	43.7 kg	10.1 kg	40.3 kg
Inlet air volume	600 [m^3/h]	600 [m^3/h]	1,200 [m^3/h]	530 [m^3/h]	1,060 [m^3/h]
No. of nozzles	1	1	2	1	2
Spray rate	39 mL/min	39 mL/min	77 mL/min	31 mL/min	62 mL/min

Coater settings for the different core types in the different drum sizes.

The difference in batch size in small- and large-scale was distinctively higher in these set of experiments, in contrast with the trials in the side-vented pan coating equipment (Perfima lab and Perfima 200). However, the determined parameters for the large-scale coating process in the IMA GS 300 coater could be adjusted. In both processes, the resulting tablets showed an equally smooth and shiny surface. Therefore, it can be suggested that both drying capacity and moisture exposure during the process were similar for both batches.

A characteristic feature of the Perfima coaters is the possibility to have high inlet air volumes. With these coaters, tablets are less susceptible to over wetting. In solid wall coaters, the air is exhausted via drying paddles located inside the core bed. As a result of this, the low air volumes used in the film-coating process increase the risk for over wetting especially during scale up. Our trials, however, showed this not to be the case. We concluded therefore that the determined parameters could be applied on the solid wall process, without over wetting.

Sustained Release Coating in Small & Large Perforated Drum Coater

Two core shapes were used for these set of experiments. As the tablet shape influences the bulk density, the batch size was determined by volume. In preliminary trials for both core types, the maximum spray rate for the equipment was determined. As expected, the oblong-shaped tablets could be coated with a distinctively lower spray rate. For these trials, the settings for spray rate and inlet air quantity could be calculated (Table 4).

The chosen parameters led to an optimal coating process in all batches. All film-coated tablets had a smooth surface. The dissolution data suggests that in addition to the coating quality, coating functionality was maintained for both tablet types throughout the scale ups. All coating trials led to similar dissolution characteristics (Figures 1 and 2).

In lab scale, the fastest possible process time was used to determine the maximum spray rate in large scale, which led to a less-homogenous distribution of the coat on the surface of the cores. As a result, the standard deviation for the release profiles of the round-shaped tablets in small scale was not amenable to large scale-up batch. During the scale-up process, both the batch size and total process time increased. The longer the process, the

more uniform the applied coat was. This resulted in release profiles showing lower standard deviation.

CONCLUSION

The ratio of spray rate to inlet air volume was a critical parameter for the surface quality irrespective of the batch size. As a result, the scale-up adjustments can easily be achieved by spray rate/inlet air volume ratio parameter. The process times in small scale have to be as short as possible to be comparable with large scale. The amount of film-coating dispersion applied on a single core is critical and must be considered when choosing the spray pattern.

This scale-up approach can be used for both side-vented as well as solid wall technology, and can be applied to thermolabile and moisture-sensitive formulations because the scale-up process ensures that moisture and temperature exposure of the cores are kept constant. The scale-up data also suggests that the instant release film-coating polymers can be transferred to functional coating polymers. However, it is necessary to determine the maximum spray rate in small scale as this is needed to calculate the spray rate and process air volume in large scale, while maintaining the same moisture exposure throughout the entire scale-up process.

ACKNOWLEDGEMENT

The authors would like to thank Dr. Florian Wildschek who was deeply involved in the development of the idea described in this article. In addition, we would like to thank IMA S.p.A. Active Division and in particular, Caterina Funaro, Giusi Mondelli, and Fiorenzo Cembali for their generous and great technical support during the practical part of this study. ◆

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BIOGRAPHIES

Thorsten Cech studied Process Technology at the University of Applied Sciences in Bingen, Germany. Before joining BASF, he worked for 15 years at different pharmaceutical companies, where he focused on the galenical development of solid oral dosage forms. Since 2005, he has headed the Pharma Application Lab at BASF Pharma Ingredients & Services Europe.

Maureen Mistry is a Technical Service Manager within the Technical Service team at BASF Pharma Ingredients and services Europe. She has more than 10 years of experience working with BASF's excipients and has worked for more than 20 years in the pharmaceutical and support industries. Ms. Mistry is responsible for technical service support for customers in the UK, Ireland, Scandinavia, The Netherlands, and sub-Saharan Africa.

Polymers for Solid Oral Dosage Forms

By: Robert Gwozdz, MPharm

INTRODUCTION

Polymers are used extensively in the development and manufacture of Solid Dosage Forms (SDFs) and serve many purposes. For Immediate Release (IR) SDFs, they are used as binders in order to increase the density, flowability, and compactibility of bulky Active Pharmaceutical Ingredients (APIs), which would otherwise not process acceptably on high-speed tablet presses and encapsulation machines. Polymers are used for non-functional (aesthetic) coatings to impart colors and favorable mouth feel to tablets without relying on the time-intensive and highly skill-based process of sugar coating, which was the only alternative prior to the advent of polymer-based coatings. Polymer-based functional coatings, such as those used for moisture or oxygen barriers, can nevertheless be formulated as IR dosage forms, still allowing quick release and absorption of the API. Cross-linked polymers that swell extensively in the presence of water and gastrointestinal fluids are used to promote disintegration of tablets and capsule plugs, and are available in commercially available powder forms designed to be readily compatible with tableting and encapsulation formulas and processes.

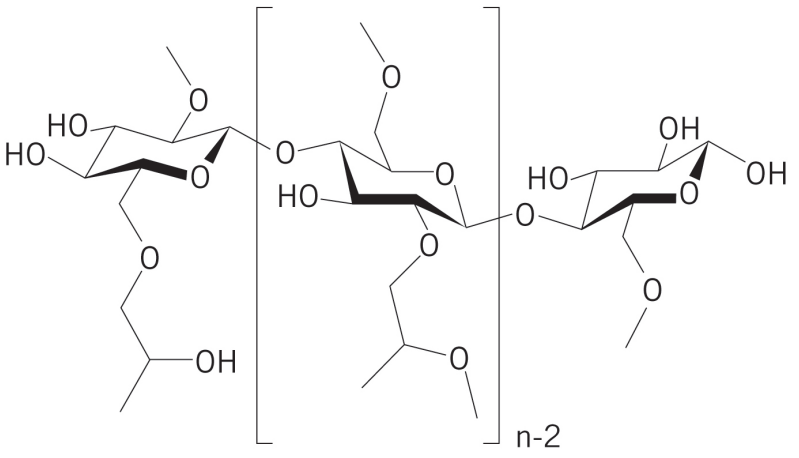
For Modified Release (MR) dosage forms, one use of polymers is for functional enteric coatings, which allow a dosage form to pass through the stomach without its internal contents being subjected to the harshly acidic and enzymatic conditions present there. This type of formulation is sometimes referred to as Delayed Release (DR). Other polymers are used for Controlled Release (CR) coatings or for CR diffusional matrices. Polymers can also be used to enhance the dissolution and bioavailability of the wide array of poorly soluble APIs that are the increasingly common products of current pharmaceutical discovery efforts. The following will present an overview of polymers used in the more exotic and technically challenging dosage forms involving MR (enteric and CR) as well as those used for enhancing the dissolution and bioavailability of poorly soluble APIs.

CONTROLLED RELEASE POLYMERS

One of the earliest distinct polymer systems for CR involved the use of hydroxypropyl methylcellulose (now officially called Hypromellose, Figure 1) for diffusional matrices. Earlier CR dosage forms were made using natural substances, such as shellac, waxes, or vegetable gums. The latter are technically polymeric in nature, but were, at least in earlier times, not well defined or well characterized. This presented challenges for reproducibility of release, although in that era, the standards for reproducibility were much less stringent than they are today. Hypromellose is available in a wide range of molecular weights (MWs) that can be

FIGURE 1

CHEMICAL STRUCTURE OF HYPROMELLOSE



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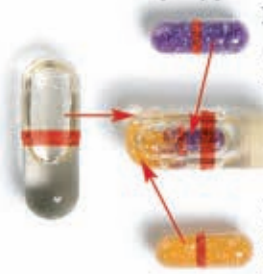
INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical, pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the company's multiphase multi-compartment delivery system used to enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.

"This is a significant development for INNERCAP Technologies NOVACAP technology," said Fred H. Miller, Chief Executive Officer at INNERCAP. "The continued growth of our patent portfolio establishes INNERCAP as one of the leading companies in this space."

The delivery system and combinations covered by the patent have the ability to deliver therapeutic entities that have never been combined previously and now can be administered together, via an oral, implanted, or suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This technology can therefore be used to enable capsule administration of compounds that are not normally administered as a combination product. The efficacy, safety, and side-effect profiles of drugs can be substantially improved using this delivery technology. It will also provide very significant quality-of-life improvements for patients and substantial economic savings for hard-pressed healthcare systems.

"INNERCAP's multi-phase, multi-compartment technology has been commercially manufactured and validated in several products, demonstrating that INNERCAP's delivery system creates real value to consumers and branded manufacturers," added Mr. Miller.

INNERCAP was represented by Cliff Davidson, Esq. of the patent firm Davidson, Davidson & Kappel, LLC (www.ddkpatent.com) based in New York City.

For more information contact us at the telephone number and email address below:

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used to modulate the rate of release. The higher MWs hydrate more slowly, and thus prolong release. Hypromellose is technically water soluble, but its rate of dissolving is highly dependent on MW. The lower MWs can be used for IR granulation binders and IR coatings, while the higher MWs gel before they dissolve, producing CR diffusional matrices that are also subject to some degree of erosion. Another technically water-soluble polymer with a similar mechanism of action is based on polyethylene oxide. This polymer has similar MW considerations as Hypromellose. Both of these substances, which are available as somewhat free-flowing powders, can sometimes be tableted using a simple Direct Compression (DC) process, although a wet granulation process may be necessary for high dosage strength products. When the percentage of API is high, and the API substance is not inherently flowable or compactable, wet granulation promotes acceptable tablet formation.

DELAYED RELEASE (DR) & SUSTAINED RELEASE (SR)

Acrylic-based polymers can achieve both DR and SR. Enteric (DR) polymers are usually protonated. These can be acrylic based (Figure 2), or based on a different class of chemistry, such as cellulose acetate phthalate. These can be purchased in powder form, but are commercially available as aqueous dispersions, which eliminates the need for extensive preparation steps. They may require the addition of some plasticizers and detackifying agents to render the polymers flexible and to prevent agglomeration during processing. The mechanism of action of enteric coatings is due to the property that they are not soluble in an acidic environment because an excess of hydronium ions renders them non-ionic. However, when they encounter the neutral pH of the intestinal tract, they deprotonate, becoming anionic, and readily dissolve. Various grades of enteric polymers have been designed to dissolve at different pH ranges, usually from 5.5 to 7.5. Stomach fluids range from pH 1.5 to 4.5, depending on the amount of food substances present.[1] When these exit from the stomach and mix with the neutral contents of the small intestine, the overall pH rises somewhat gradually. If a particular API needs to bypass the stomach to be protected against the acidic environment, but the formulator's goal is for it to be released quickly in the proximal portion of the small intestine, a polymer that dissolves at pH 5.5 might be chosen. Polymers that dissolve at higher pHs can be used to deliver the API to a certain section of the gastrointestinal tract, to take advantage of an "absorption window" or to inhibit degradation. It is desirable for some APIs to reach the more distal large intestine before they are released, either to avoid degradation or because they are intended to act locally (non-systemically) at that site. In this case, a polymer that dissolves only when the colonic pH of 7.5 is reached would be used.

Acrylic-based so-called reverse enteric polymers are non-ionic and somewhat hydrophobic and do not dissolve at neutral pH (for example in the mouth). These polymers are therefore used to mask the taste of bitter or foul-tasting APIs. Suspensions of particles coated with these polymers can be rendered organoleptically acceptable, but in the stomach

TABLE 1

SOLUMER FINGERPRINTS

Formulating lipophilic crystalline drugs results in a self-assembled drug-polymer complex. This provides two features that are required for improved bioavailability:

- Depression of melting temperature and energy
- Formation of colloidal dispersions upon contact with aqueous media

			Formulation		
	T_{melt} (°C)	ΔH_{melt} (J/g)	T_{melt} (°C)	ΔH_{melt} (J/g_{drug})	Particle size nm
Reservatrol	267.4	253.6	199.1	14.0	1224
Hesperetin	231.0	166.2	No peak of melting		1310
Nifedipine	172.4	113.4	140.9	8.4	749
Fenofibrate	81.5	74.3	64.4	9.3	669
Tacrolimus	135.0	60.5	118.0	52.0	836
Clarithromycin	227.6	70.2	207.9	40.1	1190
Albendazole	215.2	209.7	161.4	31.2	555
Fenbendazole	239.2	166.3	203.7	8.9	892
Itraconazole	169.7	84.4	155.6	21.9	910

FIGURE 2

CHEMICAL STRUCTURE OF ACRYLIC-BASED ENTERIC POLYMER

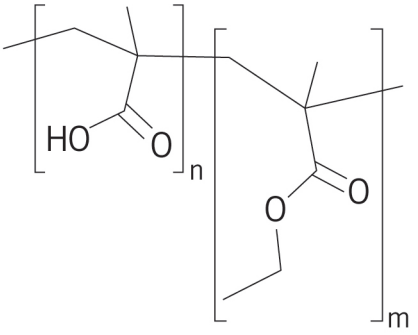
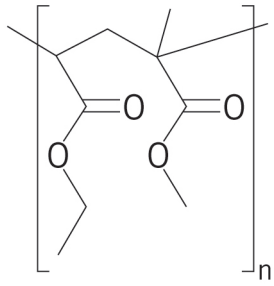


FIGURE 3

CHEMICAL STRUCTURE OF ACRYLIC-BASED CONTROLLED RELEASE POLYMER



where the pH level is lower, the polymer becomes ionic, and the drug is readily released.

Non-ionic acrylic-based polymers (Figure 3) can be formed into diffusion coatings. These coatings can be deposited onto whole tablets or onto beads that can then be filled into hard gelatin capsules or compressed into tablets. The latter can be accomplished by using a suitable "cushioning agent," such as microcrystalline cellulose, which prevents damage to the functional coating during the relatively high stress forces generated during the tableting process.

Ethyl cellulose is a water-insoluble, but organically soluble, hydrophobic polymer. It can be sprayed onto whole tablets or beads from an organic solution or from commercially available aqueous dispersions. The former process creates a molecularly coherent film; the latter process creates a coalesced latex film, similar to that produced by water-based latex paints. The advantage of a solvent-based process is the lack of dependence on a "curing" step; the disadvantage is the need to deal with organic solvents.

The latex-based process obviates the need for organic solvents, but is highly dependent on the precision of the coating process as the batch-to-batch consistency of the release profile requires predictable latex coalescence, which is a function of the curing temperature and time. While it appears this should be straight-forward, in practice, reproducibility is sometimes an issue.

Ethyl cellulose and other polymer films can be impregnated with so-called "pore formers." These are often water-soluble small molecules, such as lactose, which are added in small amounts to the spray solution or suspension. Once incorporated into the polymer film, these will dissolve and leach out, creating pores. This technique can be used to modulate the diffusional release. In this example, the release would be increased somewhat.

Another class of polymers that can be used for CR matrices or coatings is based on polyvinyl acetate. This is also commercially available as a dispersion that requires a plasticizer and a detackifying agent.

