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January 2013 Vol 13 No 1 www.drug-dev.com

Universal Tumor Targeting

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

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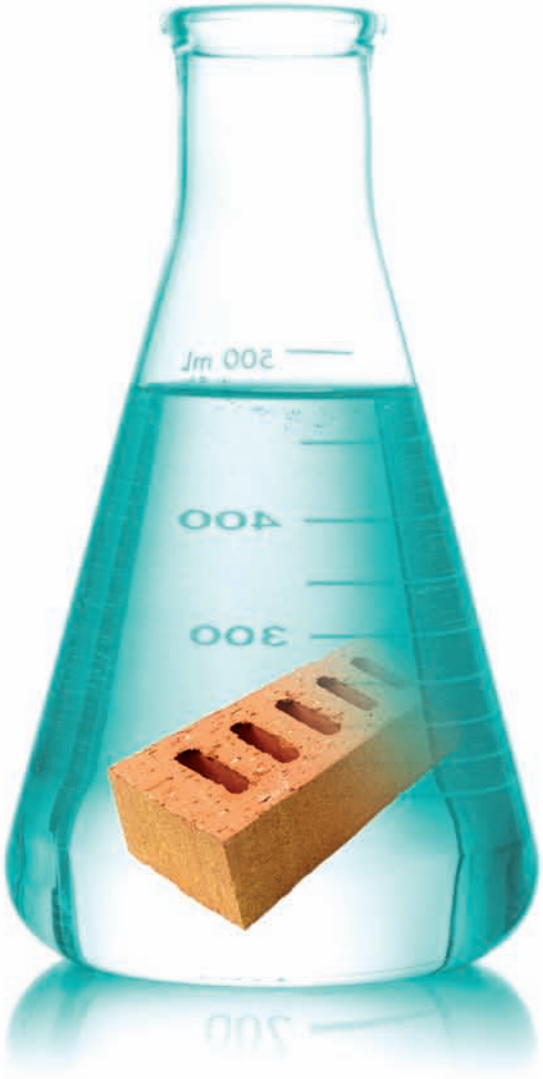

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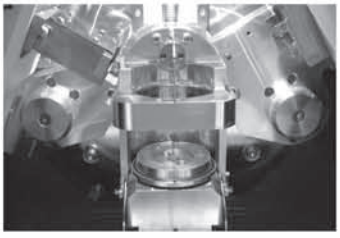

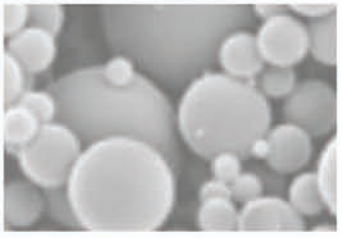

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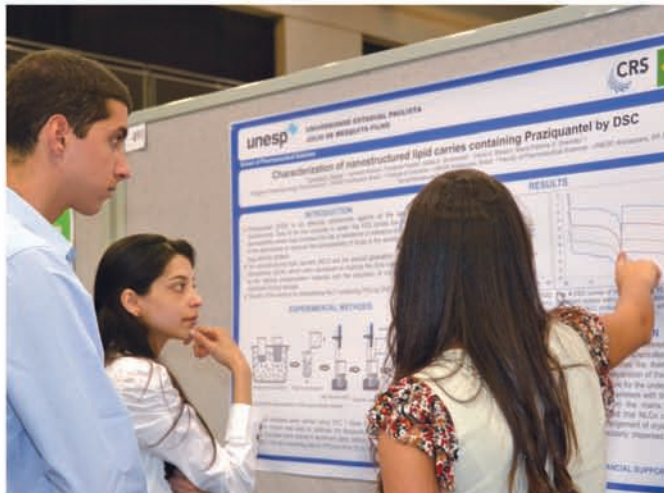


Governor Jindal, AgraTech International Announce New Chitosan Facility; Will Be Sole Domestic Supplier

Governor Bobby Jindal and AgraTech International Inc. Chairman Richard DeMarco recently announced the company will renovate a former Opelousas bottling facility, creating 50 new direct jobs and making a $10-million capital investment. The biotech venture will convert seafood shell waste into commercial products for the automotive, defense, and medical sectors. The new direct jobs will pay an average salary of $50,000, plus benefits, and LED estimates the project will result in an additional 51 new indirect jobs.

Raw shrimp, crawfish, and crab shells will be converted into chitosan for products ranging from water-repellant coatings on windshields to enhanced sunscreen lotions, nasal sprays to treat nosebleeds, and dental membranes for implant surgery. In addition to a 37,500-square-foot facility in Opelousas, LA, AgraTech International will establish a research partnership with the University of Louisiana at Lafayette.

Governor Jindal said, "This announcement is great news for Acadiana, and our entire state. The new facility will mill shrimp, crawfish, and crab shells - waste that previously had to be discarded and added an additional cost to Louisiana's seafood industry. Turning a negative into a positive for the Louisiana economy, AgraTech will convert these seafood shells into chitosan that will be used in new products for the medical, automotive, and defense industries. AgraTech could have invested in other states, but chose Louisiana because of our strong business climate, incomparable workforce, and our world-class seafood industry. The bottom line is that Agratech's decision to invest here is not only good news for our economy and our workers, but also our seafood industry and for our higher education community."

Based in New Jersey, AgraTech International secured a long-term lease on space at the former Yoo-Hoo chocolate drink bottling plant that closed 3 years ago in Opelousas. The site places the company within close reach of a 100-million-pound annual supply of crustacean waste. AgraTech also will conduct research activity at the University of Louisiana's College of Engineering in Lafayette, where the company will provide instruction and research assistance to students and faculty in exchange for lab space.

"Chitosan production is a totally green endeavor: It is a natural, renewable, nontoxic, and nonhazardous, biodegradable product," said Mr. DeMarco, who's also President and CEO of AgraTech International. "AgraTech will be the sole domestic commercial supplier of high-quality chitosan. From our Opelousas location, the company intends to remain in the vanguard of chitosan research, developing new chitosan-based products."

In addition to medical applications, AgraTech will manufacture and license the technology to produce a chitosan-based, water-repellant coating permanently bonded to glass. Water-barrier applications in the automotive, construction, defense, and optics sectors hold significant potential in what the company estimates is a more than $36-billion market. AgraTech and the University of Louisiana at Lafayette are negotiating a research partnership agreement to enhance market applications for the company and research opportunities for the campus.

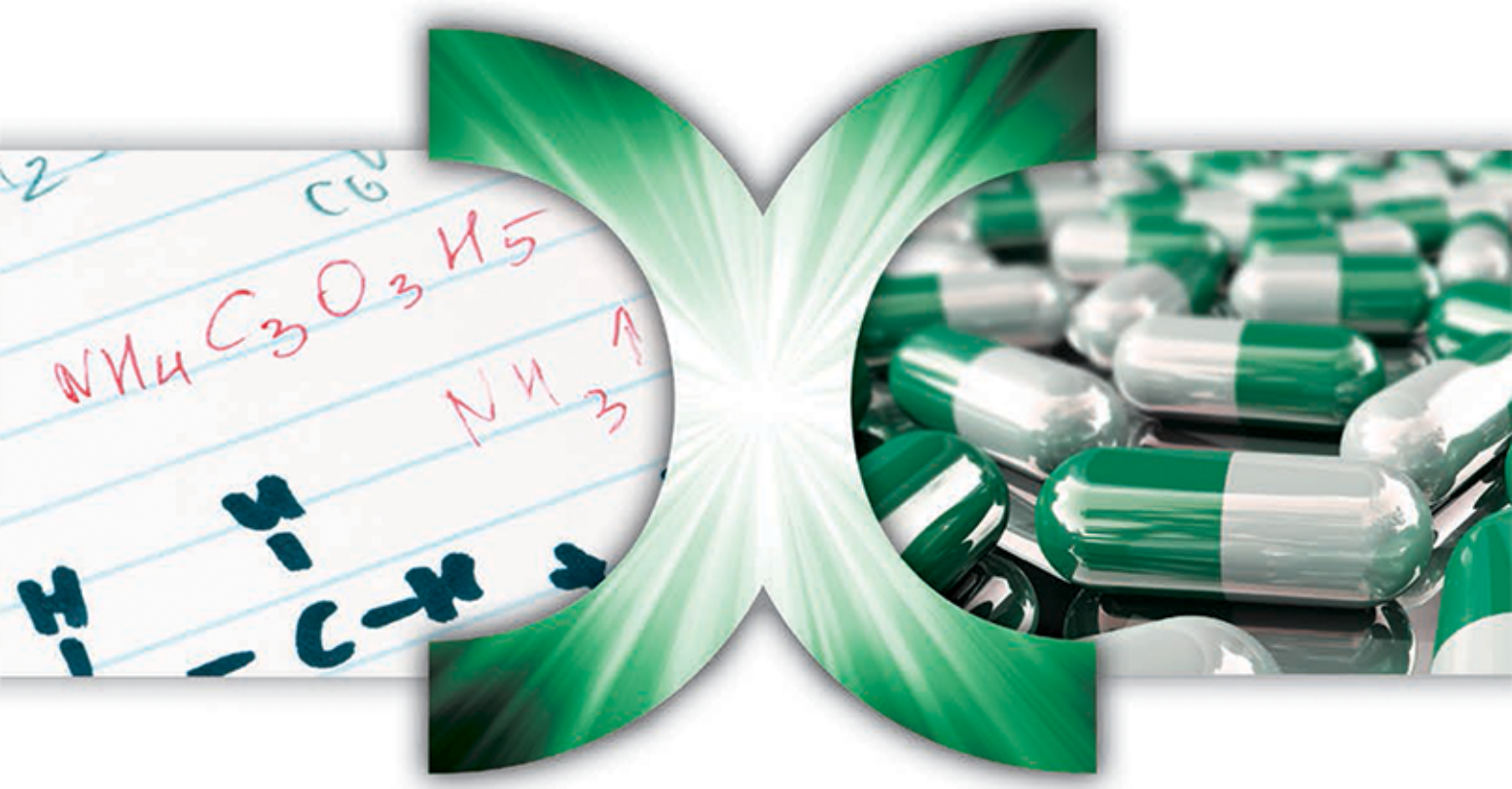
"The university is always seeking innovative partnerships to enhance the economic diversity and development of the state," said President Joseph Savoie of the University of Louisiana at Lafayette. "The scientific work conducted by AgraTech complements research by our faculty. Arrangements such as this are beneficial for business, the university, the region, and the state. When companies such as AgraTech have a campus presence, it enhances our ability to engage undergraduates, as well as graduate students, in the types of research that will lead to the creation of more jobs and further economic opportunities."

Acadiana Economic Development and the St. Landry Economic Industrial Development District helped recruit AgraTech International to the Acadiana Region, and the company is expected to utilize Louisiana's R&D Tax Credit, Enterprise Zone, and Industrial Tax Exemption incentives.