HOT MELT EXTRUSION

Hot Melt Extrusion (HME) has been used for decades to compound different materials into thermoplastic polymer melts, and is used in the pharmaceutical industry as a method to increase bioavailability of poorly water-soluble compounds when the API is compounded into an erodible polymer and in drug-eluting devices when the API is compounded into a non-erodible polymer (such as ethylene vinyl acetate or polyurethanes). The process of compounding allows both particle size reduction and mixing so that APIs can be incorporated into the polymer in dispersed form or, if the API solubility in the molten polymer is high enough, as a molecular solution. Because the extrudate cools rapidly upon exiting the extruder, any API that is dissolved in the polymer at the mixing temperature may quickly recrystallize into nanoparticulates or may be unable to recrystallize upon cooling, leading to supersaturated solid solutions. In the latter cases, stability of the product must be closely followed as recrystallization of the API over time is possible, especially at elevated storage temperatures and high API loadings. This may adversely impact the bioavailability due to formation of larger crystalline particulates of the API, and thus shorten the shelf-life of the final product. As with any dosage form, material selection is critical in the development of a successful product. For most applications, the polymer should be thermoplastic, stable at the temperatures used in the processing, and chemically compatible with the API during extrusion. For solid oral dosage forms, water-soluble polymers are usually chosen from among polymers already used in pharmaceutical products, such as polyethylene glycol and polyvinylpyrrolidinone. With the increased interest in using HME for pharmaceutical products, major polymer suppliers are beginning to offer polymers specifically designed for pharmaceutical applications. HME allows the API to be mixed with the polymer under the minimum of shear and thermal stresses, potentially minimizing the formation of process-related API degradants. Antioxidants are often included within the formulation, and the short residence time in the barrel (typically on the order of minutes) also helps to minimize thermal degradation compared to batch mixing and other compounding processes. For standard solid oral dosage forms, the compounded polymer and API may be extruded and cut directly into a slug, which can be encapsulated

into a hard or soft gelatin capsule, or can be extruded into spaghetti-like rods, cut into small cylinders, and spheronized while still warm and pliable using suitable equipment, such as a spheronizer. Another technique involves cryo-grinding the mixture to a powder followed by processing into a more conventional solid dosage form. Often the powder requires a densification step, such as roller compaction, and the addition of other excipients to enhance flow, compactibility, processability, and disintegration properties.

SPRAY-DRYING

Another technique to produce nanoparticulates of API dispersed in polymeric matrices is spray-drying a solution of the API and polymer. Though this may appear to be straightforward, to achieve the optimum dispersion and smallest particle size, careful consideration must be given to the composition of the polymeric matrix and feed solution. Key parameters include the API's solubility in various organic solvents, the API's molecular weight, the solubilities of the polymeric excipients, and the compatibility of the API and polymeric excipients in the spray-drying solution. Combinations of different polymer types, if properly formulated, can provide improved performance as compared to a single polymer type. A recent example of spray-drying technology is the Solumer technology, which employs a combination of a hydrophilic and amphiphilic polymer[2,3] The drug product exhibits modified thermal behavior, including depressed melting temperature and enthalpy of melting of the drug (Table 1), spontaneous formation of nanocolloidal dispersions upon contact with aqueous media, and enhanced dissolution rate/solubility of the drug in aqueous media as well as prolonged supersaturation in relevant biological fluids, and GI site-targeted release of the drug. The resulting free-flowing powder that typically results from spray-drying processes can contain high levels of API of 25% or more and are amenable to processing by various techniques into solid oral dosage forms.

SUMMARY

Having an understanding of polymer chemistry, including mechanisms of action, is critical for the solid dosage formulator. Knowledge of what specific polymers and polymer-based excipient products are available in the market, from both functional and regulatory perspectives, provide the formulator with a broad base of options and strategies for achieving virtually any type of release profile. ◆

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BIOGRAPHY

Robert Gwozdz is responsible for solid dosage form development at Particle Sciences Inc. Before joining Particle Sciences, he held formulation positions at Teva Pharmaceuticals and American Home Products, developing both NCEs and generic products. He earned his BS in Biology from Penn State University and a Masters in Pharmaceutics from Temple University. Mr. Gwozdz has more than 30 years of experience in Pharmaceutical Research and Development and Process Engineering, specializing in modified release and enhancement of bioavailability.

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Special Feature

Are CDMOs Bailing Out the Pharma Industry?

By: Cindy H. Dubin, Contributor

Yes, contract development and manufacturing organizations (CDMOs) have stepped up to bail out pharma companies that are under pressure to cut costs and get product to market faster, according to a report from Global Industry Analysts Inc.[1]

Add to that the decrease in research productivity, the expiry of patents on blockbuster drugs, and budget constraints on procuring extensive equipment, and what you get is an increase in manufacturing and formulation outsourcing. In 2009, estimates valued the total market contract manufacturing at $10.5 billion and formulation development at $1.3 billion.[2] Global Industry Analysts expects contract manufacturing to reach $40.7 billion by 2015.

Drug Development & Delivery magazine recently posed a series of questions to several CDMOs to find out how they are positioned to help pharma navigate the waters of patent expirations, rising costs, shrinking timelines, and budget constraints. The participants included E. Morrey Atkinson, PhD, CSO, VP of R&D and Drug Substance Manufacturing, Cook Pharmica; Jeffery C. Basham, VP, Business Development, Metrics, Inc.; Elliott Berger, VP, Global Marketing & Strategy, Catalent Pharma Solutions; Kim Black-Washington, Director, Strategic Development & Marketing, Xcelience; Brad Gold, PhD, Director, Pharmaceutical Development & New Technology, Metrics, Inc.; Charles W. Gray, Jr., PhD, Senior VP, R&D, Ei Inc.; Brandon M. Griffin, VP, Sales & Marketing, Advantar Laboratories, Inc.; Jan-Olav Henck, PhD, CSO, Aptuit LLC; Paul Maffuid, Executive VP, Operations LLC, AAI Pharma; Brian McMillan, VP, Product Development and Co-founder of CoreRx, Inc.; Stuart Needleman, President and Chief Operating Officer, Aptuit LLC; Terry Novak, President, Norwich Pharmaceuticals; Michael Ruff, PharmD, CPIP, VP, Pharmaceutical Development, Metrics, Inc.; Frank Sorce, Director, Business Development & Marketing, UPM Pharmaceuticals.

Q: How is outsourcing development and manufacturing currently "bailing out" pharma?

Mr. Maffuid: Contracting work to partners provides clients integrated drug product development and manufacturing resources that are available only when they need them. This eliminates the need to establish an integrated CMC team and the necessary laboratory and manufacturing centers to achieve the same level of efficiency.

Ms. Black-Washington: The pharmaceutical sector is undergoing a period of rapid change, and in an effort to address pressures related to innovation and rapid progression of compounds, we see pharma re-evaluating how they outsource. A number of drivers influence total R&D spend and the subsequent decision to outsource versus keep work in-house, including regulatory concerns, pipeline productivity initiatives, cost containment mandates, need to access proprietary expertise, and project complexity. In the current economy, where pharma is under pressure to do more with less, the need to maximize pipeline efforts, accelerate candidate development, and reduce spend makes outsourcing an attractive option. While this trend was certainly strong for late-stage clinical and commercial manufacturing in 2010 and 2011, we see this trend now includes the early stage formulation development and clinical supplies manufacturing, packaging, and labeling service sector.

Dr. Atkinson: The fact that CDMOs are now available that are compliant, cost-effective, and capable means that a pharma company can diversify risk by having products developed and produced with third parties. Top-tier CMOs can run a development and manufacturing

program that is comparable to in-house capabilities at pharmaceutical companies. As many pharma companies seek alternatives to minimize risk, the risk of using a CMO is now seen as relatively low. Regulatory agencies are now familiar with the CMO model, and successful submissions from third-party manufacturers are commonplace in the industry.

Mr. Griffin: Economically, the leading reason is for better cost control and budgeting; by reducing overhead and limiting associated risk of superfluous infrastructure investments without the long-term assurance of market success, companies can solicit the resources they need, when they need them and not be financially subject to underutilized labor and assets. Additionally, with larger clinical or even commercial programs, pharmaceutical companies can often leverage their buying power with vendors to further drive down overall costs of getting their drug to market. Strategically, outsourcing allows a pharmaceutical company to more quickly utilize the expertise or secure talent available from the vendor if it does not exist in-house; contract service organizations work on numerous projects of differing scope in any given year all with their own unique challenges, so over time, there is naturally a more profound base of experience gained or general know-how developed that can be leveraged by a pharmaceutical company through its vendor.

Mr. Basham: The primary needs are cost control and speed to development, assuming quality is a given. The flexibility for starting and stopping programs based on go/no-go decisions allows for more work to be ongoing and then cost-savings if a no-go decision can come early in the process. If preclinical does not go well, there are no further costs, or if first time in man fails, there are no further costs. So at any point in the process from start to commercialization, the hangover of extended costs of people, equipment, and other assets can be shut off with cost savings. The CDMO can absorb this as its costs are spread over many clients at various stages of the development timeline.

Mr. Sorce: I think it's pretty clear that over the past several years CDMOs have made significant investments in their service capabilities and equipment trains, either through organic internal growth, or via merger and acquisitions. These service offerings have not only become wider (more end to end), but deeper as well. When I say "deeper," I am referring to enhancing the services that may have already been offered by any particular CDMO. So it will remain critical to provide more one-stop shopping with good depth to handle a variety of compounds and complex formulation challenges, while continuing to work with compressed time lines and more conservative budgets.

Mr. Novak: In the end, outsourcing allows pharma to turn fixed costs into variable costs, which has become even more important as branded products are going generic quicker, blockbusters are few and far between, and the success rate of a product coming to market continues to be low. As newer branded products become more complex to manufacture (eg, highly potent, lower humidity requirements, etc) it makes little sense for pharma to make the necessary investment in infrastructure.

Q: What is the advantage of outsourcing to productivity and efficiency in development and manufacturing?

Mr. Berger: Efficiency and productivity come from expertise and volume in a specific activity, particularly in highly sophisticated and complex pharmaceutical environments. In the highly involved drug development and supply value chain, it is impossible for any one organization to build and economically operate all such activities in-house. Partnering with an expert provider that has a great deal of experience solving complex challenges for multiple partners and running a high volume of projects efficiently is of great benefit. Another key area, where such partnerships are vital, is in access and joint exploration of new delivery technologies. Specialized drug delivery companies often pioneer new approaches to deliver the most challenging molecules to market and provide a way for new compounds in the pharma pipeline to find the right therapeutic profile to make it to

market. Individual pharma companies usually don't have the breadth of pipelines that would justify investment in such innovations, and it tends to lay outside of their discovery expertise areas. A partnership in these cases really provides a strong boost to pipeline productivity.

Mr. Basham: The advantage on productivity and efficiency for the pharma company is in utilization of people assets. Each lead scientist can manage multiple projects and/or products in development or multiple segments of the development project. For manufacturing, this is even more efficient as the lead manager can manage multiple CMO relationships handling multiple products. This is what we see within our client base.

Mr. Needleman: Understandably, pharmaceutical company CEOs are focused on profitability; earnings per share driven by top line growth. They are challenged to advance a portfolio of candidates and simultaneously need to reduce their operational costs. Outsourcing, whether complete packages or transactional work, helps them gain efficiencies. By outsourcing, pharmaceutical companies can reduce internal fixed costs by contracting for the services only when they need them.

Mr. McMillan: The efficiency and productivity comparing outsourcing versus internal development in Big Pharma is remarkable. Decisions are made and implemented in not only days but hours. Also, there is high emphasis on educated, systematic decision- making leading to less investment in research dollars. Bottom line, this is one of the most important considerations when running today's development programs.

Dr. Gray: One key advantage is agility. It is often the case with larger companies that there are multiple layers of decision-makers that can stunt progress of development and manufacturing initiatives. Outsourcing can be an effective tool in circumventing these challenges. Another key advantage is skill. The volume and diversity of products encountered in the outsource environment builds a high degree of skill. A craft is honed through repetition and exposure. When agility and skill are applied correctly, the result is reduced development times and efficient manufacturing operations.

Dr. Atkinson: A greater workload can be carried forward with the addition of third-party capabilities in development and manufacturing. Contract development and manufacturing is a direct cost to a company, and can easily be planned, budgeted, and controlled. In-house efforts require capital expenditure, personnel, and overhead costs, and other expenses. Therefore, to be maximally productive, in-house capacity needs to be fully utilized. Even if this is the case, which is seldom, excess work can also be performed using a third party, therefore increasing the overall productivity of an organization.

Q: How can you, as a provider, help pharma mitigate the patent cliff?

Mr. Novak: The patent cliff is inevitable; however, a CDMO with competitive pricing can minimize the effect by allowing the pharma company to remain competitive in the post-patent market. Also, through closer collaboration between the CMO and client at the outset of a project regarding the client's product strategy, a CDMO can use its development know-how to possibly extend the patent life as well as increase efforts to reduce manufacturing costs.

Mr. Griffin: As a contract laboratory, our approach to helping pharmaceutical companies negate the patent cliff is two-fold. First, with respect to an impending patent expiration, we work with companies to evaluate and/or develop formulation alternatives that may provide longevity to their existing drug portfolio. Such considerations can include the alternative routes of administration, liquid-versus-lyophilized formulation evaluations, alternative concentrations, or dosages. The strong market performance of generics and biosimilars in recent years demonstrates time is one of the most critical elements for many proprietary drug makers to get to their submission as quickly as possible, so we work with them to outline a clear path of development based upon the collective experience of our team and/or strategic partners. Second, for proprietary drugs in development, we work with clients to ensure the analytical development and formulation portions of their drug program (the CMC sections) are not rate-limiting steps to a successful filing.

Dr. Henck: The patent cliff is an ongoing concern for all pharmaceutical companies, and a good outsourcing partner can assist with product lifecycle management. We generate solid-state patents for our clients and help them

extend their patent portfolios. We help them to get additional IP in place that can potentially take over the role of the composition of matter patents. When a company owns the composition of matter patent for a drug molecule, the patent life starts well before a company can market the product. Depending on the indication, the majority of the composition of matter patent lifetime may expire before the drug actually goes on the market. We can start earlier through our lead optimization services and lifecycle management approaches, including patent prosecution and potentially, patent litigation support.

Dr. Gray: Strategic thinking is the best way to minimize the effect of patent cliffs on the revenue potential of the product/product lines. Most prescription drug delivery systems are not complex and easy to replicate, especially with topical products. The use of novel drug delivery technologies can serve as a formidable barrier to generic intrusion.

Mr. Berger: An alternative strategy to negate the patent cliff is to bring new and high-quality molecules into and through the early development funnel as quickly as possible. Efficient and qualified platform technologies and workflows (eg, solubility, stability, and formulation screening) enable rapid assessment of factors that enhance key performance measures such as bioavailability. Another strategy involves maximizing the value of a treatment through its life cycle with patient-centric reformulations or line extensions.

Mr. Sorce: With the proper funding via a fairly broad development contract, a provider can investigate various new formulations that can lead to brand extensions, in the form of additional dosage forms, extended release options, or by combining two existing drugs. This type of work can be extremely difficult and provide some intermittent frustration, but probably provides the most excitement for development scientists. If just one of these options is successful, it can lead to a tremendous return on investment for a sponsor company.

Q: What is the importance of a preformulation program when outsourcing formulation development?

Dr. Gray: A key pitfall of modern product development is not incorporating enough scientific rigor into the earliest stages of development as speed to market becomes the key driver. In general, a thorough understanding of the chemical and physical characteristics of active ingredients, excipients, and their relationships to one another can help focus formulation activities on those efforts that are likely to succeed with a high degree of certainty and have the intended effect. The intended effect would be safe and stable formulations that are designed to efficiently target health conditions or disease states. The formulation vehicle has been proven to contribute significantly to the effectiveness of pharmaceutical products. A well-conceived preformulation plan can help ensure the contribution of the delivery system is maximized.

Mr. Maffuid: Preformulation studies are cases of learning before doing - the research is critical to forecasting and navigating the major challenges often seen in the product development and manufacturing processes. The overall goal of preformulation is to investigate and characterize the physical and chemical properties of both small- and large-molecule drug substances and products. Preformulation studies, because they provide researchers with a greater understanding of the properties of a product, help us build greater quality assurance into product development and manufacturing. Further, preformulation studies often guide the medicinal chemist to the optimal molecule, providing the basis for understanding the best dosing vehicles and manufacturing processes. Preformulation studies are critical to mapping an efficient drug development and manufacturing program.

Ms. Black-Washington: When outsourcing drug preformulation work, it is important to consider a provider that offers more than a predefined set of solution. A good contract research organization will work with clients to understand the drug development goals, the physical and chemical properties of the compound itself, put this in the context of budget, and create a preformulation strategy that addresses each of these aspects. Working together in this way ensures the best chance of drug candidate success.

Dr. Gold & Dr. Ruff: The preformulation program provides a rationale for the ensuing formulation and analytical development design. Initial preformulation

activities center around potential modification of the molecule, to optimize its stability, bioavailability, and solubility. This testing directs the formulation scientist in selecting the excipients, their levels, and the manufacturing process. The preformulation work also directs the analytical chemist in analytical method development for the drug substance and the resulting drug product. Therefore, a properly executed preformulation program is critical to ensure that formulation and analytical development can proceed rapidly and with the greatest opportunity of success.

Mr. Griffin: The importance of preformulation in formulation development is essential to characterizing the physiochemical properties of an API and ultimately moving the program forward while minimizing potential waste of the expensive drug substance as well as drug product. Furthermore, without careful consideration for downstream scales of production, the potential for costly reformulations or alternatives in production due to insufficient early stage development goes up exponentially. In recent years, we are seeing more poorly soluble compounds ("brick dust") in development, which present many new challenges with respect to overcoming poor dissolution rates, low bioavailability, and overall product stability. Comprehensive preformulation in drug development is paramount to the systematic success of early stage programs and more resilient formulations that will last through the drug development cycle.

Mr. Berger: With more and more molecules coming through the pipeline suffering from bioavailability and therapeutic profile optimization challenges, it's no wonder that more than 60% of these decisions take place in Phase I or earlier, according to a Catalent Drug Delivery survey. This makes proper preformulation and early development activities so much more important to ensure the right profile for the molecule not only to be able to get into the right delivery solution and dose form, but also get through the regulatory process and emerge with the right requirements for doctors, payers, and patients.

Dr. Henck: Besides the chemical, the physical properties of a drug substance are of great importance, particularly understanding the solubility in water. It is not uncommon that solubility issues surface when the drug is taken from research into development. Many times, solubility issues will be uncovered by the drug development team. But more and more at pharmaceutical companies, scientists are coming together to understand the properties of the drug. Companies are challenged to improve solubility to avoid going into a clinical Phase l study with such limited information that they are doomed to fail.

Q: What are some current trends in drug development and manufacturing affecting the CDMO market?

Mr. Berger: A key current trend in drug development is the increasing complexity of molecules entering the pipeline with increased challenges in delivering the right therapeutic or delivery profile to meet the stringent requirements of increasingly diverse stakeholders, including regulators, payers, doctors, and patients. This is leading to increasing importance of sophisticated drug development processes using advanced drug development techniques and innovative delivery solutions.

Ms. Black-Washington: Quality-by-Design (QbD) has certainly taken on greater significance as a topic of industry discussion, but interpretation of what the FDA wants, as well as implementation of QbD concepts can really vary from company to company. We believe over the next 5 to 10 years, the industry will converge on a more precise definition of what this means and that service providers who are able to assist companies in implementing QbD into their early drug development programs will be able to set themselves apart from the pack. Using formal experimental design and QbD principles per ICH, FDA, and EMA guidelines, a foundation can be laid for formulation and process optimization based on current client project needs.

Mr. Needleman: The industry is moving from action-oriented tactical outsourcing to more strategic outsourcing. More and more, pharmaceutical services companies are becoming extended arms of pharmaceutical companies and are part of the decision-making process. Pharma companies recognize our expertise, and technologies allow them to concentrate on what they are good at. Clients appreciate that we address the challenges that may slow them down because these are the problems we tackle everyday. As the industry moves from tactical to strategic outsourcing, there needs to be more dialogue about the science and technical aspects of the project. From

the onset, an open sharing of scientific information and knowledge between the client and the outsourcer can avoid problems that may develop later on in the process and engineer a better drug development process.◆

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The Case for Automating the Contract Lifecycle

By: James Burke

INTRODUCTION

A while ago, I had the opportunity to speak with a former colleague, another veteran of the early Contract Lifecycle Management (CLM) implementation wars. While comparing battle scars, I asked him, "Have you ever had a client that really knew, going in, what it was they wanted to accomplish in implementing this technology?" "Not really," he replied, "I guess it's still a new concept."

During a recent conversation with a client, the discussion devolved into an esoteric disagreement about how to state the case for implementing an Enterprise CLM (ECLM) solution: Return-on-Investment (ROI) justification or anecdotal evidence of problems to address risk. The client was reluctant to be measured against ROI numbers, but had plenty of evidence of past transgressions (lost revenue and incurred costs) that would justify implementing some sort of warning mechanism.

In a seminal 2007 work addressing the CLM market against technology vendors, Andrew Bartels of Forrester stated:

"Growth is becoming explosive, thanks to a cycle of CLM technology fueling new models for business relationships, which stimulates new demand for CLM tools."[1]

This leads me to conclude there was an early adopter "tail wagging the dog/dog wagging the tail" situation that continues today. In regard to the likely growth of CLM adoption, Bartels goes on to state:

"We estimate, based on client counts that we have gotten from all the leading vendors, that almost 2,000 companies have bought a CLM solution. That is still well below the 9,000 businesses and non-profits that have purchased eProcurement products or the almost 4,000 that have bought eSourcing applications. However, the 23% Compound Annual Growth Rate (CAGR) suggests that the number of CLM buyers will exceed 4,000 by 2011."[1]

Many organizations are indeed realizing the importance of implementing more robust CLM solutions, but fail to realize the full potential benefits of such automation.

Early adopters of Enterprise Resource Planning (ERP) technology typically endured lengthy and problematic implementations. As a result, this led to a process of 5-year re-assessments and re-implementations in order to fulfill the original promise of automating resource planning across the enterprise. In order to compete, companies would need to create a culture in which process efficiency and the tools of technology available melded to form a competitive advantage in a reasonable time frame. CLM technology is no different. Many thought-leading adopters of CLM technology in the early 2000s are re-assessing their programs and re-implementing the technology using an enterprise-wide approach. There are several reasons for CLM program "churn" such as:

- No clear and attainable "roadmap" for incremental adoption of functionality.
- Not sufficiently attacking and refining contracting business processes separate from the technology.
- Lack of effective change management during the implementation of new contract

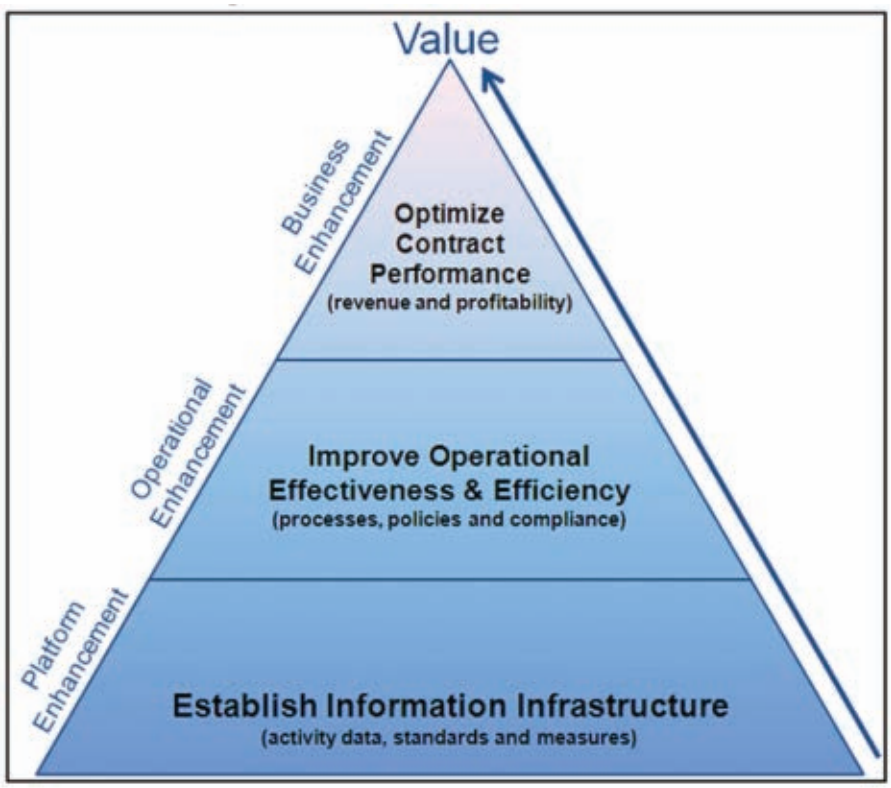
management programs and technology.

- Not establishing the critical data elements for reporting and analytics.
- Lack of data governance standards.
- Not leveraging automation functionality to its full potential (ie, clause library and fallback/alternative playbook language).
- Underestimating the effort of loading the legacy contract repositories (resulting in project over-run).
- Not establishing an enterprise or corporate governance for contracting across the organization.

In order to fully realize benefits from CLM, companies should use the following holistic approach to contract management:

- Establish corporate governance and oversight for contract processes throughout the enterprise.
- Avoid shying away from reviewing, rationalizing, and proposing changes to contract language and template structures. Use the CLM tool to constantly monitor and review the effectiveness of the changes.
- Create a single enterprise repository (or at a minimum, a data warehouse from multiple repositories) for reporting and analytics.

FIGURE 1



Building Value for the CLM Process

- Create and monitor metrics for achieving specific ROI that has a critical impact to the business.
- Look for strategic integration points with other company systems to gain efficiencies in data flow and integrity.

In terms of developing a plan for implementation, companies are starting to recognize the impact of scope in implementing automation solutions in support of contracting. A 2009 survey conducted by the International Association for Contract and Commercial Management concluded "Repository/database and milestone alerts most important life cycle software functions"[3] Ninety-four percent of respondents believed the Contract Database had the most important functionality. The next three areas of functionality by importance were contract milestone alerts/management reports (83%), capturing existing paper/electronic contracts (78%), and secure document/records repository (74%).[2]

So establishing the basics of a contract repository with critical data elements and quality data should be the primary focus of any first phase of an implementation project. Here is where focus on conversion of legacy contracts or existing repositories is sometimes underestimated. Figure 1 shows

FIGURE 1

Key Challenges	Solutions
Contracting is a "local function"	All business units use a consistent CLM system
Manual contracting processes	Automated CLM tool is used for authoring all appropriate contract types
Databases or spreadsheets control the contracting processes	CLM tool is used to control the process, such as monitoring of language and structured data changes
Manual workflows govern the process	Automated request, first-draft, negotiation, execution and post-execution processes
Manual amendments and renewals	Renewals are controlled and automated; Amendments generated and authored by CLM tool
Contracts are stored departmentally in files folders or a shared drive	All contracts are digitized and searchable in context
Manual entry of obligations and contract specifics	Real-time interfaces drive upstream and downstream process integration
Manual tracking	Automated, proactive monitoring of all milestones and commitments
Low confidence level for compliance	Auditable, tracked, automatically captured approvals with defined rules minimizes compliance risk
No formal performance metrics	Defined and automatically published metrics for contract and process performance

Representative CLM Challenges & Solutions

how building the pyramid of a contract management program starts with establishing an effective data repository.

In order to develop an effective long-term CLM solution and realize true value, companies should:

- Establish the appropriate information infrastructure.
- Focus on improving operational effectiveness and efficiency.
- Ultimately use the data to optimize contract performance in terms of revenue and profitability.

Regarding CLM technology, it is important to take the time to thoroughly review and select the appropriate system. As with most technology, the most expensive or robust may not be the best to satisfy your actual requirements, although it may look like the obvious choice. In my experience, around 85% of CLM technology has roughly the equivalent functionality and only about 10% to 15% really differentiates them. It is in that small percentage that most companies find their most important requirements lay in order to extend their implementation to fully utilize ECLM functionality. Examples of these differentiating areas include:

- Microsoft Word Integration and clause library capabilities (intelligent document assembly).
- Security model.
- Search/Query capabilities and reporting.
- Review and approval workflow (including post execution workflow).
- Integration framework with upstream and downstream systems.

Conducting an overall analysis of your contracting process without focusing specifically on the technology can pinpoint gaps and assist in prioritization of requirements. This will uncover areas for establishing a short- and long-term strategy. Figure 2 shows examples of key challenges found in such an analysis and representative solutions.

Establishing a well-structured program against this framework can lead to realization of sustained value in terms of business performance. For example:

- Contract process cycle time has been reduced from 10 to 30 days to 1 to 3 days, and typically a 40% reduction can be utilized as a reliable estimate in preparing ROI justification.
- Revenue and profitability gains of approximately 10% have been realized.
- The Legal Department has been able to attain productivity gains to address higher value work.

In order to focus clients on fully realizing the benefits of ECLM technology, I use The Three Rs of Contract Lifecycle Management:

Risk Mitigation: Leveraging clause library-approved language and monitoring changes through automatic review and approval processes is the key to mitigating risk.

Revenue Maximization: The CLM tool can be used to monitor pricing and discounts (compliance with pricing rules) in the negotiation cycle and shortening the quote to cash cycle through integration with upstream and downstream systems.

Rogue Spend Abatement: Many companies are implementing strategic sourcing and Procure-to-Pay initiatives. Obviously CLM technology can help to shorten the contracting cycle, but integrations to the Regulatory Factor (RFx) and payment systems can help ensure data integrity and allow for reporting on or halting of rogue spend.

In all three areas, the use of CLM technology should only be part of an overall program to review and streamline contracting processes across the enterprise. Companies fail in realizing benefits from CLM technology by settling for only gaining the efficiencies of the automation of contract creation and approval processes instead of focusing on improving the overall contracting process and the quality of data.

There's no doubt that intelligent use of automation technology can mitigate risk, especially in light of healthcare reform and requirements for compliance with local, state, and federal statutes. It can also improve the bottom line by addressing contract "leakage."

My grandfather was a laconic "old world" Yankee from down east. He was a master carpenter, as was his father, using tools of the trade handed down from one generation to the next. I would often hear quaint aphorisms from him, two of which I still use today. He would say "Measure thrice and cut once." This is a model of efficiency that I still use in my personal and professional life. And . . . "If it ain't broke, don't fix it."

Companies adopting ECLM solutions to automate the contract lifecycle would be well advised to heed these two pearls of wisdom. Understand the business problem you are trying to solve and do the diligence to see where automation makes sense and where it doesn't make sense for your contracting process. And if it's working, automation may not necessarily improve the process, so make sure the efficiency isn't going to break something that already works. ◆

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BIOGRAPHY

James Burke joined Alliance Life Sciences in 2004, bringing with him an extensive background of over 8 years in contract management, including experience from contract management systems implementation projects at over 10 life sciences companies. Since joining, Mr. Burke has expanded the Contract Management practice to virtually all of Alliance's pharmaceutical clients, with projects ranging from managed support initiatives to custom solution development and business intelligence projects. Prior to joining Alliance, he was a Director in iMANY's Professional Services organization.

MARKET BRIEF

US Market for IV Packaging to Reach $295 Million in 2014

By: Bill Martineau, MBA, Freedonia Group

INTRODUCTION

IV packaging is divided among three principal types of containers: semi-rigid plastic containers, flexible plastic mini-bags, and rigid glass containers. US demand for this packaging (including captive production) is projected to increase 2.6% annually to 840 million units, valued at $295 million, in 2014. Gains will follow large volume parenteral (LVP) usage patterns in hospitals, nursing homes, ambulatory medical facilities, the home healthcare market, and the emergency care services market. Overall, IV containers will provide very limited sales opportunities to packaging companies as the three major manufacturers of LVPs (Baxter International, B. Braun, and Hospira) meet the majority of their packaging requirements through captive and contract production.

LVPs encompass sterile diluents, electrolytes, irrigating fluids, blood derivatives, nutritional preparations, and premixed injectable drugs administered in quantities of 50 milliliters or more. The sterile formulation of LVPs necessitates the use of containers with strong barrier properties. Moreover, because containers serve as the main component of IV delivery systems, they require special design modifications to accommodate the inclusion of accessories, such as administration sets and screw-in vials. Accordingly, LVPs represent one of the highest value-added applications for pharmaceutical packaging. Nonetheless, demand for IV containers will expand at a lackluster pace due to trends promoting short hospital stays and less invasive surgeries. In addition, steady improvements in oral and topical drugs will eliminate the need for IV therapy in an increasing number of cases.

SEMI-RIGID PLASTIC CONTAINERS

Semi-rigid plastic containers will continue to account for the largest share of IV packaging consumption in both units and dollars. Demand for these containers will advance 2.2% annually to 430 million units, valued at $180 million, in 2014. Applications in the packaging of electrolyte solutions, diluents, blood derivatives, irrigating fluids, and parenteral nutritional preparations will account for growth. The value of demand posted by semi-rigid IV containers will benefit from increasing preferences among hospitals and home healthcare organizations for higher cost, ready-to-use IV systems. However, trends toward less-invasive surgery, short hospital stays, and the earlier post-operative substitution of alternative drug therapies will moderate overall growth opportunities for these containers.