"The seafood industry has long been an important part of Acadiana's economy, providing a source of income for the fishermen and the seafood processors and served up as a main ingredient in our top-quality restaurants," said Chairman Mike Tarantino of Acadiana Economic Development. "This industry has always sought avenues that will bring added value to their products. By utilizing a costly industry waste product, AgraTech brings a unique feature that makes sense both economically and environmentally."

Renovation and equipping of the facility will begin in early 2013, with commercial operations planned by the end of the second quarter 2013. AgraTech will hire 10 people in its first year and increase its staff to 50 employees within 5 years.

AgraTech International Inc. has developed a biotech enterprise focused on chitosan, a natural material processed from crustacean shell waste (shrimp, crawfish, crab). Demand for chitosan continues to outpace supply as new uses for chitosan are being discovered and new chitosan-based products are developed. AgraTech has developed an efficient, flexible process for manufacturing high-purity chitosan that allows for multiple product applications and eliminates substantial hauling fees for disposal of the waste. For more information, visit www.agratech.net.



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Radius & 3M Announce Exclusive Agreement

Radius Health, Inc. and 3M Drug Delivery Systems recently announced an exclusive partnership agreement for development and commercialization of BA058-transdermal (TD). BA058 is a novel, synthetic proprietary peptide analog of human parathyroid hormone related protein or hPTHrP, a bone building anabolic compound with the potential to treat patients with osteoporosis at high risk of fracture. This agreement updates the general development agreement announced in May 2011 by the two companies for BA058-TD.

BA058-transdermal (TD) is being studied in a Phase II clinical trial in healthy postmenopausal women with osteoporosis at 10 clinical centers. BA058-TD is a short-wear time patch based on 3M's patented Microstructured Transdermal System technology. The transdermal patch is expected to combine ease of use, convenience, and self-administration attributes of a patch with the bone building efficacy of the BA058 compound.

"We are excited that 3M Drug Delivery Systems, which has long demonstrated a commitment to quality, safety, and innovation, is partnering with us to bring a novel approach of drug delivery to the underserved osteoporosis patient population," said Michael Wyzga, Radius President and Chief Executive Officer. "Our study data for BA058-TD showed that a 5-minute wear time of the patch delivers peak drug levels consistent with subcutaneous injection and we hope to see increased patient compliance with 3M's innovative technology."

3M Drug Delivery Systems has partnered with pharmaceutical companies worldwide for more than 50 years, providing customized solutions to drug delivery.

"We are pleased to be part of Radius' mission of advancing therapeutics for healthy aging with its deep expertise in osteoporosis," added Ingrid Blair, MTS/TDD Business Vice President of 3M Drug Delivery Systems. "With this exclusive agreement, 3M and Radius demonstrate our commitment to this innovative therapeutic treatment and this unique drug delivery mechanism. We believe this new drug potentially will improve the health of patients with severe osteoporosis and that 3M's microneedle patch technology may improve medication compliance among patients."

BA058 is also being studied as a daily subcutaneous injection (BA058-SC) in a Phase III study with 2,400 patients for fracture prevention in women with postmenopausal osteoporosis at high risk of fracture. Phase II human testing of the injectable BA058-SC showed that BA058 significantly increased bone mineral density (BMD) at the lumbar spine and femoral neck (a common osteoporotic fracture site located in the hip joint) after six months of therapy.

Blend Therapeutics Secures $16 Million

Blend Therapeutics, Inc. recently announced it has secured a $16-million Series B financing. Blend is pioneering an integrative model for discovering novel molecular entities with new mechanisms of action purposely designed for Blend's proprietary nanoparticles. By synergistically developing both the molecule and the nanoparticle together, Blend can make medicines more targeted, more effective, and more tolerable.

NanoDimension led the Series B round with participation from other existing investors, Flagship Ventures, and New Enterprise Associates. Proceeds from the financing will be used to expand Blend's product and business development teams and to advance the company's lead programs through studies to enable filing of an investigational new drug (IND) application with the US FDA.

The funding will enable Blend to pursue its initial focus in oncology as the company continues research and development of new classes of platinum drugs. The company will expand the development of its proprietary molecules for oncology, which include a portfolio of mono-functional platinums that have an entirely different mode of DNA platination and unprecedented biological differentiation compared to that of existing platinum drugs. Blend's platinum drug discovery program is fueled by chemical insights provided by structural and innovative mechanistic studies of Dr. Stephen J. Lippard, who is a founder of Blend and the Arthur Amos Noyes Professor of Chemistry at the Massachusetts Institute of Technology.

"Blend has made great progress translating its novel, integrated, new molecule discovery engine and nanoparticle engineering platform into exciting first-in-class product candidates in oncology," said Ed Kania, Managing Partner and Chairman of Flagship Ventures. "We share the patient-focused and product-driven vision of the team at Blend, and we are excited to be joining with NanoDimension and NEA to support the Blend team with our collective resources and strategic reach as they advance their anti-cancer drug candidates."

"This Series B investment clearly recognizes the value that the Blend team created since the last financing a year ago and will enable the company to pursue untapped opportunities with broad potential impact in oncology as we develop cancer therapies with superior selectivity and efficacy," added Mark Iwicki, President and Chief Executive Officer of Blend Therapeutics. "With several product candidates in multi-billion dollar categories in our pipeline, this financing will allow us to advance two lead molecules through IND-enabling studies, each of which involves a novel platinum molecule with new modes of action for cancer therapy."

Atlantic Pharmaceuticals Makes Major Announcement

Atlantic Pharmaceuticals, Inc. recently announced that new patents have been issued by the USPTO relating to its tamper-resistant SMART/Script drug delivery platform. US Patent Nos. 8,187,636 and 8,349,362 contain claims that cover Atlantic's proprietary tamper-resistant platform, which are designed to resist dose dumping of orally delivered opioids and may sequester and reduce drug release of a drug that has been subjected to a variety of physical methods of tampering. The technology can be applied to immediate as well as sustained release drug candidates.

"We believe SMART/Script is a unique technology that may have a significant effect on prescription drug abuse and misuse," said Anthony Soscia, President of Atlantic Pharmaceuticals. "These patents further add to our intellectual property portfolio and provide us with extensive coverage until 2028 for our novel, tamper-resistant technology."

SMART/Script (SMART, Simple, controllable, resistant, insoluble, physical trap), a novel, patented drug delivery platform, was designed to prevent easy drug extraction and to deter the abuse of medications via known routes of abuse, including chewing, snorting, and injecting. Orally delivered tamper-prone pharmaceuticals are frequently subjected to abuse and misuse via chewing and swallowing or crushing and either snorting or injecting the resultant powdered drug. A product formulated with SMART/Script however, resists dose dumping in water or alcohol and can be used with a broad range of opioids and non-opioids in immediate or extended release forms. SMART/Script is also unique among competitive technologies in that physical tampering of the dosage form may reduce the release rate of the drug from the dosage when subject to certain forms of physical tampering as opposed to increasing it.

Atlantic Pharmaceuticals is a specialty pharmaceutical company using its patented technology to produce novel therapeutics that resist attempts at tampering and may be useful to reduce abuse of certain prescription drugs. Based on the company's proprietary technology, SMART/Script, Atlantic is developing a pipeline of tamper-resistant opioids that are nearing pivotal testing.

The company's lead SMART/Script candidate, ATLP-02, is an immediate release formulation of oxycodone that is in development and will be covered by the issued patents. In addition, these patents will also cover other product candidates being formulated using the SMART/Script technology. The company finalized a Pre-Investigational New Drug Meeting with the FDA in March 2011 for ATLP-02. SMART/Script has also been recognized as a leading technology that may potentially decrease tampering with medication by the Center for Lawful Access and Abuse Deterrence.

Raptor Signs $50-Million Agreement With HealthCare Royalty Partners

Raptor Pharmaceutical Corp. recently announced it has signed a $50-million loan agreement with HealthCare Royalty Partners to help fund the commercialization of PROCYSBI, the branded name of RP103 for the potential treatment of nephropathic cystinosis, and advance the company's development programs.

Under the terms of the agreement, Raptor will receive $25 million at closing and an additional $25 million upon US FDA approval of PROCYSBI. The First Tranche and Second Tranche Loans, which mature on December 31, 2019, bear interest at an annual fixed rate of 10.75% and a Synthetic Royalty variable rate, tiered down, based on a percentage of future PROCYSBI sales. The loan is interest-only for the first 2 years.

"This loan agreement with HC Royalty further validates the growing value of PROCYSBI and Raptor's pipeline. We believe that the proceeds of this financing will provide us with the necessary capital to fund our activities through FDA approval of PROCYSBI, based on our current assumptions for the timing of a potential FDA approval of PROCYSBI, as well as to fund our plans to launch PROCYSBI in the US, if approved by the FDA," said Christopher Starr, Raptor's CEO. "At closing of the first Tranche, we will have over $55 million in cash on our balance sheet, with an additional $25 million to be funded under the Second Tranche Loan upon FDA approval of PROCYSBI."

"There is significant unmet market need for a more tolerable cystinosis treatment with a less burdensome dosing schedule, and we believe PROCYSBI will fill that need for patients once it is approved by the FDA," added Clarke B. Futch, Founding Managing Director at HC Royalty. "We are pleased to partner with Raptor to help fund the commercialization of this important orphan drug."

RP103 is an oral, delayed, and extended-release medication containing enteric-coated spheronized micro-beads of cysteamine bitartrate. PROCYSBI is the branded name of RP103 for the potential treatment of cystinosis. The New Drug Application and Marketing Authorization Application for RP103 for the potential treatment of nephropathic cystinosis have been submitted to the FDA and the European Medicines Agency, respectively, and the NDA has been assigned a PDUFA date of January 30, 2013.

RP103 is also in clinical development for the potential treatment of Huntington's disease and non-alcoholic steatohepatitis (NASH). In cystinosis patients, RP103 may reduce cellular toxicity by continuously removing cystine from the lysosome. RP103, which can also cross the blood-brain barrier, was engineered specifically to allow release of cysteamine bitartrate micro-spheres in the duodenum for optimal absorption while simultaneously enabling administration every 12-hours for the potential treatment of cystinosis.

Management Insight

Pharming Infertile Fields: Three Strategies for Growth in a Going-Nowhere Economy

Based on the book Build, Borrow, or Buy: Solving the Growth Dilemma by Laurence Capron & Will Mitchell

By: Derek Hennecke, CEO & President, Xcelience

Part 1 of a 6-part series offering an overview of this year's six best business books with insights into what they can teach the Pharma industry.

In a healthy growing economy, you and I are both business oracles. We plow investments into fertile fields and they grow. Success is a ripe apple in arm's reach.

It's been a long time since we've seen such crops, and with the Conference Board forecasting GDP growth of 1.4% next quarter, we are still in this interminable drought. Investments grow slowly, languishing, their limbs drooping, and their fruit pale and tasteless. Others wither and die in the fields.

In this climate, you must scrutinize not only our own investment choices, but also those of the people you do business with. If you choose the wrong vendor, you may unwittingly tie your own fortunes to another's dying horse. This month's column is your guide to analyzing the growth strategies of the companies around you.