Capacities of semi-rigid plastic IV containers range from 50 to 4,000 milliliters, depending on the type of product enclosed. Biologicals and nutritional preparations are normally packaged in 50- to 250-milliliter volumes, while larger containers are used mostly for diluents and irrigating solutions. Historically, PVC comprised the leading material employed in the production of these configurations. However, this trend has changed due to the risk of adverse patient reactions to the plasticizer di(ethylhexy)phthalate (DEHP), a stabilizing agent for PVC. DEHP has been linked to infertility and hormonal imbalances in laboratory animals. Accordingly, the FDA is advocating that all medical products and packages based on PVC and DEHP either be adapted to alternative materials or include a label warning about the potential risk.

In response to the DEHP issue, the three major producers of IV solutions are adapting new plastics to their containers.

B. Braun Medical has already eliminated the use of PVC in IV packaging. The company's EXCEL and PAB IV containers are now composed of specialized polypropylene materials. Baxter and Hospira are actively developing alternatives to PVC. In addition to polypropylene, other resins replacing PVC in IV containers include thermoplastic polyesters, nylon, and various coextrusions.

The most widely used IV containers incorporate a semi-rigid plastic structure with one or two tubular portals that connect into an IV administration set. These containers also include an extended plastic strip at the top to allow for hanging on an IV stand. Semi-rigid diluent containers are often used together with piggy-back vials to deliver active medication, such as injectable antibiotics and pain control agents. Alternatively, IV drugs can be injected or otherwise added directly into the parenteral container and delivered by a single line into the patient.

The most widely used semi-rigid IV container system on the market is Hospira's ADD-VANTAGE. The core of this system is a specially designed diluent container with a circular top portal that connects to a small volume plastic vial of parenteral medication. When the vial is affixed to the container, the active drug blends with the diluent and creates the finished IV solution. The ADD-VANTAGE system allows IV preparations to be mixed directly at the site of administration. This feature eliminates the stability problems associated with conventional mini-bags. Approximately 30 parenteral drugs in approximately 60 dosage strengths are available in ADD-VANTAGE-adaptable vials.

Through 2014 and beyond, semi-rigid plastic containers will maintain the largest share of usage among IV packaging. This trend will reflect their overall cost effectiveness and adaptability to virtually all types of LVPs. Although moderated by advances in less-invasive patient procedures, LVP demand will continue to expand based on aging demographic patterns and the increasing prevalence of serious diseases and disorders treated by IV therapy.

TABLE 1

Item	1999	2004	2009	2014	2019
IV Containers Demand (mil $)	**160**	**205**	**250**	**295**	**340**
Semi-Rigid Plastic Containers	92	122	150	180	210
Mini-Bags	41	56	77	95	115
Glass Containers	27	27	23	20	15
cents/unit	28.8	31.1	33.8	35.1	36.2
IV Containers Demand (mil units)	**555**	**660**	**740**	**840**	**940**
Semi-Rigid Plastic Containers	295	345	385	430	470
Mini-Bags	230	280	335	395	460
Glass Containers	30	35	20	15	10

IV Containers - US Demand by Type

MINI-BAGS

Demand for flexible IV mini-bags is forecast to increase 3.4% annually to 395 million units, valued at $95 million, in 2014. Ease of use and infection prevention advantages, along with upward trends in hospital admissions and home healthcare treatments, will foster gains. Sterile, flexible IV mini-bags are the containers of choice for packaging premixed parenteral drug preparations. These containers provide a ready-to-use format consisting of an active drug mixed with an appropriate diluent solution. They eliminate the need for independent admixture preparation and thereby provide significant time, labor-saving, and waste-reduction advantages. Most widely used parenteral drugs are available in mini-bags, including virtually all injectable antibiotics as well as the majority of leading analgesic, anticonvulsant, cardiovascular, psychotherapeutic, and respiratory preparations.

IV mini-bags usually contain 50- or 100-milliliter volumes of solution and are sold in quantities ranging from 12 to 48 units. With the use of polyvinyl chloride decreasing, PETG, polypropylene, and various polyethylene-based coextrusions are emerging as the leading raw materials employed in the production of these containers. The only significant disadvantage of the mini-bag involves shelf-life. Some solutions packaged in the container must be stored in a frozen environment and thawed no more than 24 hours prior to use. Newer, higher-grade plastics, such as PETG copolyester, are overcoming this disadvantage by leading to the development of containers that keep solutions stable at room temperature. Leading brands of

MARKET BRIEF

IV mini-bag systems include Baxter's VIAFLEX, VIAFLEX PLUS, and GALAXY lines and Hospira's FIRSTCHOICE.

In addition to room temperature stability, advances in polymers are enabling IV mini-bags to capture applications away from glass containers. For example, Baxter now offers its BUMINATE human albumin 25% solution in a GALAXY mini-bag composed of a proprietary, high-barrier plastic film. Previously, a high risk of contamination restricted the packaging of this biological to glass containers. The new GALAXY package provides a shelf-life of 2 years and eliminates the need for preparing admixtures in hospital pharmacies.

One of the highest value-added IV mini-bag systems on the market is the DUPLEX configuration developed by B. Braun. The DUPLEX is a dual-compartment flexible plastic IV bag that stores unit doses of drug powder and diluent separately in the same container. The healthcare professional squeezes the bag to break the quick-release seal, mixing the drug and diluent just prior to administration. Designed to simplify the intravenous delivery of antibiotics, the DUPLEX container reduces product waste, eliminates the use of vials from the preparatory process, and is equipped with a standard bar code to reduce dosage errors and track inventory. In addition, the system employs special oxygen and moisture barrier technologies to protect the drug powder from vapor and oxygen transfer through the bag, which extends product shelf-life.

Based on infection control considerations and increasing applications in the treatment of serious infections, antibiotics will continue to lead demand for premixed IV solutions. Parenteral nutritional solutions will also sustain a high, expanding level of sales. However, growth opportunities will slow due to the increasing availability of improved oral formulations of vitamins and minerals. Premixed pain control agents will see above average gains in demand boosted by a rising number of cancer and major surgical patients. Anti-cancer drugs, cardiovascular agents, and blood derivatives will account for the fastest growth opportunities among remaining premixed solutions due primarily to the proprietary status of many leading types.

GLASS CONTAINERS

The market for glass IV containers will decrease 5.6% annually to 15 million units, valued at $20 million, in 2014. Continuing loss of applications to high-barrier plastic configurations will erode demand. Available glass IV containers range in capacity from 500 to 4,000 milliliters. They are used principally in the packaging of unstable parenteral drugs and biologicals highly vulnerable to contamination. In these applications, glass still retains slight advantages over plastics in terms of barrier and resistance properties. However, the range of parenteral solutions requiring glass packaging will continue to diminish as the protective and containment properties of plastic materials improve. Gerresheimer and SCHOTT are among the principal suppliers of glass IV containers to the US market.

An in-depth report on this and other related topics can be obtained by contacting the Freedonia Group at www.freedoniagroup.com.

BIOGRAPHY

Mr. Bill Martineau is an authority on the healthcare industry. He has performed in-depth research in areas of biotechnology, pharmaceuticals, medical packaging, and related areas, producing titles such as: *U.S. Pharmaceutical Packaging, Cardiac Implants, Nanotechnology in Healthcare, Drug Delivery Systems,* and *Biochips*. Prior to joining Freedonia, he was Manager of Market Development at American Sterilizer Company, where he gained experience in healthcare research and strategic planning. At Invenex Laboratories, he served as Product Manager, responsible for the administration of a line of injectable pharmaceuticals. He also served as Senior Health Care Analyst at Predicasts Inc. and Manager of Market Research at Life Technologies Inc. (a division of The Dexter Corporation). Mr. Martineau earned his BA in Management and his MBA in Marketing and Finance from Kent State University.

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Design & Development of Atorvastatin Orally Disintegrating Tablets & Their Evaluation by Electronic Tongue

By: Rakesh Kumar Bhasin, MPharm, and Pradip Kumar Ghosh, PhD

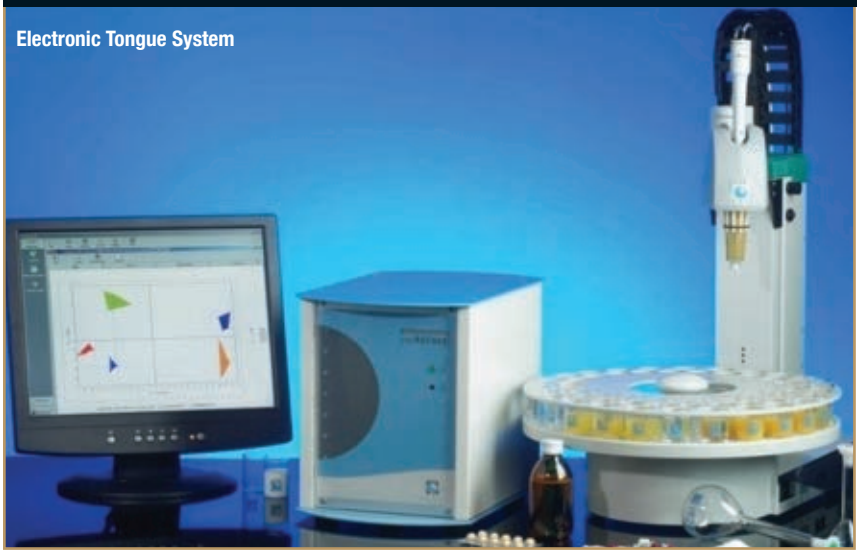
ABSTRACT

The aim of this study was to design and develop a good taste-masked atorvastatin orally disintegrating tablet (ODT) that matched the in vitro release profile of Lipitor® marketed by Pfizer. Several taste-masking polymers were tested with varying results; however, the final formulation would match the in vitro release profile of the swallow tablet. Taste of the ODT was evaluated by electronic tongue and human volunteers. The results of the electronic tongue system and human volunteers were in line with each other, indicating to the authors that the electronic tongue system can be used for taste evaluation of ODTs and determine which flavor is most suitable for the particular formulation. This electronic tongue system can be very useful in developing a best taste-masked formulation without administering the potent drug to healthy human volunteers or scientists.

INTRODUCTION

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and has a pKa of 4.46.[1] The aim of the present study was to develop ODTs that mask the disagreeable taste of atorvastatin by using a combination of hydrophilic polymers like Eudragit® EPO and a water-insoluble polymer. Eudragit® EPO enhances the solubility and dissolution rate of atorvastatin calcium in acidic pH, thus enhancing the bioavailability of atorvastatin.[2] Water-insoluble polymer retards the dissolution rate of atorvastatin in acid medium. The objective was to use these two types of polymers in such a way to provide ideal taste-masking to the formulation while at the same time, providing a comparable to the marketed reference product (Lipitor® swallow tablets) in terms of in vitro drug release.[3] The taste-masked ODTs were evaluated using an electronic tongue.

FIGURE 1



MATERIALS

The active ingredient and excipients selected for the formulation of the ODTs are presented Table 1. All other reagents and chemicals were of analytical or HPLC grade and used as received.

METHODS

Manufacturing of Orally Disintegrating Tablets

Microcrystalline cellulose (MCC) and mannitol were sifted together through a No. 40 mesh and loaded in a fluid bed processor (FBP) bowl. Atorvastatin calcium, polymer (ethyl cellulose or HPMC as per the manufacturing formula), and Eudragit® EPO were sifted together through a No. 20 mesh, dissolved in methanol, and stirred until it became clear in color. This solution was sprayed over MCC and mannitol using the top spray configuration of the bowl of the FBP with a product temperature of about less than 45°C. The blend in the FBP was dried to obtain loss on drying (LOD) less than 2% w/w. These dried granules were sifted together with aspartame, crospovidone, mannitol, and colloidal silicon dioxide and then blended for 7 minutes. Magnesium stearate was sifted through a No. 60 mesh and added to the aforementioned blend, then blended for 3 minutes. This lubricated blend was compressed with suitable tooling using a rotary compression machine. Taste of these tablets was evaluated using healthy human volunteers as well as an electronic tongue.

Preparation of Placebo

Three placebos (P03, P04, and P05) were prepared as per the composition presented in Table 2 but without the atorvastatin calcium drug. The manufacturing process was followed exactly as explained earlier.

Electronic Tongue, Its Principle & Application

Different ODT formulations of atorvastatin were evaluated using an electronic tongue. The electronic tongue system (Astree/Alpha MOS) is illustrated in Figure 1.

The system principle can be compared to the human taste-sensing process. A liquid sample is "tasted" with the liquid sensors, which can play the role of the human gustatory receptor. The response is then processed in the same way as the human brain (Figure 2). The Astree Electronic Tongue is an array of sensors. The technology used is currently based on electrochemical sensors and measure up to 7 sensors at the same time. The sensors (ZZ, AB, GA, BB, CA, DA, and JE) are composed of a sensitive organic-coated membrane to analyze the samples and a transducer, which allows converting the response of the membrane into signals that will be analyzed.

Interpretation of data with multiple variables, such as several sensors and multiple samples, requires the use of statistical interpretation methods. Chemometric techniques provide a way for presenting the data in an understandable format designed for evaluating the taste of the product.

Preparation of pH 2.1 SGF (Simulated Gastric Fasted State) Dissolution Medium4

First, 20 g of sodium chloride and 25 g of sodium lauryl sulfate were placed in a suitable container. After adding 5000 ml of purified water, the solution was mixed to dissolve the material completely. Next, 8.5 ml of concentrated hydrochloric acid was mixed in the solution and diluted to 10,000 ml with purified water. Lastly, in a suitable container, the solution was mixed and degassed.

TABLE 1

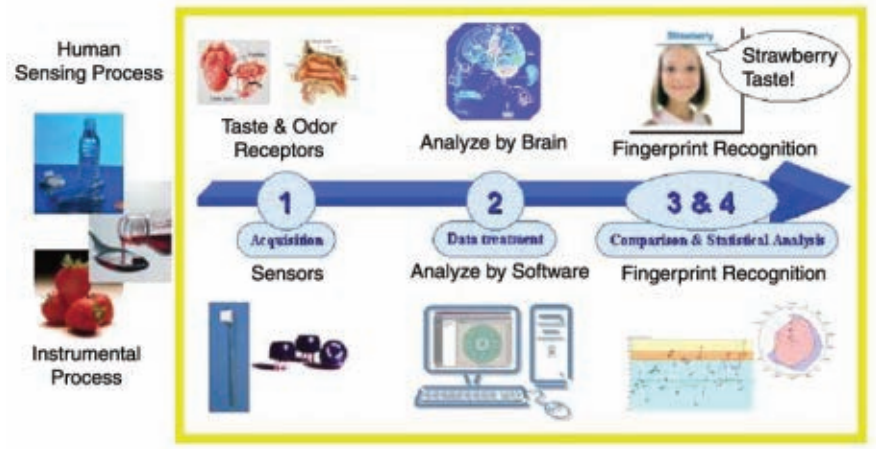
Category	Ingredients	Manufacturer's Name
Active Ingredient	Atorvastatin Calcium	Dr. Reddy's Labs
Diluent	Basic Butylated Methacrylate Copolymer (Eudragit® EPO)	Rohm
Polymer	Ethyl Cellulose (EC)	Colorcon
Polymer	Hydroxy Propyl Methyl Cellulose (HPMC)	Colorcon
Diluent	Microcrystalline Cellulose NF (Avicel PH112)	FMC Corporation
Diluent	Mannitol	Roquett
Solvent	Methanol NF	Merck
Disintegrant	Crospovidone	BASF
Sweetener	Aspartame	Nutra Sweet
Flavor	Peppermint	Givaudan
Flavor	Orange Vanilla	Virginia dare
Glidant	Colloidal SiO2	Evonik Degussa Corporation
Lubricant	Magnesium Stearate	Ferro Corporation
Oxygen Absorbent	Stabilox®	Multisorb Technologies Inc

Evaluation of Atorvastatin ODTs

TABLET HARDNESS TEST: The strength of a tablet is expressed as tensile strength (kg/cm2).[5] The tablet crushing load, which is the force required to break the tablet into halves, was measured by using a Venkel Hardness tester (VK 200). The tablet is placed properly between the measuring jaw against the sensing jaw. After pressing the test button, the power jaw begins to move toward the tablet and presses against the sensing jaw. When the tablet fractures, the moving jaw stops, and the hardness value is displayed on the red LED on the front panel.

FRIABILITY: A friability test is performed to assess the effect of friction and shocks, which may often cause the tablet to chip, cap, or break.[5] An Electrolab friabilator was used for this purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of 6 inches with each revolution. A preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

FIGURE 2



Human Sensing Process & Instrumental Process

DISINTEGRATION TIME: The disintegration time of the tablet was measured in water (37°C ± 2°C) by the Electrolab disintegration apparatus, complying as per EP/USP pharmacopoeia.[5]

IN VITRO RELEASE PROFILE OF FORMULATED TABLETS: Dissolution profiles of the atorvastatin calcium ODTs was determined at 37°C ± 0.5°C at a stirring rate of 75 rpm using the paddle method (USP apparatus Type 2). In addition, the drug-release profile from a marketed product, Lipitor® Immediate Release (swallow) tablets was examined for comparison purposes. The dissolution medium was a physiologicaly relevant medium that is 2.1 SGF as suggested by Dressman et al.[4] At each sampling time, an equal volume of the test medium was replaced. Filtered samples were appropriately diluted and assayed for drug concentration by HPLC. Drug concentrations were determined at a wavelength of 246 nm and expressed as the percentage of drug released over time.

ESTIMATION OF DRUG CONTENT OF FORMULATED TABLETS: The drug content of the atorvastatin ODT formulations was measured using the HPLC method. Ten tablets were taken in a volumetric flask (1000 ml) and were dispersed in 100 ml of purified water. Then 100 ml of methanol and 700 ml of diluent (acetonitrile and water in an equal ratio) were added and sonicated for 30 minutes. The final volume make up was done using diluent. This solution was centrifuged, and clear supernatant solution (5 ml) was taken up in a 50-ml volumetric flask, and diluent (acetonitrile and water in equal ratio) was added to make up the volume. Then 20 microliters of this clear solution was injected into a chromatographic condition using a Novapak C18 column, and absorbance was measured at 246 nm using a UV detector.[6]

EVALUATION OF TASTE BY ELECTONIC TONGUE: Three different formualtions along with their placebo were taken, and their solution was prepared using 80% of isopropyl alcohol. These solutions were subjected to anlysis using an electronic tongue as described earlier.

Variation between the placebo and drug product is observed over principal component analysis (PCA).

EVALUATION OF TASTE BY HEALTHY VOLUNEERS: Three formulations of atorvastatin ODT (F03, F04, and F05) were given to four healthy human volunteers and who were asked to evaluate taste of the formulation and acceptability. The tablet was placed on the tongue, and the volunteers were instructed not to chew the tablet. The subjects were asked to spit out the content of the oral cavity after tablet disintegration and rinse their mouths with water. Volunteers were asked to wait for half an hour between testing of the formulations.

RESULTS & DISCUSSION

Evaluation of Taste by Electronic Tongue

Based on laboratory trials, three formulations (F03, F04, and F05) were shortlisted in terms of taste for further evaluation. All other parameters, such as hardness, disintegration time, and drug content were similar in these three formulations. Upon principal component analysis, if the distance between the placebo and its formulation is less, it is considered to be a better formulation. The distance for all three chosen formulations and the three placebos was determined by electronic tongue and is presented in Figure 3. The distance between the placebo (P03) and

TABLE 2

S. No	Ingredients	Formulations Composition (%w/w)		
		F03	F04	F05
1	Atorvastatin Calcium	0.83	0.83	0.83
2	Basic Butylated Methacrylate Copolymer (Eudragit® EPO)	1.94	1.94	1.94
3	Hydroxy Propyl Methyl Cellulose (HPMC)	**0.97**	**0.00**	**0.00**
4	Ethyl Cellulose	**0.00**	**0.97**	**0.97**
5	Microcrystalline Cellulose NF (Avicel PH112)	24.19	24.19	24.19
6	Mannitol (Powder Grade)	24.49	24.49	24.49
7	Isopropyl Alcohol	Qs	Qs	Qs
	Extragranular Ingredients			
8	Aspartame	4.84	4.84	4.84
9	Mannitol (Granular Grade)	31.61	31.61	31.61
10	Crospovidone NF	8.06	8.06	8.06
11	Peppermint Flavor	0.97	**0.97**	0.00
12	Orange Vanilla Flavor	0.00	0.00	**0.97**
13	Colloidal Silicon Dioxide	0.16	0.16	0.16
14	Magnesium Stearate NF	1.94	1.94	1.94

Composition of Atorvastatin Oral Disintegrating Tablets (5 and 10 mg)

formulation (F03) was the highest (311), while the distance between placebo (P05) and formulation (F05) was 146, and the distance between placebo (P04) and formulation (F04) was the least (53). This indicates formulation F04 is the most ideal among the formulations, according to electronic tongue evaluation.

Evaluation of Taste by Healthy Volunteers

Three formulations were evaluated by the human volunteers. Formulation (F03) was found to be unacceptable to all the subjects. Formulation (F05) was found to be better than F03. Formulation (F04) was found to be most acceptable. These findings were in line with the evaluation conducted by the electronic tongue, which clearly indicates the electronic tongue is an effective tool in determining the taste of the product and helps in finding the best formulation with respect to taste.

All three formulations contain Eudragit® EPO in the same concentration. Formulation trials with different concentrations of polymers (HPMC and ethyl cellulose) were taken and initially evaluated for taste. Formulation F03 contains a combination of Eudragit® EPO and HPMC. HPMC is water soluble, so it does not provide good taste-masking in the oral cavity and releases some drug in the oral cavity.[7] Formulation F04 contains a combination of Eudragit® EPO and ethyl cellulose. Ethyl cellulose being an insoluble polymer provides good taste-masking and does not allow drug to release in the oral cavity.[7] Selection of flavor is also very critical for taste-masking. The only difference between formulations F04 and F05 is in flavor. Formulation F04 contains peppermint flavor, whereas the formulation F05 contains orange/vanilla flavor. The formulation with peppermint flavor was most acceptable as per both human volunteers and the electronic tongue. Peppermint flavor provides cool after-taste and leaves a better mouth feel. Smell contributes significantly to taste.[8] This is due to aromas being released into the nasal passage as the tablet is getting disintegrated into the oral cavity. The brain interprets the combined signals from the nasal passages and the taste buds as a taste/flavor. It is the authors' beliefs that the cooling sensation of mint flavor and its aroma are what made formulation (F03) more acceptable.

TABLE 3

Time (min)	% Dissolution (Cumulative)			
	Liptor 10 mg (Swallow)	Atorvastatin ODT 10 mg (F03)	Atorvastatin ODT 10 mg (F04)	Atorvastatin ODT 10 mg (F05)
0	0	0	0	0
5	98	99	97	97
10	99	99	97	97
15	98	99	97	97
30	99	99	98	98
45	99	99	98	98

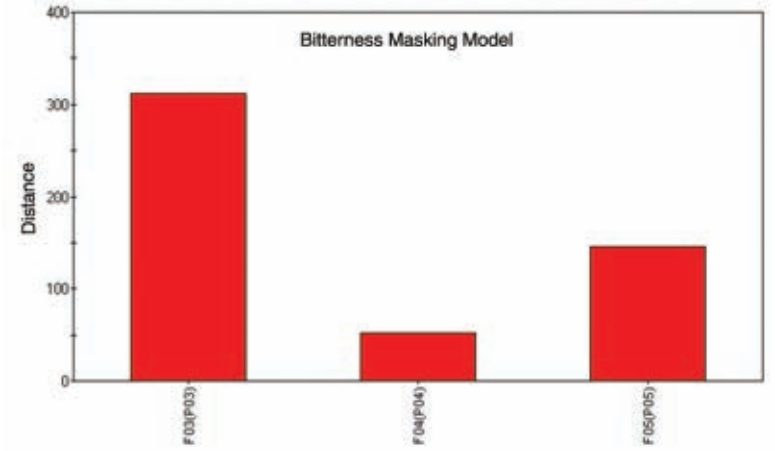
Dissolution Profile of Lipitor® 10-mg Swallow Tablet & Atorvastatin ODT (F03, F04 & F05)

Dissolution profiles of Lipitor® swallow tablet (10 mg) and atorvastatin ODT 10-mg formulations (F03, F04, and F05) were conducted, and their results are tabulated in Table 3. Dissolution of all three formulations (F03, F04, and F05) match with the marketed product Lipitor® 10 mg (swallow) tablet. However, apart from dissolution parameter, taste-masking is also a very important parameter for any ODT. A pleasant taste inside the mouth becomes critical for patient acceptance. Considering the aforementioned, formulation F04 was finalized, which is superior with regard to taste-masking as compared to the other formulations.

Stability Studies

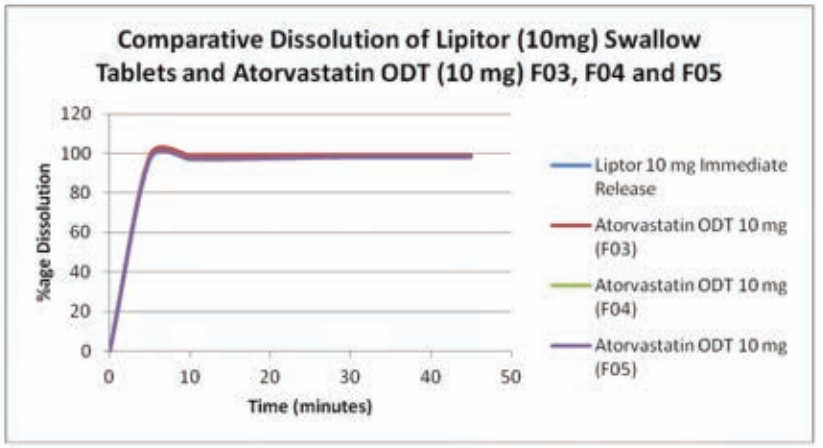
Formulation (F04) was packed in HDPE bottles with Stabilox (Oxygen absorbent) and charged for stability at 40°C ± 75% RH and evaluated for description, hardness, friability, disintegration time, drug content, and dissolution for 1 month.[9] The formulation was found to be stable at accelerated conditions for 1 month.

FIGURE 3



Distance of Formulations (F03, F04 & F05) With Respect to Their Placebos

FIGURE 4



Comparative Dissolution of Lipitor® (10 mg) Swallow Tablets & Atorvastatin ODT (10 mg) F03, F04 & F05

SUMMARY & CONCLUSIONS

We demonstrated that atorvastatin ODTs have been prepared that are similar in quality attribute (in vitro dissolution profile) to the marketed Lipitor® swallow formulation, and also overcame the disadvantage associated with the swallowing of conventional tablets. The electronic tongue has been used to evaluate the taste of the formulations, and the results are in line with the observations of healthy human volunteers. It can be concluded the electronic tongue can very well replace human volunteers for determining taste of the reviewed ODTs as the results are quite reliable. This electronic tongue system will avoid undue exposure of potent drugs to healthy human volunteers, while still allowing for the development of good optimized tablets that are acceptable to targeted patient populations.

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BIOGRAPHIES

Rakesh Kumar Bhasin is currently working as Associate Director - Research & Development in Dr. Reddy's Lab. He earned his MPharm from UIPS, Panjab University, Chandigarh, India, in 1995 and his MBA from IGNOU, New Delhi, India, in 2001. Engaged for over 16 years in the research and development area in various reputed pharmaceutical companies, he has developed more than 12 ODTs. Mr. Bhasin's main focus of research is novel drug delivery systems, including ODTs, nanoparticles, and sustained- and delayed-release formulations. He has presented research work at various pharmaceutical conferences and has filed 5 international patent applications.

Dr. Pradip Kumar Ghosh is currently working as Senior Manager - Research & Development in Dr. Reddy's Lab. He earned his MPharm from Jadavpur University, Kolkata, India, and his PhD from MS University, Vododara, India. He has been engaged for over 10 years in research and development in various reputed pharmaceutical industries (Sun, Jubilant, Dr Reddy's Lab). His main focus of research is novel drug delivery systems, including nanoparticles, microemulsions, sustained- and delayed- release formulations, and ODTs. Dr. Ghosh has published 17 research articles in various peer-reviewed national and international journals and also filed 5 international patent applications. He has also co-authored a book chapter on vesicular drug delivery systems.

DRUG DEVELOPMENT ratio Executive

RATIO, INC.: MAKING SELF-INJECTION SIMPLE, SAFE & AFFORDABLE

Mr. Ben Moga
President
Ratio, Inc.

"The patch injector technology Ratio has developed is designed for delivery of liquid formulations of therapeutics that cannot be dosed conveniently or safely by conventional needle-and-syringe approaches. This includes therapeutics with solubility issues (eg, mAbs) and/or therapeutics that have biologic issues, such as short half-lives or side effects associated with peak plasma levels. By employing Ratio's patch injector technology, therapeutics can be administered in large volumes (up to 5 mL) over short or long periods of time to overcome solubility/viscosity issues, avoid peak plasma issues, and/or address issues of short half-life."

When David Beebe, Professor of Biomedical Engineering at the University of Wisconsin-Madison, visualized the notion of a product that can self-regulate the injection of drugs into the blood stream, it was an idea only on paper. But, his experiments with a closed-loop insulin delivery system using a glucose-sensing hydrogel valve made that idea come to life. He translated the technology out of the lab and co-founded Ratio, Inc. to develop a drug delivery pump worn on the skin to deliver vaccines and other large molecules.

Fast-forward 6 years and add translational assistance by the Coulter Foundation, seed funding from angel investors, and an entrepreneurial design engineer along the way. The company is now developing a patch injector with a cost-performance advantage. Ratio's lead product, NuPrivo-SC, is a subcutaneous bolus injection system that eliminates the "pinch-and-poke" method of contemporary, prefilled systems and replaces it with a simplified "bandage-with-a-button" method that delivers volumes of up to 1.5 mL via a hypodermic needle over a 2-minute period. Powered by the original hydrogel pump concept from Dr. Beebe's laboratory, the NuPrivo product line is safe, highly usable, and affordable. Mr. Ben Moga, President of Ratio, Inc., recently spoke with Drug Development & Delivery about the company's focus on self-injection in a homecare setting. Ratio is pitting the patch injector against conventional autoinjectors in what is projected to be a $15.8-billion injectable drug delivery device market by 2015, with self-injection systems showing the highest growth potential, expected to reach $1.2 billion by 2015.[1]

Q: What are the benefits of a hydrogel, and how does it work to control the flow of drug from the product to the patient?

A: From Ratio's perspective, a hydrogel is simply a swelling polymer. It provides a low-cost and safe mechanism for repeatable delivery of a controlled injection. The hydrogel begins to swell upon activation and pushes on a collapsible drug pouch as it expands. The pressure created inside the pouch forces the injection into the tissue. The basic proof-of-concept (POC) question during R&D was straightforward: Does the hydrogel create enough pressure to drive the injection? Ratio has demonstrated basic POC in animal trials.

We have also demonstrated repeatability of 8-hour injections on the benchtop that have the potential to deliver tough molecules such as insulin. In short, Ratio is able to replace a power source (battery, spring, or human hand) and complex, moving parts with a swelling hydrogel that is programmable using simple polymer chemistry. The result is an affordable patch injector that can address a broad range of drug delivery challenges.

Q: What delivery needs will the pump patch meet in the self-injection market?

A: The patch injector technology Ratio has developed is designed for delivery of liquid formulations of therapeutics that cannot be dosed conveniently or safely by conventional needle-and-syringe approaches. This includes therapeutics with solubility issues (eg, mAbs) and/or therapeutics that have biologic issues, such as short half-lives or side effects associated with peak plasma levels. By employing Ratio's patch injector technology, therapeutics can be administered in large volumes (up to 5 mL) over short or long periods of time to overcome solubility/viscosity issues, avoid peak plasma issues, and/or address issues of short half-life.

Q: Is pharma showing interest in the pump patch?

A: There are two distinct market opportunities for NuPrivo. First is life cycle management of marketed drug products. Companies currently using prefilled systems are interested in our platform. The patch injector is a way to enhance a marketed drug using a premier delivery system. Ratio provides unique product differentiation over pen injectors/prefilled syringes combined with the end goal of improving the user experience. Both are important for market penetration and retention.

Second is the patch injector assists in pipeline development of injectables. NuPrivo can deliver large-volume/highly viscous solutions over short or extended periods of time using a highly self-administrable system. This opens up the dosing playbook and will assist in formulation development for targeted populations using increasingly personalized treatments. Autoinjectors, by comparison, often limit the volume and viscosity of the drug being delivered.

Q: How would you define Ratio's business model?