There are really only three ways to grow a business. First, you may build from the ground up - a new plant, new people, and new equipment. Second, you may borrow new capabilities from others - by contracting or allying with another company. Lastly, you can buy another business, and then carefully stitch it into your existing business. Ultimately, the decision of whether to build, borrow, or

buy a new capability is as important as the decision to adopt the new capability itself, and the choice can make or break the business.

How do you choose? Capron and Mitchell, authors of *Build, Borrow, or Buy: Solving the Growth Dilemma*, have spent decades developing a framework to answer this question. Their insightful book is the new bible of business growth; a go-to place to analyze and understand business decision-making and forecast business growth. If I were to summarize their book in a nutshell, it would be this: Build if you can. If you can't build, borrow. If you can't borrow, buy.

BUILD

Build if you can. If you build, your new capability will be custom-designed to meet your clients' needs. Your new capability will be a product of your own genes. You will love it unconditionally, because it's your own. At the risk of overstating things, you and your management team will experience the warm glow that comes after giving birth. Of course, not everyone can build a new capability, as Capron and Mitchell aptly point out. To build, you must already have in-house the knowledge, processes, and incentive systems you're going to need.

Eli Lilly developed Zyprexa in its own labs. The new drug was a natural fit because it built on the existing knowledge base Eli Lilly had used to develop Prozac. It was also a strong organizational fit because Zyprexa used existing technical expertise in central nervous system therapies, both in development and in clinical trials. It also had a market similar to that of prior products, and used compatible regulatory and marketing procedures and familiar evaluation techniques.

Just because a company has the in-house capabilities, however, doesn't necessarily mean a build strategy is called for. If, for example, your current staff gets all cloak and dagger when they see the new people coming in, your strategy is doomed. Insiders can be expected to put up a fight when their culture or processes are threatened, and when they are faced with obsolescence, expect the gloves to come off.

Take the example of Schering Plough, used in *Build, Borrow, or Buy*. Schering Plough only ever used the build strategy. After the blockbuster success of Claritin, the company needed to fill the pipeline. Company scientists struggled and failed to come up with their own successor. When a desperate management team began to put forward outside alternatives, the organization vehemently resisted. Management waited too long before forcing the issue, and a formidable inner battle ensued. When the dust cleared, the old team found itself not only under new management but also in an unlikely alliance with competitor Merck, working on an anti-cholesterol drug. Even this drastic measure resulted in only lackluster sales, so when it failed, the gig was up. With no pipeline, Merck acquired Schering Plough in 2009.

Ironically, Merck itself had suffered a similar tumult a decade earlier because of internal resistance to outside intrusion. Management eventually forced the in-house labs to accept external sourcing, and the company later earned a reputation for adeptness in sourcing from contracts, alliances, and small purchases.

In my own company, Xcelience, we use the build strategy most often. Sometimes the choice is simple. Sometimes it's not. We recently added new equipment capabilities, including a GeoPyc Envelope Density Analyzer and AccuPyc Gas Pycnometer to support our existing roller compactor work. Micromeritics' Geopyc is an ideal tool for the determination of the bulk density of roller compactions and the ribbon created during the process. And the Gas pycnometer is a perfect match for measuring the density (really the volume) of almost any type of solid. In 2012, we added extrusion and spheronization capabilities to produce pellets, and that has been very successful. We might have partnered with another to add these capabilities, but we chose to bring them in-house. We were honest with our first client about our limited experience with the technologies, but we made it work, and we've since developed the requisite experience. Obviously, these new capabilities did not threaten our internal resources. We also learned what we didn't know and recently hired another formulator to support us in that. Easy implementation.

The decision to add clinical packaging to our capabilities was much more complex. Using the *Build, Borrow, or Buy* template, which I was already a fan of when we made the decision to add clinical packaging about a year ago, we began with some knowledge questions.

The first question was, did we already have - or could we easily hire - the in-house knowledge and expertise to master clinical packaging? The answer was yes. We didn't already have clinical packaging expertise, but we were willing and able to bring industry-leading expertise on board.

The second question was, would the new people fit our current system of incentives and culture? The answer was again, a resounding, yes. The idea met with no sense of internal competition or

feelings of cannibalization, as might happen for example if a commercial packager were to try to get into clinical packaging. You may recall Sharp, a commercial packager, recently purchased Bilcare, a clinical packager. This was not an impulse buy - Sharp had tried for a couple of years to build a clinical packaging unit in-house, but finally decided that it would have to buy. Commercial and clinical packaging are strange bedfellows; they are destined to compete for resources, and the larger, more lucrative commercial packaging department will always win.

With positive answers to the key questions, the build strategy was a fit for Xcelience. In addition, we had a client who was willing to commit to our new venture, and granted us high-level access to their own staff to help us set up the right systems. With our own people and the client's expertise specifications, we had the foundation to build a new, 25,000-sq-ft, purpose-built facility devoted entirely to clinical packaging, which we opened in September. To this combination of in-house industry experts and client support, we sprinkled a liberal dose of specialized clinical packaging consultants, and we were able to create a new capability in-house, and to a higher level of quality than any of our competition.

It wasn't easy. Building is costly and takes time, and any small company has to struggle to free the resources to pour into a new venture. We were careful to make sure that the whole organization bore their share of the burden. But for Xcelience, the changes necessary to bring about this new capability internally were relatively minor. Had they not been, we would have moved down the ladder to the next possible strategy: borrowing.

Borrow

Far less threatening to your internal organization is the option of borrowing. Borrowing means either contracting with another organization for a certain capability, or forming a less formal alliance with the same goal. Like renting a vacation home, a car, or a bike, there can be advantages over building or buying. In fact, according to Mitchell and Capron, most businesses undervalue this strategy. They believe they need to have complete control over the capability, when in fact they don't. Moreover, borrowing often gives them more control than they expected.

For one thing, borrowing can work faster than any other strategy. Let's say your company decides it needs a new software technology to win that million-dollar contract that will be awarded next month. Building would take months. Even buying a company, with all its incumbent ritual negotiation dances, deals to secure capital, due diligences, and so forth, takes far too long. But if you could contract with a known supplier, there's a reasonable chance you might be able to make it happen with two afternoon meetings and one three-course dinner (your tab, most likely).

A drug product company looking to backwardly integrate into APIs would be a great candidate for borrowing. Building your own API company is rarely an option; the capital required for API development is huge, as are the risks, but more than that, the chances of an organizational fit are infinitesimal. API companies are led and managed from top to bottom by organic chemists. The ways of thinking are different. A drug company would be far better off contracting, forming an alliance or a joint venture with an API company.

Borrowing can also be a better choice when your organizational knowledge base is weak. Mitchell and Capron use the example of Abbott Lab's expansion into India. Even though Abbott has great strengths in marketing and regulatory systems and has put them into practice successfully in North America, Europe, and beyond, they knew enough to know that they didn't know India.

Borrowing is relatively risk-free, but relatively risk-free is not the same as risk- free. Borrower beware, as Toys "R" Us would certainly warn you. Toys "R" Us made a larger-than-life-sized mistake in committing to a long-running play date with online retailer Amazon, according to Mitchell and Capron. In making the deal, Toys "R" Us saw nothing more than the opening of a new channel to sell toys. Amazon, however, saw the opportunity to learn a new industry, and so it did. It learned it so well that shortly thereafter Amazon purchased its own line of competing toys to sell on the site. Toys "R" Us had unwittingly created a new competitor for itself, and a really, really good one at that. In 2004, Toys "R" Us sued Amazon claiming that Amazon had taken advantage of their relationship, and the judge agreed with a settlement of $51 million to Toys "R" Us. It was still nowhere near enough to compensate for the creation of a new superhero-powered toy retailer. In hindsight, if Toys "R" Us had set up a simple contract to sell goods, things might have gone differently. It was the decision to partner with them, sharing info about sourcing and product management that led to irreparable harm. In this case, it would have been better to keep their contracts simple and share only what they must.

Lastly, don't borrow if you don't need it. Every year, I consider bringing

micro or USP compendial testing in-house. It would be - well - tidy to possess this capability. And every year I decide against it. This is so easy and inexpensive to outsource, there is plenty of capacity in the US for raw material testing, and bringing it in-house would never be a deciding factor for a client choosing to use Xcelience's services. Better to let someone else do it.

Buy

Buying is enticing. Why take the time to build, with that "buy it now" button beckoning from the corner of the screen? Company shareholders want results yesterday; building takes time. Borrowing means having to play nicely in the sandbox with a partner; buying offers complete control.

But buying a company is significantly different than buying on Amazon. Where will the money come from? If you have the money in-house, so much the easier, but unless your last name is Cook (or formerly Jobs), you probably don't have millions lying around. And buying is expensive. It's not like buying a car, where you are buying just the metal and screws and glass, the labor, and a profit margin for the factory and dealer. You must pay not only for the bricks and mortar and inventory that you would also pay for if you were building, but also for a multiple of the company's future earnings. An existing company has a track record and if it's a good one, it's going to cost you. A lot. Five to ten times the company's profit in the current year is a reasonable price to pay. Let's be perfectly clear: you are paying for profits not yet generated, and there's no guarantee that those profits will continue to flow under new management.

If you don't have the cash on hand, you will need banks or private equity. Banks are fine, but their lending potential is limited, and your balanced books may or may not be to their liking. Private Equity (PE) capitalists are better equipped to listen to the unique intricacies of a particularly exciting buying opportunity, and they offer a wealth of experience to temper your buying impulses and guide you in cutting a good deal. But they, too, have their own agendas, which include delivering three times returns to their investors within a three to five-year timeframe. These goals may conflict with your own long-term growth goals.

Buying a company is not unlike the dating scene. Many companies will flirt with you, if they know you are on the market and you've been building your books. Then, one day, you meet the perfect purchase. You think you are logical and rational, but your heart races, and your eyes begin to cloud. She is nothing less than perfect. You line up your financing, and make your intentions known. She has other offers on the table, and you play the game, upping your offer and adjusting your terms to secure her affections. She offers you the deal. Your heart soars, and your thoughts turn to integration.

Not so fast, young man. The first step in the deal is a LOI (Letter of Intent). That means that for 60 days (or similar), she will not entertain any other offers. In that time, you may perform a due diligence. A due diligence is when she opens her files and all the interested parties in the deal swarm over her to ascertain if everything she said in the flirting stages is as it was said to be. Unexpected things will come to light; they always do. Many of the income streams that she said were ongoing may turn out to be one-time sources of income that are going off patent. You may still love her and be determined that two can live cheaper than one, but your PE is turned off. As the nascent deal collapses, you must, with trembling hands and broken heart, break up and return to the dating scene.

Still, at the risk of being trite, it is better to have loved and lost… and if buying is your best choice, you must get out there again until you find your soul mate.