A: We are focused on out-licensing in order to bring maximum value to a combination product effort. Our operating perspective is lean in that we don't ask shareholders to invest in equipment or facilities but instead rely on the capabilities of our experienced supply chain partners to help get the product to market. Ratio's supply chain capabilities include sourcing of raw materials, part processing, device assembly, sterilization, fill/finish, and final packaging.

Q: How does a product like the pump patch satisfy the needs of pharma, physicians, and payers?

A: Through cost and simplicity. Users want simple; pharma wants safe; and payers want affordable. As our name suggests, Ratio is combining these factors into one complete system. We've simplified the user experience to applying a Band-Aid™ and pushing a button. Ratio has given a lot of thought to making physicians comfortable with outpatient treatment and accommodating a wide population of end users. The low cost of goods also offers a significant advantage in an increasingly cost-conscious healthcare industry.

Q: What place do you envision the pump patch holding in the self-injection market?

A: Autoinjectors currently on the market typically require patients to pinch a subcutaneous layer of skin within their fingers and use their other hand to inject. This can be an ergonomic challenge, especially for folks who have dexterity challenges. Additionally, the time required for drug delivery can be customized with NuPrivo-SC, depending on the preferred trade-off between wearability of the device and pain associated with time of the injection. All said, NuPrivo is designed for homecare with human factors and self-administration in mind.

Q: What other products based on the hydrogel pump are in Ratio's pipeline?

A: Ratio is developing NuPrivo-CI, a wearable delivery system for continuous infusion that enables clinicians to exploit the far-reaching therapeutic benefits of drug infusion over an extended period of time. Therapeutic markets include diabetes, pain management, and anti-emetics–niche applications.

Also under development for intradermal injection is NuPrivo-ID, which is based on our proprietary hollow microneedle technology. This product aims to reduce sharps risk as well as decrease pain and trauma that accompany standard injections. The focus here is intradermal delivery of vaccines, which provides a unique user interface and has the potential to enhance the user's immune response by delivering directly to the dermal cells of immunological interest. Initially, the first generation of this product would likely appear in a clinical setting, but 5 to 10 years down the road, I can see them being mailed to the patient or administered at a pharmacy.

Q: What is the biggest hurdle your product/company faces?

A: Like many drug delivery companies, Ratio has the challenge of establishing mutually beneficial pharma partnerships. In our case, the next hurdle is to demonstrate that a drug partner's product is safe in our drug container and that we have properly contemplated human factors. We've gotten very positive feedback as to the aesthetics and usability of NuPrivo. Our basic POC data is compelling. Now, pharma partners want to see drug stability and device usability data in order to reduce risk. The Ratio design team has taken great pains to ensure a range of drugs can be stored safely in our drug container for shelf-life of the product and that a broad range of end users can operate the device. This is a dynamic industry. There is a lot of dialogue regarding collaboration, and Ratio aims to be on the creative side of establishing value-added partnerships. Both parties can work together early on to match the drug delivery system and the preferred drug characteristics in order to launch a safe and effective end product. It is important for us to find partners who think along the same lines as Ratio in terms of reducing risk, hitting milestones, and launching in a concerted effort.

Q: What is the one mistake you must avoid going forward?

A: As a young company, we have to avoid being sidetracked by interesting projects that have no market validation. There is a temptation for early-stage companies to get excited by the next best thing, but you have to have a successful launch of your first and second products before you can aggressively pursue complimentary opportunities.◆

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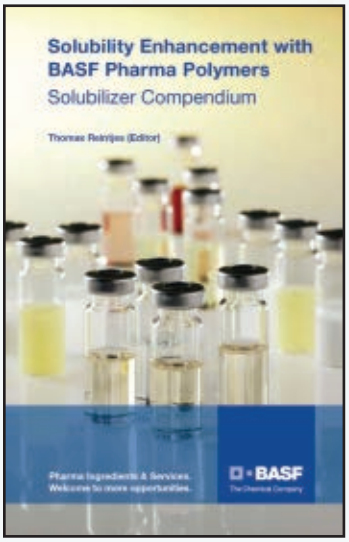
Technology & Services Showcase

Drug Development Services

AAIPharma Services Corp. is a leading provider of services that encompass the entire pharmaceutical drug development process from early development through commercialization. The company, which has the benefit of more than 30 years of experience, specializes in analytical chemistry, formulation development, clinical packaging, oral drug delivery, and contract manufacturing. Headquartered in Wilmington, NC, AAIPharma Services serves more than 300 large pharmaceutical and biotechnology companies. Our clients say we are experienced, responsive, and dependable in: starting rapidly, meeting timelines, seeing obstacles before they occur, and responding quickly when things change. Let us move your project forward reliably. For more information, contact AAIPharma Services Corp. at (800) 575-4224, email at services@aaipharma.com, or visit **www.aaipharma.com**.

Solubilizer Compendium



BASF's new solubilizer compendium is a must-read for anyone working with APIs that exhibit poor solubility and bioavailability. It leverages BASF's vast expertise in solubilization and bioavailabilty enhancement, and is the result of many years of research. The publication provides a valuable overview of all relevant BASF excipients (Kolliphor™ grades, Soluplus®, and selected Kollidon® grades), and offers helpful advice on creating solid solutions and dispersions. What's more, it includes a chapter dedicated to high-throughput screening as a means of selecting the right excipient or combination of excipients for a poorly soluble drug. Visit www.innovate-excipients.basf.com to download the compendium as a PDF, or to request a free hard copy. BASF's solubility enhancement experts are happy to answer all your questions. Just send an e-mail to **pharma-ingredients@basf.com**.

Gum Base Supplier

Cafosa, part of the Wrigley/Mars group of companies leading the chewing gum market, is the world's leading Gum Base supplier for confectionery, nutraceutical, and pharmaceutical applications. Gum Base is the main ingredient used to produce chewing gum, a combination of polymers, resins, and softeners plus an inorganic filler that gives different textures and chewing properties to chewing gum depending on its composition. Cafosa has developed an innovative concept for the pharmaceutical industry: Health in Gum is an excipient, a directly compressible powder gum containing a mix of Gum Base and polyols to which you can add your API, so you can create medicated chewing gum by adding your APIs to Health in Gum powder. Health in Gum offers an innovative drug delivery system for your products. There is no need for specific chewing gum production equipment. For more information visit Cafosa at **www.healthingum.com**.

Analytical Testing & Consulting

Gateway Analytical provides analytical testing and consulting services that can help ensure product quality throughout your product development lifecycle. Specializing in advanced characterization and pharmaceutical forensics, we support provide unique services, such as chemical imaging for layer thickness analysis, ingredient-specific particle-size analysis, polymorph characterization, as well as investigation of deviation and nonconformance issues. With more than 15 years of experience, you can rely on our expertise in analytical testing and consulting to help you solve your toughest challenges. Our scientists have the diverse industry expertise and the technical know-how to meet your unique needs quickly and efficiently. For more information, contact Gateway Analytical at (724) 443-1900 or visit **www.gatewayanalytical.com**.

Technology & Services Showcase

Recombinant Human Albumin

Manufactured specifically for the biopharmaceutical and medical device markets, Novozymes Biopharma's animal-free, recombinant human albumins (rAlbumins) are applicable in formulation, drug delivery, and medical device coating. Proven to stabilize proteins by preventing aggregation, oxidation, or adsorption of the active drug, Novozymes' rAlbumins are pure, high-quality ingredients that can help customers deliver safer products to the market faster. Albucult® is supplied as an ingredient for the manufacture of pharmaceutical drugs, medical devices, and advanced cell therapy products. Approved for use in the manufacture of human therapeutics, Recombumin® is the world's first commercially available, GMP-manufactured, animal-free rAlbumin developed for drug and vaccine manufacturing. Novozymes' rAlbumins are manufactured to regulatory standards to deliver a secure supply of batch-to-batch consistency and increased efficiency for customers looking for a compliant albumin alternative. For more information on Novozymes' rAlbumins, visit **www.biopharma.novozymes.com**.

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When it comes to drug delivery, NuSil provides numerous solutions that fit a variety of device needs. While most silicone products are customized for individual delivery systems, all are developed with FDA regulatory concerns in mind. In addition to its role as a supplier, NuSil offers research and development capabilities for those looking for proprietary, custom formulations. Regardless of batch size, NuSil delivers quality, high-performance silicone materials based on your unique property requirements, as well as provides precise, custom formulations. NuSil offers an even wider range of silicone material and compound options for transdermal, transmucosal, implanted intrathecal, and external delivery devices, as well as ingestible materials. For more information, contact NuSil Technology at (805) 684-8780 or visit **www.nusil.com**.

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DRUG DEVELOPMENT
3M Executive

James D. Ingebrand
Vice President &
General Manager

3M Drug Delivery Systems

"Third, and most interestingly in my mind, I really want to do a much better job of helping our customers and the market really understand what makes 3M so unique. We are ultimately a technology company. We are involved in so many different markets, and have so many diverse technologies. Within 3M, we talk about harnessing the chain reaction of new ideas, and that's really where our innovation comes from. We are able to tap into many different technologies across the company, and because they are all under the 3M roof, we don't have to go outside to look for them."

3M Drug Delivery Systems: Helping Customers Compete & Innovate

3M Drug Delivery Systems (DDS) is dedicated to the development and manufacturing of inhalation, transdermal, topical, and oral products and components. The division leverages 3M's proprietary technology, know-how, and 50-year track record in pharmaceutical product development and manufacturing to offer its clients the experience, services, and capacity to meet their needs. In 2010, Drug Development & Delivery spoke with James Vaughan, who was then Vice President and General Manager of 3M DDS. In his interview, Mr. Vaughan discussed 3M's approach to changes in the global market and advancements in the company's transdermal and inhalation technologies. Recently, James D. Ingebrand has been appointed as Mr. Vaughan's successor and is continuing to advance 3M's services through dedication to customer satisfaction, progressing the division's core technologies, and building awareness of the unlimited supply of technologies and expertise that fall under the umbrella of 3M Company. Mr. Ingebrand comes to the position after nearly 30 years within 3M, bringing experience from the 3M Health Care Specialties Department, 3M Infection Prevention Division, and the 3M Dental Division. Within the 3M DDS Division, he has served both domestically and in the United Kingdom. Drug Development & Delivery recently interviewed Mr. Ingebrand to discuss his priorities for the years ahead and recent developments in 3M's technologies.

Q: Congratulations on your appointment. As you step into this leadership role, what priorities do you have for the company in 2012?

A: The global marketplace has continued to grow at a rapid rate since you last spoke with us in 2010. As James Vaughan previously stated, 3M DDS has stepped in to help fill gaps for pharmaceutical companies that are reducing their research and development effort by providing our expertise in supply chain management and global facilities for outsourcing needs, along with offering assistance through our analytical work and

regulatory help. These services are imperative for our customers and 3M DDS strives to continue to grow in these areas. With this in mind, there are three things we are focusing on. First and foremost, we always want to take care of our customers. That means we want to deliver fully on our commitments, and ideally exceed their expectations. This is true both for development customers as well as our long-term supply and manufacturing customers.

Second, we want to maintain the very high standards for safety and compliance that we've always had. We want to continue to operate as a very ethical company at all of our locations around the world, which is something we'll continue to focus on in our ongoing geographic expansion.

Third, and most interestingly in my mind, I really want to do a much better job of helping our customers and the market really understand what makes 3M so unique. We are ultimately a technology company. We are involved in so many different markets, and have so many diverse technologies. Within 3M, we talk about "harnessing the chain reaction of new ideas," and that's really where our innovation comes from. We are able to tap into many different technologies across the company, and because they are all under the 3M roof, we don't have to go outside to look for them.

These technologies have very real applications in drug delivery. There is a lot of science in something as typical as a transdermal patch, from adhesive chemistry and materials science, to film technology, to membrane technology, to coatings, and those are all core technologies that exist within 3M.

Additionally, on the newer frontier, our Microstructured Transdermal System (MTS) also stems from a technology that is used in everything from flat screen TVs to abrasives.

Therefore, it's a priority for me in the next year to help our customers understand what makes 3M unique, because once they learn this, they will develop a real appreciation and confidence in our capabilities.

Q: Looking ahead, what is your long-term vision for 3M DDS?

A: We continue to be very focused on transdermal and inhalation technologies, and I don't expect that to change fundamentally. We are extremely proud that our technologies are used in 50% of all metered dose inhaler systems worldwide, and 80% of all transdermal systems in the US. But we are also very excited about bringing forward MTS technology. We believe its capabilities are quite unique.

Additionally, I am looking to bring more to the market in terms of helping our customers with life cycle management. We can bring differentiation from the very beginning of a product's life cycle, or even at its end to help extend its useful life.

Finally, our long-term vision is to continue our expansion internationally. We see the market evolving with growth in Latin America and in the Asia-Pacific region, and it's important to us that we are well-positioned to take advantage of that.

Q: Microneedles have a promising future in the delivering of vaccines. What can we look forward to seeing with the MTS platform from 3M DDS?

A: We believe MTS technologies will play a key role in the growth of the biologics market, which is projected to grow from $120.1 billion in 2009 to $170 billion by 2015. By delivering a vaccine to the intradermal space, which is rich in immune cells, the technology has the potential to improve efficacy and also be dose sparing. This holds the added potential of ultimately reducing the number of doses needed for a vaccination. We are also seeing companies explore MTS technologies to treat chronic conditions, such as rheumatoid arthritis and MS, because this new delivery system has the potential to improve compliance and be easier to administer for both patients and caregivers.

We have made significant progress in this area within the past 2 years. In developing one of the first high-volume intradermal delivery systems (our hMTS device, which delivers up to 2 mL of formulation), we have learned a lot about the potential of intradermal delivery. Currently, we are fast-tracking the

development of our hMTS device. Our testing has shown that the singe-use device is easy to use and requires a minimal number of steps for patients to perform. The device has scored well in placebo trials in terms of function and in usability.

Additionally, we've conducted a number of PK studies with the device in swine. One recent study compared delivery of Humira® with our hMTS device versus the autoinjector that is currently marketed with this product, and found that a full therapeutic dose of the drug was delivered by the hMTS and was very well tolerated in the swine, with the injection site being barely visible after 1 hour. Additionally, the testing showed the hMTS delivery resulted in slightly faster absorption and better bioavailability than the syringe delivery.

These results are consistent with the findings of other studies we have completed on proteins and antibodies. The technology also shows potential to improve the bioavailability of monoclonal antibodies, which have provided significant therapeutic benefits for many patients. We are excited to have the opportunity to improve a therapy that has been so effective.

In recent developments for the sMTS technology, a customer of ours, Radius Health, recently announced positive results of a Phase Ib clinical study to evaluate its transdermal BA058 Microneedle Patch. BA058 is the company's novel anabolic drug for the treatment of osteoporosis. Radius Health's successful trial demonstrated the ability of the BA058 Microneedle Patch to safely and rapidly deliver the drug over a short wear time, with no increased exposure resulting from longer wear, as well as supportive biochemical evidence of bone-building activity following 7 days of dosing. The study identified an optimal wear time of 5 minutes, as well as effective sites of application. These results support our plan to pursue a Phase II study in the coming year, and we believe the final product will increase efficacy, improve therapeutic outcomes, and provide ease-of-use for patients.

Q: With more than 50 years of experience within the inhalation drug delivery industry, what upcoming inhalation offerings can we expect to see from 3M DDS?

A: This is another product area in which we have continued to develop our offerings since our last discussion with your publication. As pharmaceutical companies develop more advanced treatments, or as they look toward life cycle management of their existing treatments, we are working hard to emphasize that patient preferences can be a significant contributor to a product's success. Patients have become increasingly influential in determining which products will be prescribed, and 3M is working to give pharmaceutical companies patient-friendly and convenient features to differentiate their products.

One telling example of this is in the case of allergic rhinitis. The leading brands of nasal sprays for this condition reach approximately $3 billion in retail sales per year, as it is the largest of the preventable chronic respiratory diseases. However, aqueous nasal sprays are often unpopular with patients, and research has shown that many would like an alternative. 3M has developed a "no-drip" nasal MDI device, which we believe can overcome the unpleasant features of traditional aqueous sprays. In addition to the no-drip benefits of this new MDI, additional features, such as ergonomic designs and dose counters, can be incorporated. Not only can these features add product differentiation, but they can also help pharmaceutical companies command a price premium.

As pioneers in MDI technology, we're constantly working to refine and improve our offerings for easier use and better compliance. Our new inhalers incorporate patient-friendly features, such as dose counters and dosing feedback mechanisms to help patients stay on top of their dosing and remaining supply.