Patheon's purchase of Banner Pharmacaps was an excellent match that will make Patheon one of the largest soft gel companies in the world. Patheon had tried for years to build its own soft gel business called P-gels, advertising heavily to support the fledgling brand. It was a good strategy for a commercial firm. Soft gels are hard to make and never a good choice for early clinical development. It's hard to say why P-gels didn't take off - it might have been internal competition for resources, lack of internal expertise in making them, or even lack of marketing prowess in the face of Catalent's market dominance. Internal build wasn't cutting it. Then, in what appeared to be a last-ditch effort to save the strategy, they purchased Banner, and Patheon was catapulted into a position of market leadership. I give this purchase two thumbs up.

Catalent's recent purchase of the clinical packaging business Aptuit is more of a head scratcher for me. Catalent already had a build strategy well underway and, according to their most recent quarterly filings, this build was already one of the company's best performing units, when analyzed completely separate from the Aptuit purchase. Management had done several things right, including selling their commercial packaging to Frazier

Healthcare, eliminating the potential for internal conflict for resources. But why then take a build strategy that's working and add the distraction of a buy, with all the inherent conflict and loss of productivity that comes with any integration? Already they've had to close down an entire site to achieve the cost savings synergies that would pay for the deal. It's possible the purchase will help them achieve economies of scale more quickly as they struggle to catch up to Fisher Clinical, but the deal creates enough friction in a previously smoothly growing operation that I have to wonder, if it wasn't broke, why'd they fix it?

AAI's purchase of Celsis Analytical at the beginning of this year is even more puzzling. AAI was already known for its analytical capability, so what was the strategic rationale for adding two more labs and 150 people? If they needed more capacity, then build it. There is no question that they had the in-house capacity as this was not a new capability. By buying these labs, not only did they accept the integration hiccups that go with any purchase, but they paid up-front for profits not yet generated, and not guaranteed. Beyond that, customers of Celsis may have chosen Celsis over AAI for a reason. There is no guarantee that clients will stay once under AAI management. It is possible AAI sees more cost-savings efficiencies from the larger scale, but given they are still in seven separate locations and don't have the scale to be the largest analytical lab, the potential economies arising from this purchase are limited.

When it comes to bad purchases, I would be remiss if I didn't mention a purchase that is much in the news lately as one of the worst buys ever: Hewlett Packard's (HP) purchase of British software maker Autonomy.

In November, HP announced a write-down of $8.8 billion of this $11 billion dollar purchase. Five billion of the write-down was due to what HP called, "serious accounting improprieties, disclosure failures, and outright misrepresentations at Autonomy Corporation that occurred prior to HP's acquisition of Autonomy and the associated impact of those improprieties, failures, and misrepresentations on the expected future financial performance of the Autonomy business over the long-term." The rest of the write-down came, as it happens, from the resulting stomach-wrenching plunge in HP's share price. This, despite HP spending two months pouring over the books, and involving Barclay's and KPMG, among other highly-reputed firms.

Autonomy, meanwhile, vigorously disputes this assertion, claiming that HP single-handed destroyed England's most valuable software company by making it a pawn in the management's own flip-flopping strategy changes. Autonomy management said that at one point, HP sales staff were even told not to sell Autonomy software.

The ultimate outcome is far worse than just a write-down and much licking of wounds. Two of the biggest players in the tech world are now fighting a public battle for their reputations in which, arguably every host and parry in the media arena damages both parties. Beyond that, HP, the Autonomy management, and a host of advisors could be up to their eyeballs in litigation for a very long time. Buyer beware! ◆

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.

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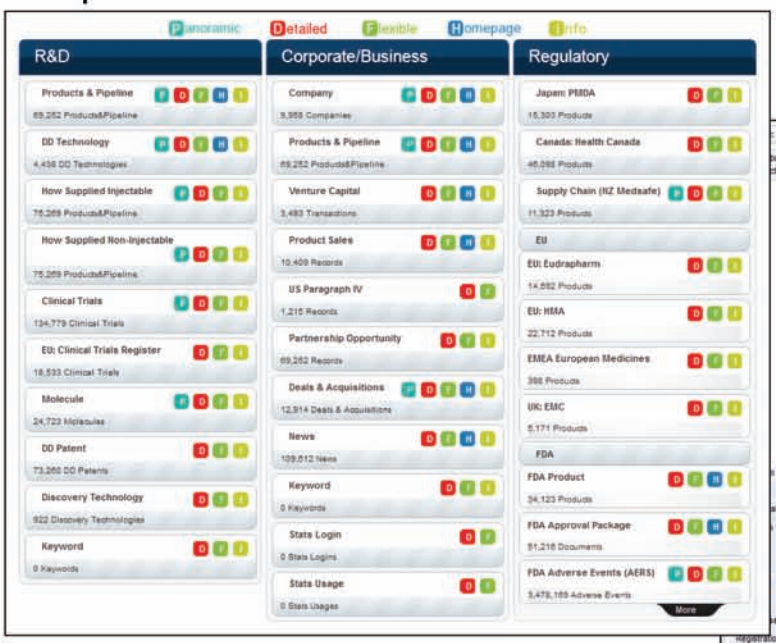

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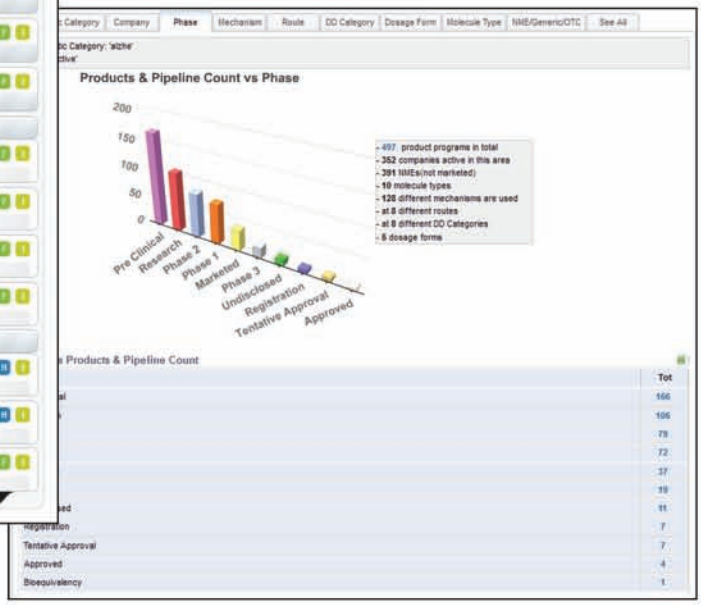

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ADVANCED DELIVERY DEVICES

Inhalers: Can't Use, Won't Use

By: Kate Farmer, PhD, MBA; Kate Farrell, MEng; Andy Pidgeon; and Anna Rickard, PhD

When ranking levels of compliance in healthcare, the use of preventive inhalers for the treatment of asthma falls pretty near the bottom. The current situation sees some of the worst reported rates of patient compliance mirrored by a shockingly high number of emergency room visits due to asthma attacks - a situation you would imagine many are working to improve. In this discussion, we aim to provide some insight into the reasons behind the low levels of compliance. We focus not only on the patient, but consider what the healthcare industry could be doing to tackle the problem, including the issue of whether it will require regulatory authority-enforced legislation to move this market forward.

DEFINING COMPLIANCE

Compliance, also commonly referred to as adherence, describes the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider.[1] Compliance problems are observed in all situations in which the self-administration of treatment is required, regardless of the type of disease, disease severity, and access to health resources, with many factors contributing to compliance difficulties.[2] Findings suggest that compliance of patients to a prescribed therapy for a variety of diseases is rarely more than 60%, with rates ranging from 15% to 93% depending on the condition.[3,4] Studies suggest that those with conditions such as HIV or cancer tend to comply more to treatment regimens than those with pulmonary disease, diabetes, and sleep disorders.[5] Poor compliance can also be associated with numerous demographic factors, including age greater than 65 years, failure to complete high school, the complexity and length of the regimen, poor

FIGURE 1A&B

The T-Haler, a new asthma training device developed by Cambridge Consultants, more than doubles proper use rates.

Based in Freiberg/Germany, teamtechnik has been making intelligent and reliable automation solutions for medical and pharmaceutical industries and for the automotive and solar technology for over 35 years. teamtechnik is considered an international leader in highly flexible automation technology. With a total of 750 employees throughout the world, the company achieves sales of over €145 million. The teamtechnik Group has production sites in Germany, Poland, China and the USA.

teamtechnik develops innovative process-optimized production solutions for medical technology that meet customers' requirements right up to serial production. The systems are designed with a modular approach, a highly flexible concept which allows the manufacturers of medical devices to adapt their production quickly and economically to changes in the market.

For cost effective production from Start-Up to High-Speed production the company has brought to market three different platforms: START-UP, the platform for prototype production to verify processes early in their final execution and for clinical trial production; TEAMED, a highly flexible and upgradeable platform for assembly and testing; and RTS, the high-speed platform for economical mass production.

These platforms are realizing almost 80% of all customer solutions in the medical technology sector. Superior process technology, SPC test systems and 100% end-of-line testing can be integrated specifically for the production of medical devices and pharmaceutical products. The teamtechnik production systems allow production compliant with global guidelines and monitoring systems such as GAMP5, FDA and CE and meet class 6 clean room specifications.

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physician-patient relationship, memory problems, and inability to pay for treatment.[5] Patient attitude and beliefs as well as their perception of disease/treatment are known to be key in ensuring compliance.[6] Patient willingness is also seen as a critical element.[6]

Broadly speaking, compliance can be broken down into two categories: voluntary and involuntary compliance. Voluntary compliance can be viewed as the patient's choice as to whether they wish to follow the agreed recommendations. Poor compliance may occur because a patient actively chooses not to attempt to follow the advice of their healthcare provider. In contrast, involuntary poor compliance may occur when a patient is intending to follow recommendations but is unable to. This may occur because a patient has not fully understood the advice or is unable to follow the advice, for example, the medication required is too expensive or a drug delivery device requires a level of dexterity beyond that of the patient. Tackling voluntary and involuntary compliance raises two distinct sets of difficulties, and both must be overcome to ensure success.

ADDRESSING RESPONSIBILITY

Compliance should, in the main, be the choice of the patient, and the aim should be for this to remain as such. However, of vital importance is that this choice is an informed one and in this, healthcare providers, pharmaceutical companies, and device manufacturers take responsibility. A healthcare provider needs to provide sufficient training and tailor treatment where possible to the patient. Importantly, pharmaceutical companies and device manufacturers have a responsibility to ensure the correct use of devices. However, the extent to which this happens in practice remains debatable. Current regulations in healthcare provisions state that "devices must be designed and manufactured in such a way that…they will not compromise the clinical condition or the safety of patients…and are compatible with a high level of protection of health and safety".[7] This includes "reducing as far as possible the risk of user error due to the ergonomic features of the device and the environment in which the device is intended to be used".[7] In addition, there must be "consideration of the technical knowledge, experience, education and training, and, where applicable, the medical and physical conditions of intended users".[7] The persistence of low compliance suggests that a more active commitment to these responsibilities is required across all parties.