We have conducted primary research in which patients spontaneously requested a simple way to know when their inhaler should be replaced. We have seen that the incorporation of a dose counter on MDI devices gives patients a feeling of security, and lets them accurately monitor their remaining doses and renew prescriptions before they've run out of medicine. Additionally, it reduces the risk of patients taking a sub-therapeutic dose by using the inhaler past the number of doses claimed on the label.

In addition to the added convenience

for the patient, we believe this feature can also help build product loyalty from the improved patient satisfaction. For pharmaceutical companies, a dose counter that offers a familiar look and feel as well as excellent technical performance can aid in regulatory approval and increase product differentiation.

For partners who are just entering the MDI realm, we offer the components and expertise to help maximize a product's chances for technical success. Our robustly designed valves and canisters reduce the risk of product failure during development. Additionally, because we are the only MDI component supplier that manufactures both valves and canisters, we are able to optimize components simultaneously to help guarantee our partners a successful fit into their program. Our partners get the convenience of working with a single source for components, and we are able to leverage our vertically integrated supply chain to ensure a continuous commercial supply.

Q: Controlling costs is vital in the pharmaceutical industry. How does 3M DDS help its customers compete in this marketplace?

A: As previously mentioned, 3M has a vast number of technologies within one company. Therefore, as we develop new products in any of our divisions, we are able to leverage our company-wide resources and proven technologies. In the realm of drug delivery, this includes films, adhesives, hardware design, coatings, and manufacturing services. This combination of services under one roof gives us technical and competitive advantages, and allows us to work very efficiently with pharmaceutical partners. Additionally, our expertise in design for manufacturability and scale-up (DFMSU) can help our customers avoid costly setbacks in the development process. Many pharmaceutical manufacturers may lack DFMSU knowledge in-house, but we provide our customers with assistance in scaling up, navigating the regulatory process, and manufacturing competitively at a commercial scale. We find that by offering assistance with DFMSU at the very beginning of the development process, we can help ensure a more economically efficient path for pharmaceutical companies.

Q: What makes 3M DDS unique in the manufacturing process and pharmaceutical market and what do you want customers to know about your company?

A: We offer a full range of cGMP manufacturing capabilities for transdermal systems, as well as transdermal components, including backings, membranes, liners, and tapes. Our transdermal manufacturing capabilities include both passive drug-in-adhesive as well as active solid microneedle systems for delivery of vaccines, proteins, and peptides.

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Particle Sizing Across the Drug Development Cycle

By: Carl Levoguer, PhD, Product Marketing Manager, Laser Particle Sizing & Imaging, Malvern Instruments

Introduction

To bring products to market more quickly and develop a more efficient manufacturing practice, the pharmaceutical industry needs appropriate analytical technology. Laser diffraction is a leading technology for particle size measurement, a major advantage being its ability to support every stage of the development cycle. This following reviews recent advances in laser diffraction and the benefits they deliver.

Decision tree 3 of ICH6A, the guideline relating to specifications, test procedures, and acceptance criteria for new drug substances and products, is a simple diagram with a far-reaching message.[1] It explains that acceptance criteria for particle size are required for any solid dosage form, or products containing undissolved drug substances, where particle size is critical to any of a number of important factors.

Dissolution, solubility, and bioavailability are all highlighted as potentially being influenced by particle size, as are content uniformity and stability. The guidance also points out that particle size and distribution can contribute to the processability of a formulation, the ease with which it can be manufactured reliably, and the maintenance of product appearance. These multiple dependencies on particle size explains why its measurement is so important in the pharmaceutical industry, from drug development and formulation right through to manufacture and QC.

For many pharmaceutical applications, the preferred technology for particle size analysis is laser diffraction. Well-established across the pharmaceutical sizing spectrum, this fast, non-destructive technique is amenable to automation and has the versatility and range to analyze the vast majority of pharmaceutical powders, suspensions, emulsions, and sprays. Recent advances have seen these intrinsic advantages wrapped in increasingly advanced instrumentation that enables the efficient use of laser diffraction analysis at all stages - beginning in the laboratory and moving through to commercial production. Here we examine how laser diffraction technology has been fashioned to powerfully support every stage of the drug development cycle.

Open Access in the Laboratory

Such is the need for data that particle size analyzers in pharmaceutical laboratories are likely to be in constant use, handling a diverse range of sample types and used by a number of different operators with varying levels of experience. This makes ease of use a defining feature of modern instrumentation and the key to greater productivity. Elsewhere in life, we've become accustomed to intuitive interfaces and software that deliver functionality to us rather than making us search for it. Today, this is what the best laboratory systems offer.

The starting point for any analysis is to define a robust and suitable measurement method. Modern analyzers (exemplified by the Malvern Mastersizer 3000) demonstrate this new approach to easier measurement with features such as a single interface with instant feedback for controlling and monitoring all the functions of the system. During method development, this makes it

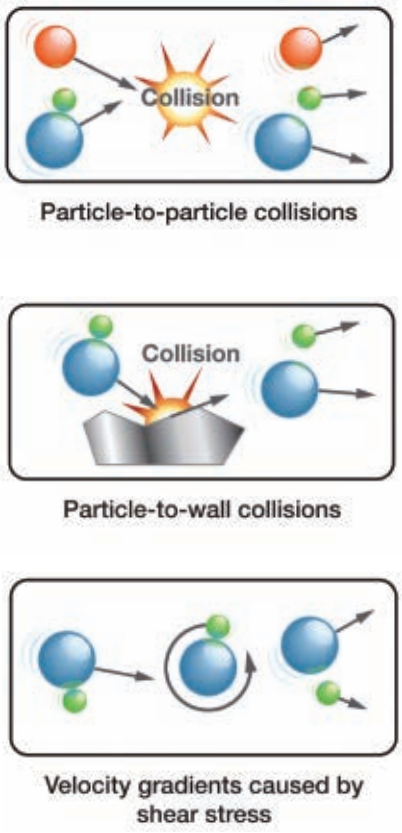

Figure 1.
Avoiding particle-to-wall collisions leads to gentle but effective dispersion, extending dry measurement to more fragile powders.

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possible to quickly and efficiently identify which settings are controlling measurement reproducibility in order to reach a solution that meets USP <429> standards. When that method is established, it is locked into the system. Standard operating procedure (SOP)-driven operation then ensures it is always properly applied.

In addition, smart tools critically and continuously assess data quality to ensure good, robust measurements. These tools are certainly a help in method development as well as throughout analysis. They pick up on issues such as inappropriate sample concentration for example, preventing compromised data from entering the information chain.

By allowing all users, no matter their level of experience, to easily and successfully use an analytical instrument, advanced software can significantly increase productivity; however, hardware developments also have a substantial role. Switching between the analysis of wet and dry samples, which is essential in the pharmaceutical environment, has been made very easy, but perhaps one of the most important gains for pharmaceutical analysis is the extension of dry measurement to a broader number of sample types.

Dry Measurement Efficiencies

The usual aim in particle size analysis is to generate data for the primary particles rather than for any agglomerated material present. Appropriate sample dispersion is therefore a necessary precursor to measurement. Dispersing samples in the dry state (as opposed to wet dispersion) has the advantages of speed and simplicity. Because no dispersants are needed, it also has less environmental impact than wet dispersion and is the preferred option for moisture-sensitive materials.

However, the extent to which dry measurement is feasible depends on both the design of the dispersion system and the properties of the particles being analyzed.

Figure 1 shows the mechanisms of dry dispersion. The collision of particles with an impaction surface can be a highly effective means of breaking up agglomerates but for some materials, may result in particle damage. Newer dispersion systems eliminate impaction surfaces and promote dispersion through the less-energetic actions of particle-particle collision and shear. This leads to gentle but effective dispersion that is suitable for a greater number of sample types than is possible using more traditional high-impaction methods. Where delicate pharmaceutical actives are concerned, this is an important development.

To summarize then, all elements of modern laser diffraction particle size analyzers have been optimized to capitalize on the fundamental advantages of the method. For pharmaceutical applications, the key achievements include fast and precise measurement across a very wide dynamic range coupled with the versatility to easily switch between sample types. Delivering the guidance and in-built support that enables users at all levels to make robust, reliable measurements is also a significant step forward. Today's laboratory systems provide the foundation for particle size optimization. They enable the definition of particle size specifications that can then move with the product through to commercialization, and allow for the application of appropriate measurement and monitoring along the way.

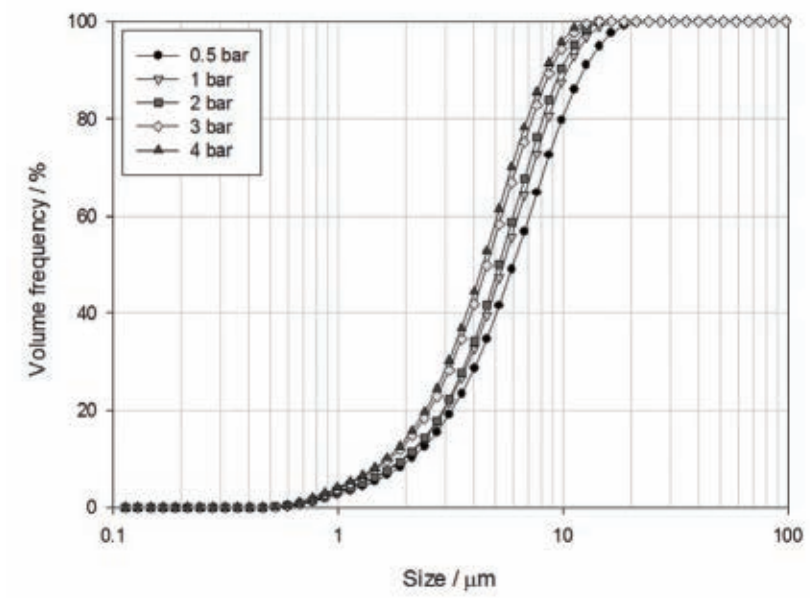

Figure 2.
Pressure titration data for the lactose samples indicates that a dispersion pressure of between 1 to 2 bar successfully de-agglomerates the sample without causing primary particle damage.

Case Study: Measuring the Fines Content of Lactose Samples

Measuring the particle size of a series of lactose samples, dispersed in the dry state, illustrates some of the capabilities of a laser diffraction system in supporting pharmaceutical development work. Each lactose sample used was made up of different relative proportions of fine and coarse material. Precise resolution of the amount of material present in each size fraction across the full measurement range of laser diffraction is a technical challenge, but one that is of practical importance. Many routine samples in pharmaceutical laboratories are highly polydisperse in some instances because the active is much finer than the excipient or because fine and coarse particles are included to optimize formulation behavior.

The use of lactose as an excipient in both oral and inhaled drug formulation is widespread. In both cases, particle size and size distribution must be closely controlled in order to meet performance goals. During tablet production, particle size and size distribution can influence powder flowability in the press and compression behavior, affecting both processing speed and the

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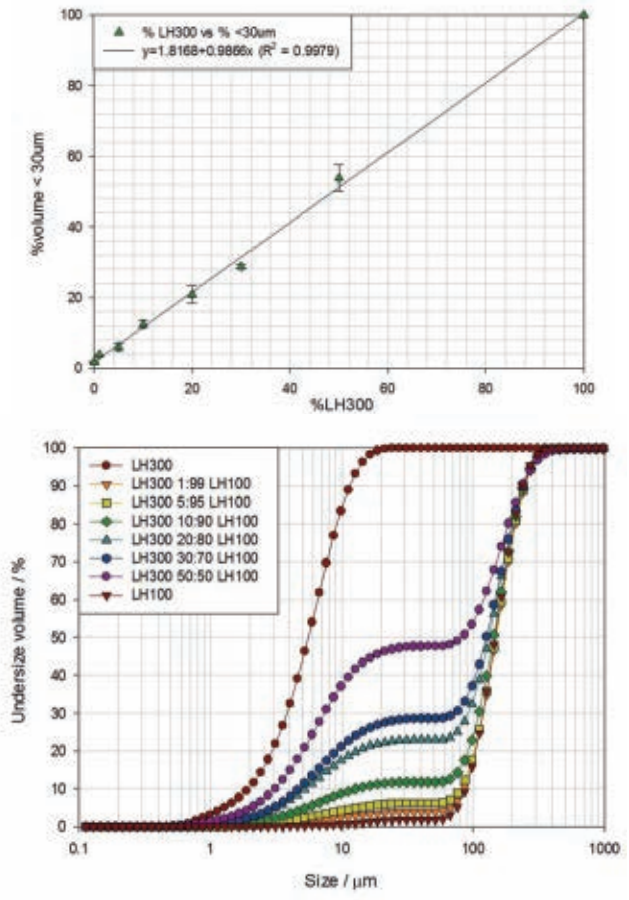

Figure 3.
Particle size distribution data highlighting the ability of laser diffraction to precisely determine the amount of fines in a mixed lactose sample.

uniformity and quality of the finished tablets. With dry powder inhaler (DPI) formulations on the other hand, the inclusion of a relatively modest level of fines (< 5% to 10 %) is a recognized way of improving aerosolization behavior and enhancing drug delivery.[2] Segregation is potentially an issue for both DPI and tableting blends, and is also dependent on particle size and size distribution.

The starting point for analysis of the samples was to develop a robust method. Figure 2 shows data from the pressure titration carried out. Energy input during dry dispersion is controlled by manipulating the pressure of the air used to disperse the sample, higher pressures being associated with more energetic dispersion. Here, the results show that as pressure is increased from 0.5 to 1 bar, there is a decrease in particle size as the agglomerated lactose particles become dispersed.

Raising the dispersion pressure from 1 to 2 bar has no further impact on the particle size that is measured. However, increasing the pressure above this up to 3 and 4 bar causes a further decrease in particle size. This illustrates the problem alluded to in the preceding discussion of dry dispersion; at higher pressures, the collision forces are high enough to cause milling of primary lactose particles. The optimum pressure range for primary particle measurements is therefore between 1 and 2 bar where the dispersion system is reliably dispersing the sample without causing particle damage.

The data shown in Figure 3 demonstrate how, when the method has been defined, laser diffraction reliably measures the particle size distribution of all the blends, even those containing only very small amounts of fines. The technique comfortably spans the range of interest and accurately resolves the amount material in each size fraction, reliably quantifying the amount of fines present, to give secure information for development.

Real-Time Measurement, When it's Needed

For certain pharmaceutical applications, particle size measurement is necessary in order to fully understand what is happening during a dynamic event, for example, in an inhaler spray. In these instances, the availability of real-time measurement systems is a major benefit of laser diffraction technology, amplified by the ease with which specifications can be transferred from laboratory instrumentation to other analytical set-ups.

Returning to the example of DPIs, there are two distinct particle sizing requirements. One relates to measuring the formulation, as manufactured and loaded into the device, the other to the size of particles delivered to the patient during use. An upper size limit of around 5 microns is typically referenced for delivery to the lung, which means that the active ingredients in DPI formulations are necessarily very fine, and correspondingly cohesive. In some formulations, carriers are used to improve ease of handling but alternatively, carrier-free delivery may be achieved through surface modification of the active.[3] Whichever approach is taken, it is essential to assess whether the particle size being delivered is sufficiently fine for deposition in the lung. This in vitro analytical requirement is common to all orally inhaled and nasal drug products.

Case Study: Characterizing the Performance of DPIs

Figure 4 shows data collected using a laser diffraction system set-up specifically for spray analysis. These measurements were carried out to support the development of a carrier-free DPI formulation containing spray-dried drug particles.[4] The addition of an excipient (L-Leucine) during spray-drying was hoped to improve dispersion. The green data relates to a micronized form of the drug, while the other three sets of data all relate to spray-dried samples containing different levels of excipient.

During laser diffraction measurement, one of the variables monitored is transmission, or obscuration. This parameter quantifies the amount of source light that is being picked up by the detector and therefore correlates with the concentration of particles in the measurement zone. A dense cloud of particles will prevent more of the light reaching the detectors, giving lower values of transmission. In spray analysis, this usually means that laser diffraction not only provides real-time particle size data but also real-time concentration data.