ASTHMA AS AN EXAMPLE: DETAILED USER INSIGHT

There are an estimated 300 million asthma sufferers worldwide, and its prevalence increases by 50% every decade.[8] On average, more than three Americans go to the emergency room every minute due to asthma attacks. In the UK, the figure is one person every seven minutes. Asthma patients often go through periods of symptom remission and are required to take preventive medication.[9] This perception of "feeling well" exacerbates low compliance and erratic use.[9] Despite an estimated 90% of deaths from asthma being preventable and an estimated 75% of hospital admissions for asthma avoidable, as few as 28% of individuals in developed countries comply with the regular taking of their preventive therapies.[10-12]

Asthma is a debilitating disease that can be deadly; however, it is a disease that can be effectively managed with treatment. By far, the most common treatment is through the use of inhalers that have a well-documented low rate of compliance. Human Factors research is important to study how people use inhaler technology, providing

FIGURE 2A&B

The Starhaler, a high performance, easy-to-use inhaler, developed by Cambridge Consultants in collaboration with Sun Pharma Advanced Research Company Ltd.

insight for Human Factors Engineering, which utilizes this information in the design of devices and systems. There are many techniques for gaining usability data; one of the most effective being one-to-one in-depth interviews. Cambridge Consultants conducted a series of extensive interview programs with asthma patients to examine inhaler use and compliance.

Aside from medication cost, which can be a major factor for non-compliance, two areas were identified as key to tackling compliance: first, encouraging patients to use their inhaler, and second, ensuring patients use their inhaler properly. Many patients do not regard inhalers as "medication," and some patients regard them as optional. Whether this should be reinforced or accommodated in inhaler design is of importance. Many patients place a low priority on using their medication; when they are busy, it is the first thing to be skipped. As people pay more attention to things they value, the aim is to make patients value their inhaled medication through device design, as patients don't stop being consumers when they are diagnosed with asthma. Designers need to make inhalers fit better into the patient's existing lifestyle and make their first interaction a positive one.

To ensure patients are using their inhalers correctly, devices are required to be more intuitive to use and the possibility to use them incorrectly needs to be reduced. Patient understanding of their therapy varies enormously. Many patients have a poor understanding of how maintenance and rescue inhalers work and sometimes use the wrong one. Patients need to know when they have taken their dose and when their next dose is needed. The patient needs to feel in control of their medication, which can be achieved through aspects such as clear dose counters and improved user feedback. The inhaler needs to be used as a vehicle to reinforce good behaviors or routines. Many patients receive very little training and have no effective follow-up on their inhaler use.

DEVICE APPROACHES TO AID COMPLIANCE

Failure to master the use of the inhaler is regarded as a main reason for inefficacy of inhaled treatment. It is commonly reported that design can improve compliance, however, in practice, distinct examples of this are limited.[13] Poor inhaler technique prevents patients receiving the full therapeutic benefit, and can often lead to more severe conditions that result in emergency room visits. Training can improve technique; however, it is mainly performed through a patient observing an inhaler-use demonstration by their healthcare provider, which is often ineffective. With this in mind, Cambridge Consultants has developed two inhaler devices with a primary focus on improving compliance.

T-Haler

Coordination of inhalation by the patient with device actuation is a major problem with current metered dose inhalers (MDIs). In addition, when using some devices, patients cannot easily tell when they have received their medication, leading to confusion or even overdosing. The T-Haler, a simple training device, could be a truly life-changing technology. Interactive software, linked to a wireless training inhaler, monitors how a patient uses their device and provides real-time feedback via an interactive video "game". The T-Haler has been developed to provide visual, engaging, and interactive feedback to the user on the steps that were performed correctly and coach the user in the areas that need improvement. This device, based on an MDI, can be used as a standalone training device or incorporated into a prescription inhaler product, retaining the original pharmaceutical primary packaging. The device provides real-time indication of correct use and could securely report poor usage and compliance issues back to the healthcare provider. Wireless data transfer from the inhaler could be achieved via a mobile phone or computer. Compliance data can be relevant to the healthcare provider and pharmaceutical companies, as well as enable new business models, such as targeted incentive programs. The T-Haler measures the following three key factors for proper inhaler use:

1. whether the patient has shaken the inhaler prior to breathing in,
2. the force with which they breathed in, and
3. when they pressed down on the canister (the step which releases the drug).

These three variables can determine the efficacy with which drugs are delivered in a real MDI device. More than 50 healthy participants, aged 18 to 60, took part in a study conducted by Cambridge Consultants to test the efficacy of the T-Haler. Before using the training system, participants were asked to use a standard inhaler, and the average success rate of the group to use this inhaler correctly was around 20% - in line with numerous other studies carried out. The participants had no prior experience with asthma or inhalers and were given no human instruction beyond being handed the T-Haler and told to begin. The on-screen interface walked the group through the process, which takes just three minutes to complete. Without any human direction, participants went from around a 20% success rate without training to a success rate of more than 60% after only three minutes with the T-Haler device. This is more than twice the compliance rate observed in other studies with trained participants. Importantly, a week later, 55% were still correctly using the device, showing that they retained what they learned.

Starhaler

The second device, the Starhaler, developed by Cambridge Consultants in collaboration with Sun Pharma Advanced Research Company Ltd, is an ergonomic inhaler designed to ensure efficient delivery of a drug to the lungs and increase the likelihood of the patient receiving their required dose. The Starhaler is an easy-to-use device for pediatric, geriatric, and adult patients and ensures a uniform dose delivery independent of patient effort. The device is equipped with a breath-activated mechanism, with only inhalation triggering the drug release. There is tactile feedback when the cap is opened and an immediate audible sound when inhaling, indicating the dose pocket is pierced and drug delivery has started. While inhaling, a whistle-like sound confirms the dose is delivered. Lactose taste provides additional confirmation on the dose delivery. Dose indexing occurs when cap is closed only after a successful inhalation, making a fail-safe dose counter. There is no dose waste if the dose is not inhaled by the patient. The airway of the inhaler has a unique design that efficiently de-agglomerates the formulation providing highly effective delivery to the lungs. It has been demonstrated that a half dose given by the Starhaler is as effective as full dose given by an alternative inhaler due to the efficient delivery system in place.[12]

MOVING FORWARD: EDUCATION, REGULATION & CREATION

Education

It is fundamental for patients to receive sufficient education and training to understand the importance of their inhaler medication as well as understand how their inhaler should be used. There is a clear disconnect between the impact of poor inhaler use and patients' understanding of this impact. According to Asthma UK, people who do not have a written personal asthma action plan are four times more likely to have an asthma attack requiring emergency hospital treatment.[14] Healthcare providers and the industry need to work to lessen this gap.

Regulation

The current regulatory situation for approving inhalers could be seen to be unsupportive of improving compliance. For example, an inhaler that is comparable to existing inhalers at peak flow but performs better at lower flow rates would need to undergo a more rigorous approval process compared with an inferior device, because of the absence of equivalence. This extended approval process for superior devices is seen by many as a barrier to progress. Regulatory authorities need to recognize the need for new technology that is more effective and respond to this by facilitating the approval of superior devices. Alternatively, the regulatory authorities are in a position to force change. They could, for example, ban the use of inhalers that cannot demonstrate good compliance from 2020. This would allow sufficient time for development while forcing the industry to improve devices, leading to increased compliance.

Creation

The need for superior devices compared with those currently dominating the market is clear. Superiority could, for example, be achieved by a breath-activated MDI or an inhaler that provides a patient-tailored reminder system or direct feedback to the healthcare provider or ideally a device that incorporates these three features. Research suggests that internet-based patient adherence interventions may be particularly effective , and web-enabled monitoring technologies will enable healthcare providers to actively engage patients in managing their health.[5] A new inhaler needs to ensure effective drug delivery with minimal opportunities for incorrect use. For device designers and manufacturers to develop such a device they require assurance from pharmaceutical companies that these progressive devices will be welcomed. In turn, pharmaceutical companies need assurance that a new device not only provides a competitive advantage over existing products but has a feasible route for gaining regulatory approval and reimbursement. The reimbursement of these, inevitably higher priced devices, can be a challenge. The reimbursement authorities need to be encouraged to reimburse devices based on overall cost of treatment if these, more innovative, devices are to be widely accepted. Reliable measures of compliance would certainly aid this.

It is, however, difficult to accurately measure compliance, and current methods are considered inaccurate and of limited use. If compliance could be accurately demonstrated, the benefit of one inhaler over another would become apparent. An inhaler that maximises the likelihood of a dose being taken correctly, records only those doses that are taken correctly, and remotely logs this compliance data, could provide pharmaceutical companies with the necessary evidence to demonstrate the advantage of their product over that of a competitor. Furthermore, accurate compliance data could be used to illustrate improved compliance results in better health outcomes and the financial benefits of this in the long-term. This would increase the likelihood of buy-in from reimbursement authorities, payers, and individual users and subsequently increase sales.

IDEALISTIC VISION FOR 2020

Sufficient data to demonstrate true compliance and associations between this, long-term health outcomes, and financial benefits, are

enabling a step-change in the inhaler market. A change that occurs without the introduction of regulatory legislation, and is instead driven by the current missed market opportunities. Any change will require co-operation from all responsible parties, but the benefits are likely to be large and they may just help us all breathe a little easier.

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BIOGRAPHIES

Dr. Kate Farmer is a Senior Healthcare Consultant leading the strategic work in this area at Cambridge Consultants. With over 15 years of experience across medical devices and pharmaceuticals, Dr. Farmer specializes in the technical and commercial assessment of products and technologies, market analysis, market strategy, licensing, and acquisitions. She earned her PhD in Molecular Biology from the University of Sheffield and her MBA from Nottingham University Business School. Dr. Farmer can be reached at kate.farmer@cambridgeconsultants.com and is happy to receive correspondence.

Kate Farrell is a Senior Engineer within the Medical Technology division of Cambridge Consultants. She specializes in and has led the design and development of drug delivery devices, being cited in subsequent patents from some of these developments. She earned her MEng in Product Design Engineering from the University of Glasgow and Glasgow School of Art, which gives her a wide interest and user focused approach to device development. Ms. Farrell has written and presented to industry peers on methods of improving the Metered Dose Inhaler technique for users.

Andy Pidgeon leads the Industrial Design and Human Factors team at Cambridge Consultants in the UK. He has been developing new products in the consumer and medical markets for over 25 years and is a vocal proponent of user centric design. Over the past few years, he has conducted hundreds of interviews across the US, Europe, and Japan, with patients and healthcare professionals as a part of new device development programs. Mr. Pidgeon has managed the design and development of novel inhalation and parenteral drug delivery systems and has been cited as the inventor on a number of patents. He lectured in Industrial Design at Oxford Brookes University and has been published across a range of journals on design, usability, and compliance.

Dr. Anna Rickard is a Healthcare Analyst at Cambridge Consultants. She works across a broad range of medical device and pharmaceutical projects providing expertise in areas such as the evaluation of candidate medical technologies, user and expert insight interview programs, and market and company assessments. Dr. Rickard earned her PhD in Nutritional Epidemiology from the University of Cambridge.

EMERGING MARKET BRIEF

Healthcare Growth Opportunities: Is Brazil the Next Big Thing in Healthcare?

By: Research Executive Swathi Allada, MBA, and Industry Analyst Willian Fujioka

INTRODUCTION

In today's global economic world, the BRIC countries (Brazil, Russia, India, and China) are setting up new horizons, promising strong potential for future growth in the healthcare market. According to Frost & Sullivan's research, it is estimated that Brazil will continue to maintain the second position among the BRIC countries, after China.

The Brazilian healthcare market is poised for rapid growth by $19.8 billion from 2011 to 2015, constituting a compound annual growth rate (CAGR) of 12.6%. The major revenue will come from the pharmaceutical/biotech sector, followed by medical devices, medical imaging, clinical diagnostics, and healthcare IT. Overall, the distribution of healthcare sectors will be maintained throughout the next 5 years.

With a Complex Set of Drivers Comes a Diversified Set of Opportunities

Throughout the past few years, private contributions in healthcare have risen with the increasing interest of investors and rising private equity investments as well as M&A activity. Furthermore, the healthcare industry in Brazil has also progressed through huge investments in R&D and the implementation of innovative healthcare delivery models.

Foreign Direct Investment & Private Equity Investment

Given the attractiveness of the Brazilian market, many multinational companies are making a foray into the market through joint ventures with local healthcare companies. For example, the American Multinational MSD (Merck & Co.) made its first foray into the Brazilian market, which is a joint venture with Supera, a company created in 2011 by the national laboratories Eurofarma and Cristalia. The expectation is that sales revenues of the new company, Supera RX, will reach $500 million by 2017 with a portfolio of innovative medications and drugs.

There has also been an increase in private equity investments across the healthcare delivery chain. For example, Brazil's national development bank, the BNDES, and the four major local pharmaceutical companies (Ache, EMS, Hypermarcas, and UniãoQuimica) established a joint venture in 2012 to develop biological drugs, most likely biosimilars. The expectation is that the new company, BioBrasil, will commence its operations in the first half of 2013 with the initial investment worth $200 million in capital from its banking partner.

Intensive M&A With Local Companies Too

The Brazilian healthcare market has also witnessed M&A deals throughout the past few years. For example:

- The Brazilian company Bergamo was acquired for $215 million by a multinational company named Amgen in 2011.
- Additionally, the acquisition of Delta, Bunker, and Probiotica by Canadian company Valeant accounted for more than $100 million in 2010 and 2011.
- The acquisition of a leading Brazilian healthcare IT company, WPD, by Agfa in 2011 has resulted in significant growth opportunities in Brazil.
- Finally, the acquisition of WhebSistemas, Tesco Informatica, and Dixtal by Philips in 2008 and 2010 has geared the global portfolio of clinical diagnostics and patient monitoring solutions in the Brazilian market.

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The number of hospitals in Brazil

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with international accreditation certificates reached 37 in 2011 and grew 117.6% in 2 years. In the São Paulo state, private hospitals are expected to receive investments of $1.5 billion in the next 5 years. With the increase in bed ratio and the change in technological updates, there is a shift in focus on examinations, diagnosis, and specialized treatments, which demands new centers.

Boom of Population With Private Insurance Plans

The number of people with private insurance plans has significantly increased due to the recent positive economic scenario and the growth of formal employment, moving from 31.8 million in 2003 to 47.6 million in 2011. This shows that for every four habitants in Brazil, one has a private insurance plan.

One of the Heaviest Disease Burdens Around the Globe

Despite improvements in basic health indicators, such as maternal and child mortality, Brazil will endure a tough battle against both infectious (dengue still has epidemics year after year) and non-communicable diseases, with special attention to obesity and diabetes. Another area is cancer: more than 2 million new cases are expected by 2015.

Medical Tourism: An Emerging Market of $2 Billion

Brazil is emerging as a major medical tourism destination, with the market expected to reach $2.1 billion by 2015 with a CAGR of 28%, leading Latin America's (LATAM's) expansion in medical tourism. Other emerging destination hubs for medical tourism in LATAM are Chile, Colombia, Costa Rica, and Mexico. The key therapeutic areas in this field are oncology, orthopedics, cardiology, plastic surgery, dental treatments, and neurology.

It is estimated that the factors driving this growth are the expansion and improvement of infrastructure, especially in hotels and airports (due to the World Cup and Olympics), including the modernization of private hospitals. However, this growth is hindered due to a lack of government regulations.

The Sixth Largest Pharma & Biotech Industry in 2015

The Brazilian pharmaceutical market is among the top 10 in the world. This market earned revenues of $26.1 billion in 2011, and it is estimated to reach $41.3 billion in 2015. The Brazilian pharmaceutical market is the largest market in LATAM, growing at a CAGR of 12.1% from 2011 to 2015.

The pharmaceutical market is currently driven by branded and non-branded generics, which will be strengthened with patent expiries of blockbusters, such as Diovan, Zyprexa, Nexium, Cialis, and Cymbalta. With this scenario, the significant number of acquisitions and strategic deals on branded and non-branded generics is expected to continue.

Controlling the indiscriminate dispensing of different types of medicines is a great challenge for Brazil's healthcare system. In response, the government program, Farmácia Popular (Popular Pharmacy), was launched in 2004. The consolidation of government policies promoted dynamic change of pharmacies and drug stores with discount rates up to 90%, which implicated the increase in sales by 123.4% in 2011. This represents a major effort by the government to exert control over Brazil's sprawling retail pharmaceutical industry and help deter the unregulated trades.

The market is also driven by an aging population, and the percentage of the elderly population (60 years and older) will significantly rise to 13.5% in 2015 from 10.1% in 2005. With the growing aging population, there would be significant incidence growth in traditional pharmaceuticals segments like cardiovascular diseases, pulmonology, neurology, and oncology, as well as non-traditional pharmaceutical segments that include cosmetics, plastic surgeries, and nutrition.

The over-the-counter (OTC) drug market estimates current growth of 15% in Brazil. The categories of OTC drugs that make Brazil the leading pharmaceutical market include nutritional supplements, multivitamins, dermocosmetics, analgesics and cold/flu.

The Fastest-Growing Sector in Healthcare by 2015

The Brazilian medical devices market is the largest in LATAM and is anticipated to reach $8.4 billion in 2015 from $4.7 billion in 2011, which is ahead of Mexico. A 15.8% CAGR is expected until 2015, which may slightly increase the participation within the region from 33.3% percent to 34.3%.

The sale of coronary stents is expected to grow from 14% to 18% in the next 5 years, with 160,000 stents sold annually in Brazil. Additionally, the trend of coronary heart diseases (CHD) mortality in LATAM is expected to triple throughout the next 2 decades.

It is estimated that the investments for oncology treatment from the Ministry of Health will surpass $280 million, and the orthopedics market will surpass $700 million by 2015. Furthermore, the implementation of a telehealth program by the federal government suggests a necessary investment of $39 million for its expansion in 2012. Also, the market for enteral and parenteral nutrition devices will demonstrate the strongest growth over the next few years.

The main risk factors, such as cardiovascular diseases, oncology, chronic diseases (diabetes and cancer), breast implants, and knee and hip replacement surgeries are increasing at a fast pace in Brazil. Added to the expansion of infrastructure for acute treatment, the Brazilian market will witness huge potential for growth in interventional devices, radiotherapy equipment, telemedicine and mobile health, and orthopedics devices.

These are the driving factors for growth in the Brazilian medical devices market and are believed to increase with the rising aging population, penetration of lower-cost versions, and reimbursement by private insurance companies. However, the medical devices market is inhibited by certain factors, such as tighter quality control for breast implants, lack of adoption of sophisticated products, and high dependence on imports and exchange variations.

A Nascent Market With Opportunities Everywhere

The Brazilian healthcare IT market earned revenues of $410 million in 2011 and is estimated to reach $714 million in 2015. Brazil's share in LATAM will surpass 47.1% in 2015 from 45.2% in 2011 with a CAGR of 14.8%. Sector growth in healthcare IT is hindered due to the lack of knowledgeable workers and also basic infrastructure, such as the Internet, electric power, etc.

The factors driving healthcare IT growth in Brazil are the penetration of IT solutions (such as electronic medical records (EMR) and health information systems) and the expansion of infrastructure, especially in hospitals. The adoption of EMR practices increased with the rise of accredited hospitals. For example, the number of hospitals with international accreditation certificates increased from 15 in 2009 to 25 in 2010.

The expansion of a strong customer base for mobile health applications (apps) for smart phones, with the revenues generated from smart phones and tablets, is another driving force for the growth of the healthcare IT sector in Brazil. It is estimated that the revenues from smart phones will reach $46.6 million in 2015, with growth of 112% annually. The apps are considered to have huge potential for growth in clinical diagnostics and education areas for diseases, medicines information, etc. It is estimated that the greatest challenge in the coming years lays in the development of effective communication that showcases the payback of healthcare IT solutions.

Reimbursement From Private Insurance Plans Will Sustain the Solid Growth of Medical Imaging

The Brazilian medical imaging market was estimated at $616 million in 2011, growing at a CAGR of 11.5% from 2011 to 2015. The medical imaging market in Brazil is anticipated to grow at a fast pace, contributing 51.2% share in Latin America, thus revenues will be increased to $952 million in 2015.

The medical imaging market is by no means left behind, with a significant amount of investments springing up for the local companies to expand their technology innovations. This is possibly due to the support from financial institutions, such as FINAME, BNDES, FINEP, and CNPq. The aging population and increase in chronic diseases are considered to be the main drivers for the medical imaging market. Portable ultrasound systems are witnessing an enormous demand from physicians and are expected to further boost the growth of the medical imaging market by 15% to 20% in 2015.

The positive factor that will drive the imaging market is the inclusion of imaging modalities, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), which help in providing imaging scans for the detection of lymphoma and lung cancer. These modalities are now being included in the list of procedures covered by private insurance plans.

Despite the positive growth in the medical imaging market, this area is experiencing certain challenges due to the low penetration of computed tomography (CT) and magnetic resonance imaging (MRI) equipment, which comprise only 4.1% of the total installed base in Brazil. Another challenge is that Brazil has an incredibly high concentration of private hospitals with relatively less-qualified healthcare professionals.

A Nearly $1 Billion Market Pushed by Government Investments

Brazil's clinical diagnostics market is expected to grow from $616 million in 2011 to $952 million by 2015, at a CAGR of 9.6%. It is estimated that the government will facilitate the expansions of molecular laboratories from 16 units to 38 units by increasing the investment opportunities in R&D. The next-generation DNA sequencing technologies and point-of-care testing will create novel market opportunities and significant growth in Brazil. It is estimated that the rate of acquisition of rapid tests for hepatitis B and C will be $3.6 million.

However, the growth of the clinical diagnostics market is restrained by factors such as lack of production expertise and accessibility of diagnostics testing in rural areas. ◆

BIOGRAPHIES

Swathi Allada is a Research Operations Executive for Frost & Sullivan's Global Healthcare Practice. She has particular expertise in the expansion of strong internal and external business relationships, as well as the demonstration of high levels of control and compliance adherence in the sales process. Ms. Allada's experience base covers a broad range of sectors, including project management, workload prioritization, consulting, and business research, as well as effective communication, presentation, and content development. She earned her Bachelor of Technology in Biotechnology, as well as her MBA in Global Business.