Figure 4 shows the evolution of particle concentration in real time following actuation of the DPI, for each of the formulations. Particle size was also measured in real-time, but the results have been summarized in table form for ease of comparison. Looking first at the concentration data, it is clear that entrainment of the different formulations from the device is markedly different. The

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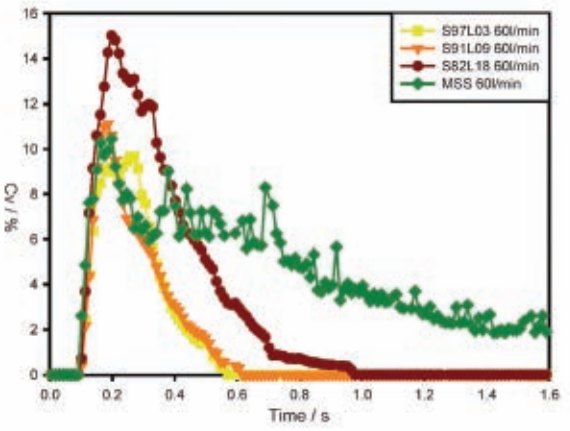
micronized sample is progressively drawn from the device at an almost constant concentration, while for the spray-dried samples, entrainment is a more rapid and contained event that is likely to be beneficial for delivery to the lung. One of these samples (red data) shows significantly better entrainment than the others, a much higher initial concentration, and delivery of more of the dose, as determined from the area under the curve.

The particle size data show that the micronized sample does not aerosolize well whether tested at a flow rate across the device of 30, 60, or even at 90 L/min. In contrast, the spray-dried samples are all delivered as finer particles, with a substantial proportion of the dose below 10 microns. Thus, the laser diffraction data indicate that spray-drying in the presence of the excipient is successful and highlight the formulation that looks most promising in terms of efficient drug delivery.



Sample	Flow Rate (l/min)	Dv(50) (µm)	%V < 10µm
S82L18	30	5.44	85.07
	60	3.89	93.28
	90	4.32	85.11
S91L09	30	5.25	84.28
	60	4.22	89.28
	90	4.87	78.22
S97L03	30	4.74	86.15
	60	3.76	89.06
	90	3.92	85.3
MSS	30	226.47	6.36
	60	94.03	30.32
	90	4.34	75.84

Figure 4.
Concentration and particle size data measured by laser diffraction to assess the impact of coating on the performance of a DPI formulation.

Efficient Process Monitoring - During Development & Into Production

The other major area in which real-time measurement is extremely useful is in process monitoring, especially in which process dynamics are fast. Over the long-term, this is likely to become increasingly important as manufacturing is driven toward more efficient production, but there are also major benefits for pilot studies. Here, continuous measurement increases experimental productivity, during for example, definition of the Design Space as advocated by Quality-by-Design.

Real-time particle size measurement has a number of applications in the processing environment, including granulation control and monitoring spray-drying. However, milling is probably the routine process in which real-time measurement currently has most impact.

Case Study: Investigating Mill Performance

When investigating how best to mill a new batch of material, whether at pilot scale or in commercial operation, there is a requirement to understand how to efficiently achieve the target particle size. A standard approach is to mill a sample, analyze the resulting material in the laboratory, and then further tweak the process to achieve a satisfactory result.

Using real-time measurement to monitor the material exiting a mill means that the effect of a process change is instantly obvious. This makes it easier to accurately identify cause and effect, scope the impact of different operating conditions, and ultimately, to efficiently produce the required particle size distribution.

Figure 5 shows real-time data from a spiral jet mill trial. Here, the impact of both injector pressure and feed rate are being assessed. Dv50, Dv90, and transmission (sample concentration) all reflect and quantify the affect of alterations to the operating parameters.

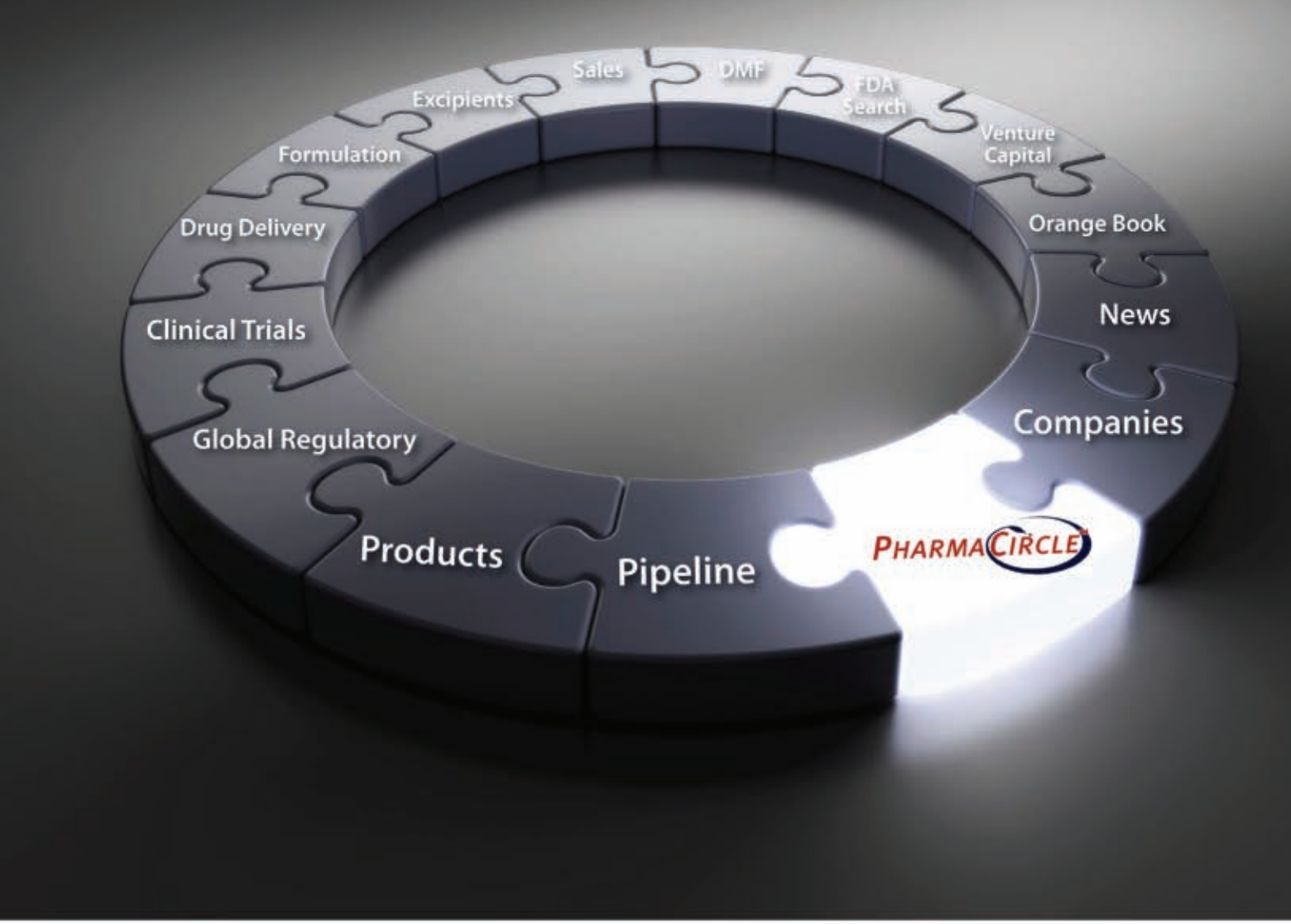
From the time-scale over which this exercise is conducted, it is obvious that the process can change very rapidly. Even so, the laser diffraction system is clearly capable of tracking performance in fine detail. This raises an important point in relation to the adoption of Process Analytical Technology (PAT) in that the time-scale for measurement must match the requirements of the process. Here, measurement times of 1 or 2 minutes would be too slow for precise monitoring.

Looking Ahead

Changes in the pharmaceutical industry, most notably a greater emphasis on efficient manufacture, are bringing with them changes in analytical requirements. The focus on in-depth understanding that underpins Quality-by-Design intensifies the need for reliable, robust techniques that efficiently secure the necessary knowledge. Process design and manufacture call for the identification of PAT that enables effective control on the basis of that know-how.

Particle size and particle size distribution are defining features of particulate materials, and their measurement is a common thread through the development cycle. In knowledge-led development, particle size measurement is complemented by other characterization techniques, such as imaging and chemical identification, that overlay size data with shape information and allow analysis of individual chemical components within the product. Such techniques are valuable in accelerating development, but moving into production, particle size remains one of the easiest particle properties to measure reliably. Consequently, it is often the parameter of choice for routine monitoring and QC wherever this delivers the necessary control.

Laser diffraction has some compelling



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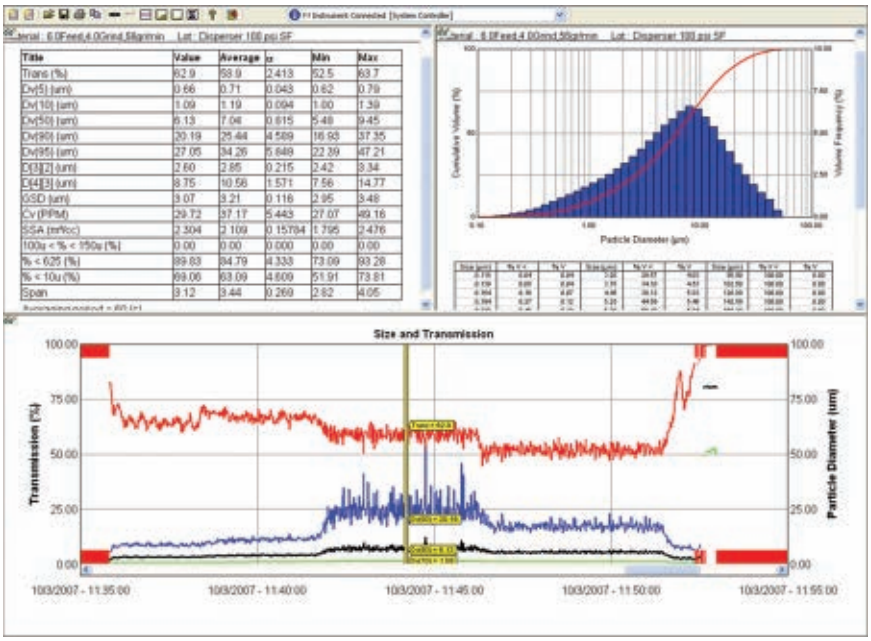

Figure 5.
Scoping mill performance is fast and efficient with real-time particle size measurement in place. The effect of process changes are instantly obvious.

advantages for particle size analysis, a prime one being speed. The latest laboratory systems answer to the need for robust measurement for every user and versatility within busy labs that cope with many and varied samples. They offer exemplary support for the effective definition of particle size specifications, in accordance with ICHQ6A. For process analysis, laser diffraction is now a proven real-time technology that has the ability to track even rapidly changing processes. Transferring a specification from lab to line has never been easier. Continuous measurement enables better and automated control, delivering real improvements in process efficiency. In combination, these advances position laser diffraction as a core analytical tool for the pharmaceutical industry, one that can transition with a pharmaceutical product from development out into successful and efficient production. ■

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The Presentation, Part II - The Dos, Don'ts, Whys & Wherefores

By: John A. Bermingham

Preparation

Follow the Boy Scout motto, *Be Prepared*. You want to be well rehearsed, comfortable with your presentation, and smooth in your delivery. An investor will quickly lose confidence in you if you are stumbling through your PowerPoint. Also, being well prepared drives your confidence, enabling you to make a dynamic presentation and give the impression that you know what you are talking about. Most importantly, make certain you have anticipated all of the questions that will be asked….and have the answers!

Questions

Listen very carefully to the questions and answer them directly and intelligently. If you do not know the answer, do not try to BS your way through it. It will be noticed, and the jockey will be quickly disqualified from riding the horse (see Part I from the March issue). Instead, be brave enough to say you do not know the answer but you will get right back to the investor with the information. This is acceptable unless it is your answer to all of the questions asked!

Rambling

When you want to tell an investor "what the time is," don't give them the history of the watch. Rambling is a deal killer. Investors are very busy people, and they do not want to work with company management who can't answer a question or make a point in a brief time frame. I have personally watched a presenter ramble on to a point where the investor looks like he is going into the fetal position in his chair due to the formation of so much negative body language aimed at the presenter. Just answer the question or make the point!

Just the Facts Ma'am

You want to make certain you present only solid facts to the investor and not make claims you cannot support or that are wishful thinking on your part. What you are trying to accomplish is to have the investor come to his own unmistakable conclusion based on the facts you presented. Or to say it another way, your facts will guide the investor to the conclusion you want. You must also be careful not to pin the BS meter by making claims that are not credible. Statements like "we will gain the No. 1 market share within 2 years" or "our revenue will quadruple over the next 3 years with profits increasing five-fold" just don't fly with investors. You want to appear credible by making factually supported statements that do not appear outlandish. Also, don't exaggerate the facts. Very often the investor will look to validate the facts you have presented, and if they find you have not told the truth, you are out. Don't say that you know the Chairman of Wal-Mart or the CEO of Unilever if the only time you have met them was to shake hands at an industry conference.

Competition

Never trash your competition even if they deserve it. Doing this is uncomfortable for the investor and will cause you to lose credibility. Rather than say your competition's products have lousy quality or they seem to catch on fire fairly often, instead say why your products are superior and/or what your competitive advantages are.

Final Thought

Regardless of whether you are going out to raise seed capital, venture capital, or a private equity investment, you should expect to receive many nos before getting to a yes. Don't be discouraged. This is a normal course in raising funds. As Winston Churchill said during WWII, "Never Never Never Give Up!" ◆

Biography

John A. Bermingham is currently the Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc). He was the President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). 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. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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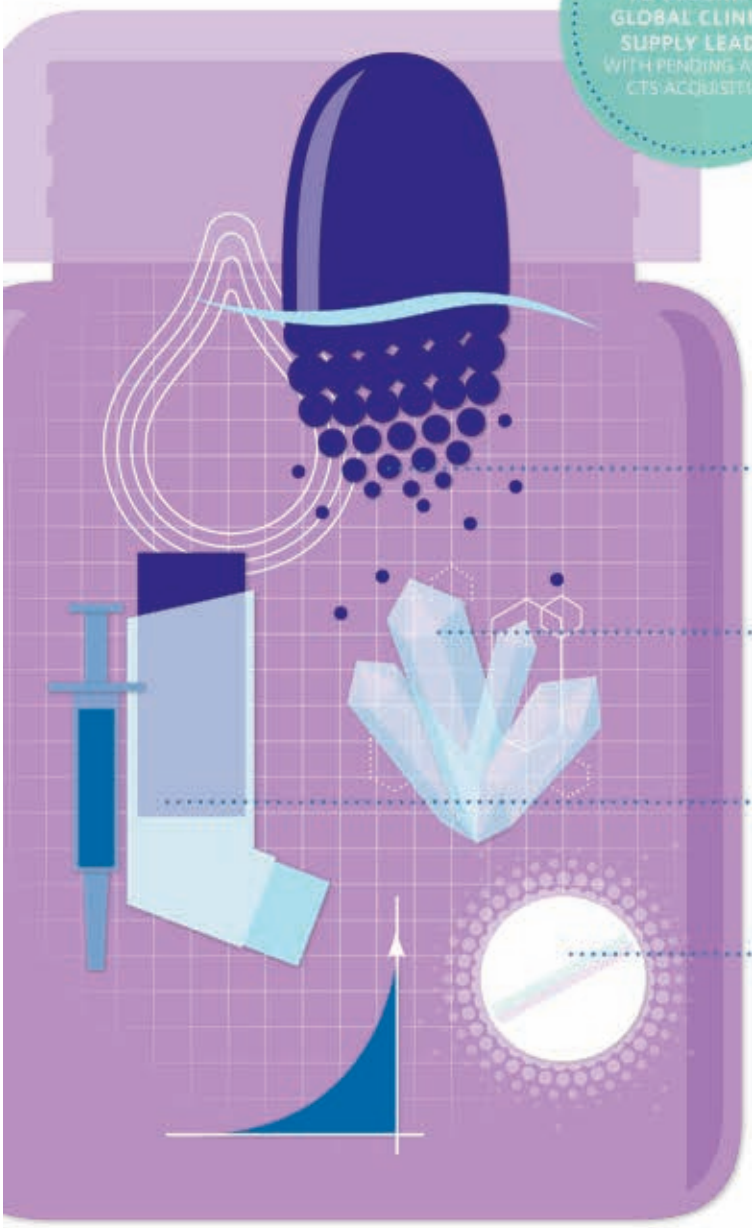

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