Willian Fujioka is an Industry Analyst for Frost & Sullivan's Global Healthcare Practice. His previous experience includes positions with Wyeth, Galderma, and Boehringer Ingelheim, where he worked on new business and portfolio studies, portal implementation, and database restructuring. His experience base covers the pharmaceutical industry, as well as market research, executive dashboards, primary/ad hoc research, data mining, database structuring, and business intelligence.

HEPAROSAN-BASED CONJUGATES

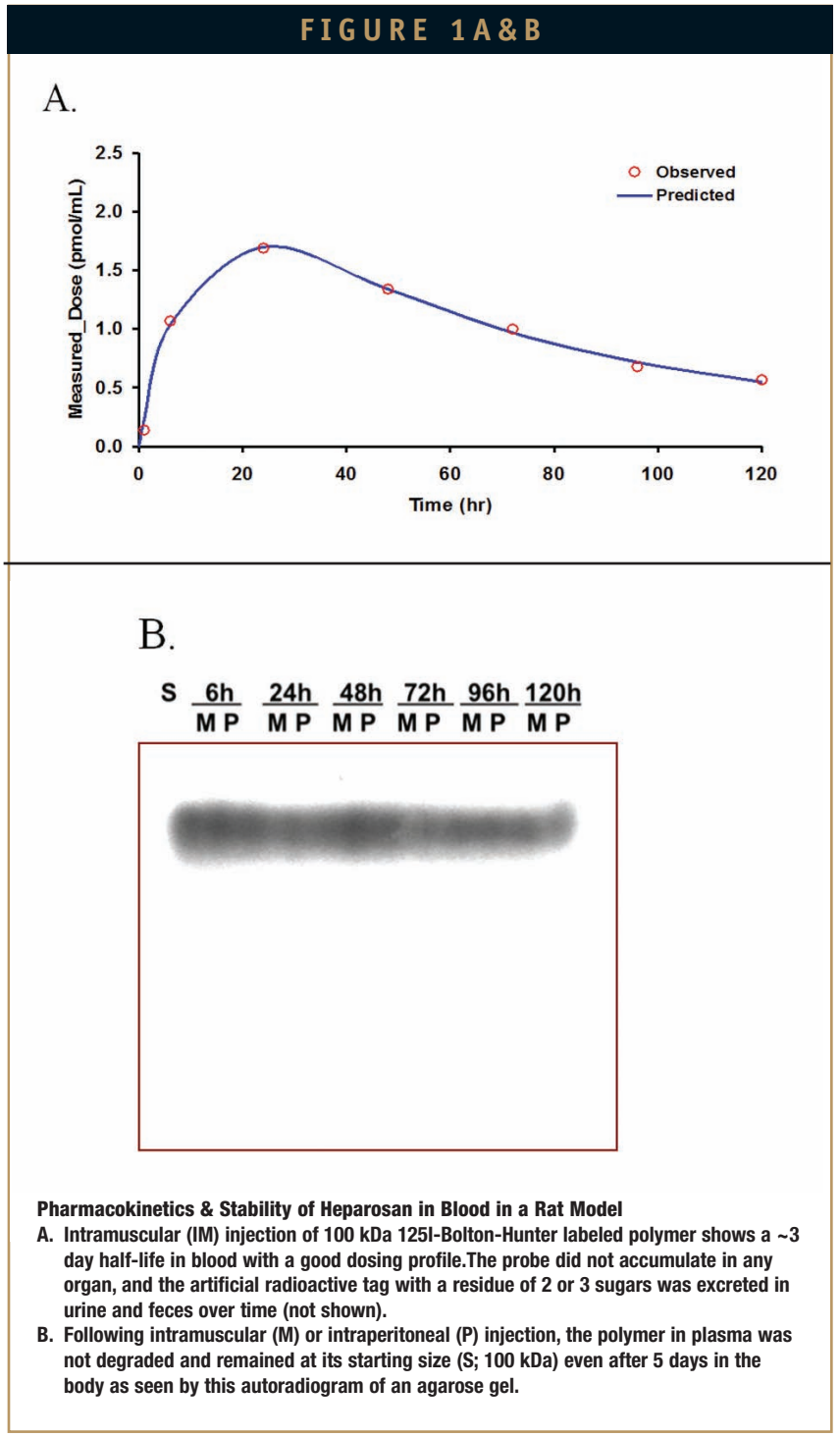
HEPtune™: A Process of Conjugating a Naturally Occurring Sugar Molecule, Heparosan, to a Drug for Enhanced Drug Delivery

By: Paul L. DeAngelis, PhD

INTRODUCTION

Caisson Biotech, LLC has developed the HEPtune™ system for creation of novel heparosan-based conjugates to enhance the therapeutic properties of pharmaceuticals by increasing product half-life, reducing immunogenicity, and increasing stability. The new vehicle is composed of heparosan, a natural polysaccharide with the structure [-4-GlcNAc-α1,4-GlcUA-β1-]$_n$ related to heparin, one of the most widely used drugs in the Pharmacopeia, but does not display "heparin" activity.[1] Heparosan is hypothesized to be biocompatible in the human body because it is a natural precursor in the heparin biosynthetic pathway and stretches of heparosan exist in human heparan sulfate chains. Certain pathogenic bacteria even exploit the "self" nature of heparosan by using a heparosan coating to evade the immune system during infection, thus, offering the potential for reduced immunogenicity of the drug conjugate.[2] Caisson's HEPtune, the attachment of a heparosan vehicle to a drug cargo, has many potentially superior

FIGURE 1A&B



Pharmacokinetics & Stability of Heparosan in Blood in a Rat Model

A. Intramuscular (IM) injection of 100 kDa 125I-Bolton-Hunter labeled polymer shows a ~3 day half-life in blood with a good dosing profile.The probe did not accumulate in any organ, and the artificial radioactive tag with a residue of 2 or 3 sugars was excreted in urine and feces over time (not shown).

B. Following intramuscular (M) or intraperitoneal (P) injection, the polymer in plasma was not degraded and remained at its starting size (S; 100 kDa) even after 5 days in the body as seen by this autoradiogram of an agarose gel.

Overlooked something?

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attributes over other vehicles. In general, heparosan-modification attributes include: the ease of generating a larger size range of monodisperse polymers, high water solubility, biocompatibility of degradation products, easy removal of polymer vehicle for analysis of cargo purity and activity, lack of accumulation in tissues, reduced immunogenicity, and new intellectual property.

OVERVIEW OF OTHER POLYMER VEHICLES VERSUS HEPAROSAN

The covalent modification of drugs with vehicles to enhance performance is a well-known strategy. PEGylation, a technology developed in the 1970-1980s, is a FDA-approved process adding poly[ethylene glycol] (PEG) to a therapeutic cargo including proteins and liposomes. PEG-drug conjugates show prolonged residence in the body, decreased degradation by metabolic enzymes, and reduced immunogenicity. However, while PEG is presently commercially viable, its artificial nature presents increasingly serious drawbacks especially for pharmaceuticals used at high doses and/or for long duration treatments.[3-8]

The liver detoxification system can create a variety of reactive PEG metabolites that are cytotoxic.[5-7] In contrast, Caisson's heparosan system, HEPtune, uses natural heparosan polymers, which are degraded into normal sugars and recycled, and thus should possess substantially lower toxicity. Another biocompatibility issue is that PEG, in certain formulations including liposomes and some enzymes, can induce anti-PEG antibodies in some patients. Anti-PEG antibodies may also be triggered by widespread use of PEG in many consumer products (eg, toothpaste, laxatives, vitamin pills). In 1984, it was reported that in naïve persons, anti-PEG antibodies were detected in ~0.2% of the samples, but as of 2001, stunningly, ~22% of healthy blood donor (n=350) samples had anti-PEG IgM or IgG.[9,10]. Obviously, anti-PEG antibodies can limit the usefulness of PEG therapeutics.[4,8,10,11] For example, some leukemia patients no longer respond to PEG-asparaginase (Oncaspar®) medication due to anti-PEG antibody levels.[10] Similarly, anti-PEG was found in gout patients treated with PEG-uricase; these persons were refractory to therapy as the drug was cleared rapidly.[12] On the other hand, heparosan as a "self" molecule, should not be immunogenic.

In addition, PEG can activate the complement system, which may explain why PEG triggers anaphylactic shock and/or other allergic reactions in some patients.[13] A heparosan polymer, as a naturally occurring "self" polymer in humans, was well tolerated in a recent Caisson rat study.[1]

Two other polysaccharides, poly[sialic acid] (PSA) and hydroxyethyl modified starch (HES), have been proposed to be "PEG-substitutes."[14,15] PSA has a polydisperse size distribution, will form aggregates unless modified, and sometimes triggers the immune system. HES is an approved plasma extender, but it has heterogeneous size and modification levels, breaks down in the blood (thus potentially complicating pharmacokinetics), and can trigger corn allergies. PSA is also not available in sizes >100 kDa. HES >60 kDa accumulates in tissues and is difficult to remove from cargo during quality testing, thus a similar case to the PEG polymer.[16] On the other hand, Caisson can synthesize 800 kDa heparosan, providing longer half-life potential, and it does not accumulate in tissues. Additionally, a gentle enzymatic method can be utilized to remove heparosan chains from the drug in vitro to facilitate analyses.

HEPAROSAN ATTRIBUTES FOR DRUG DELIVERY

Long Life in the Extracellular Space & Plasma

Without O-sulfation on the polymer chain, heparosan is resistant to cleavage by the mammalian heparanase that typically digests heparin.[17] Also, heparosan is not bound by Hyaluronan Receptor for Endocytosis (HARE), a liver receptor that normally clears hyaluronan and heparin very efficiently from the bloodstream.[18] Caisson thus hypothesized that heparosan would be very stable and would persist in the extracellular spaces of the body in an intact fashion. Caisson pharmacokinetics studies in rats showed that indeed heparosan had a long plasma half-life and is stable in the bloodstream (Figure 1A & 1B).

Safe Processing by Lysosomal Enzymes

If heparosan is internalized into cells (eg, via pinocytosis, etc) and transported to lysosomes, it should be degraded by resident glucuronidase and hexosaminidase enzymes, similar to other glycosaminoglycans, such as heparin or hyaluronan; Caisson's preliminary data in rats (not shown) verify this prediction.[19] A key advantage for therapeutic modifications with heparosan is that its degradation products, GlcNAc and GlcUA, are normal monosaccharides, which are non-toxic (unlike PEG metabolites) and can be recycled by cells.

Lack of Immunogenicity

Some patients react immunologically to PEG following exposure to certain formulations.[4,8,20] Because heparosan is a naturally occurring sugar polymer in mammals, Caisson predicts that it will not be immunogenic. Generally speaking, molecules that normally exist in the body are regarded as "self" and therefore not subjected to attack by antibodies, phagocytes, or the complement system. This fact is employed by certain pathogenic bacteria that camouflage themselves with heparosan molecules; *Pasteurella multocida* Type D and *Escherichia coli* K5 both produce heparosan coatings that hide them from many host defenses.[2] Only a few monoclonal antibodies to the heparosan polymer have ever been reported; the rare anti-heparosan-producing clones were identified after immunizing with extremely antigenic bacterial membranes or key-hole limpet hemocyanin conjugates.[21,22]

Lack of Anticoagulant Bioactivity

The normal roles of heparin/heparan sulfate in vertebrates include inhibiting blood coagulation. Caisson has verified that without O-sulfation on the polymer, heparosan does not affect clotting of human plasma even when used at 15,000-fold higher levels than heparin on a mass basis.

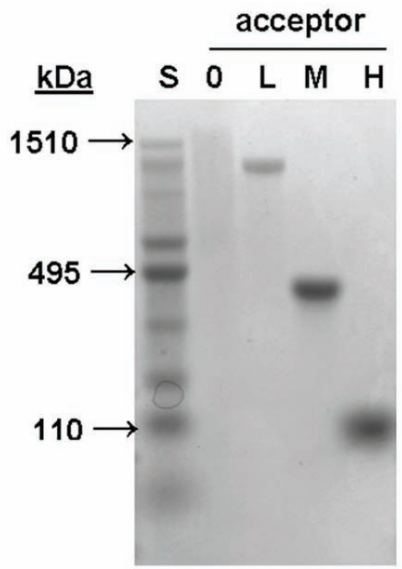
Lack of Toxicity

Caisson tested the effects of high doses of heparosan (100 mg/kg body weight) in healthy rats via intravenous injection (once on days 1 and 8); this translates to ~100-fold to 2,000-fold higher levels than its expected use in humans. There were no adverse effects as measured by blood or urine chemistry, hematology, or histology.

Synthesis of Narrow Size Distribution (Monodisperse) Heparosan

Caisson, and its affiliate companies, have cloned and patented a bacterial polymerizing enzyme called heparosan synthase, PmHS1. This catalyst is harnessed for the chemoenzymatic synthesis of sugar polymers with a very narrow size distribution, termed "monodisperse."[23] The use of an acceptor in PmHS1-catalyzed reactions synchronizes polymerization, and the concentration of acceptor tightly controls the size of the heparosan product (Figure 2; heparosan of different sizes run as tight bands). Depending on the size, the polydispersity ranges from 1.01 to 1.18 (1=ideal). This patented method is also amenable to defined and reproducible chemical activation of heparosan to facilitate coupling of a protein cargo.

FIGURE 2



Synthesis of Monodisperse Heparosan Polymers
The use of an acceptor allows control of size distribution and the final molecular weight. Increasing amounts of acceptor (lanes: 0, none; Low; Medium; High concentration) were added to reactions containing UDP-sugar precursors and heparosan synthase catalysts. Polymer was analyzed on a 1.2% agarose gel with Stains-All detection. (S, Select-HA™ LoLadder and HiLadder (Hyalose, LLC); sizes marked in kDa). PmHS1 in presence of acceptor forms products with a narrow size distribution (polydispersity M_w/M_n = 1.06 to 1.18; for reference, the value of an ideal monodisperse polymer is 1). The size may be readily stoichiometrically controlled (as indicated by the three different size bands of 800 kDa, 380 kDa, and 100 kDa from top to bottom in the L, M, and H, lanes, respectively) by adjusting the ratio of acceptor: UDP-sugar.

Conjugation of Heparosan to Protein Therapeutics with Retention of Biological Activity

Caisson has coupled heparosan to amine, carbonyl, or sulfhydryl groups of a variety of biologics, including cytokines,

hormones, and antibodies (not shown). These heparosan-modified drugs are either more potent or have equal biological potency when compared to similarly sized PEGylated versions.

SUMMARY

Heparosan is a stealthy molecule well suited for use as a drug delivery vehicle due to its natural origin and properties in the body. Therefore, heparosan-modified therapeutics may offer improved pharmacokinetics, drug performance properties, as well as new options for treatment and hope for patients, especially those undergoing life-long treatments. Furthermore, defined heparosan polymers should facilitate quality control and FDA approval.

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BIOGRAPHY

Dr. Paul L. DeAngelis is Chief Scientist of Caisson Biotech, LLC, a biopharmaceutical company with a patented heparosan-based drug delivery technology. He has been a glycobiology researcher since 1981 in the fields of carbohydrate/protein interaction and polysaccharide biosynthesis using the experimental tools of molecular biology, enzyme biochemistry, and carbohydrate analysis. Dr. DeAngelis' laboratory discovered several new hyaluronan synthases, the first chondroitin synthase and two novel distinct heparosan synthases. His overall basic science goal is to understand the fundamental mechanisms of naturally occurring enzymes. As a result of this work, sugar synthesis was vastly improved with respect to speed, controllability, and purity. Biotechnological applications include the design of novel hybrid polysaccharide molecules for medical applications; the formation of biocompatible coatings and surfaces; the synthesis of defined oligosaccharides that have potential for use as anticancer agents, anticoagulants, or immune system stimulators; and the synthesis of sugar-based drug delivery systems. Dr. DeAngelis is a Presidential Professor in the Department of Biochemistry & Molecular Biology at the University of Oklahoma Health Sciences Center, having previously received a BA from Harvard and his PhD From the University of California, Irvine in 1990.

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OCULAR DELIVERY

EyeSol™ a Novel Topical Ocular Drug Delivery System for Poorly Soluble Drugs

By: Dieter Scherer, PhD; Eva Alvarez-Gonzalez, PhD; and Anthony Pettigrew, MSc

INTRODUCTION

One of the biggest challenges currently facing the pharmaceutical industry is the development of more efficient drug delivery systems. For instance, the anterior part of the eye is amongst the most readily accessible organs, in terms of location in the human body; however, drug delivery to eye tissue is particularly problematic. This is reflected by the notoriously poor bioavailability of topical ocular drug formulations of 5% or less.[1]

To make matters even more complicated, due to combinatorial chemistry and high throughput screening implemented throughout the past 20 years, up to 75% of new chemical entities (NCEs) are considered poorly soluble even for oral administration, according to the biopharmaceutics classification system (BCS), where the considered volume is 5000-fold higher compared to an aqueous eye drop.[2-4]

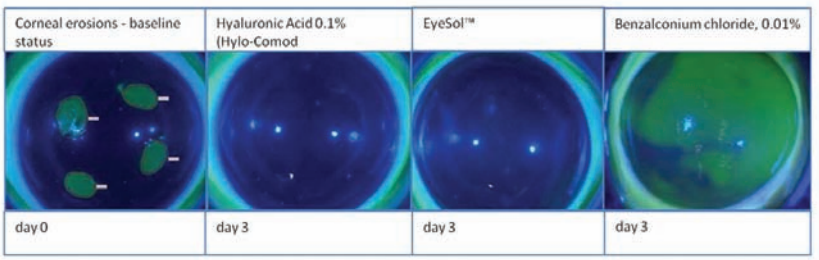
Three major issues need to be addressed for ocular formulations: safety, bioavailability and stability. If this wasn't hard enough, the final cost of goods has to be reasonable and handling has to be simple to achieve good compliance. At best, current ophthalmic formulations are a compromise with significant room for improvement.

CHALLENGES OF TOPICAL OCULAR DRUG DELIVERY

The very nature of the eye makes any drug treatment particularly challenging. The eye is a very sensitive organ immediately reacting to both mechanical and chemical irritation. Therefore, formulation options are limited. The amount of fluids that may be applied to the eye without creating a "spill over" effect, drained away through the lacrimal duct, or just running down the cheek is less than 20 microliters. A standard water drop of about 40 to 50 microliters will activate the blinking reflex and most of the topically administered drugs are washed away within 15 to 30 seconds following instillation.[5] To achieve good bioavailability, sufficient drug needs to be incorporated into the ocular delivery system fitting into a drop. In a second step, the hurdles of rapid turnover, lacrimal drainage, reflex blinking, and dilution by tears must all be overcome.

The issue of poorly water-soluble drugs is well known in the scientific community, resulting in the BCS classification system for oral drug

FIGURE 1



Tolerability test of different ocular formulations. Results of the EVEIT test after 3 days. Comparison of 0.1% Hyaluronic Acid preparation, EyeSol, and 0.01% benzalconium chloride preparation.

delivery.[6] In short, a drug is considered poorly soluble if the required dose is not dissolved in 250 milliliters of aqueous medium. An aqueous eye drop is only 40 to 50 microliters or about 5000 times less volume. This exacerbates the solubility problem by several orders of magnitude.

For other routes of administration, we have a wide variety of excipients, including solvents and/or surfactants to overcome such issues. Due to the sensitivity of the eye, they either cannot be used at all or only in very minute quantities. Surfactants like sodium lauryl sulphate or solvents like acetone cannot be used for ophthalmic delivery. Indeed, the amount of alcohol approved for an ophthalmic dosage form is very much limited (according to the FDA inactive ingredient list); the highest approved concentration is 1.4%, in contrast to intravenous (iv) applications with 49%.

The drug load of oil-in-water emulsions is also limited. The drug has to be dissolved in the inner phase, the oil. The amount of the inner phase very much depends on the amount of surfactants used; which in turn is also limited to avoid irritation, thereby limiting the inner phase.

In addition, only liquid or semi-solid dosage formulations may be applied. The number of solvents that can be administered into the eye is also very limited. The same applies for surfactants used regularly in topical and oral formulations. Everyone has personal experience with dish soaps, hair shampoo, etc.

To make the situation even more complicated, there is also a risk of infection when contaminated preparations are administered. Even if they are well tolerated, such as certain oils, they may affect vision due to having a different refractive index compared with water, enviably leading to blurred vision. The natural choice for ophthalmic formulations appears to be aqueous solutions. However, water is only the starting point; factors such as selection of the appropriate salt of the drug substance, solubility, therapeutic concentration required, ocular toxicity, pKa, pH effect on stability and solubility, tonicity, buffer capacity, viscosity, choice of preservative for ocular comfort, and ease of manufacturing all must be considered.

Salts are used in order to dissolve a drug in a protic solvent, such as water; however, being presented in a charged form affects the bioavailability, as the upper cell layers of the cornea are hydrophobic. In order to increase bioavailability, the contact time with eye tissue may be increased by increasing the viscosity. An alternative approach may be to increase the drug concentration in the formulation; obviously, this is problematic for poorly soluble drugs. Already very small particles > 10 microns in the anterior part of the eye lead to mechanical irritation, including blinking, and increased tear flux causing irritation to the patient.

Aqueous formulations have to be manufactured aseptically, undergoing sterile filtration or whenever possible, heat sterilization. Manufacturing requires specially designed, environmentally controlled areas. All of which increases the cost substantially.

All-in-all, this leaves a very limited formulation window for aqueous-based ocular drug delivery, including emulsions and suspensions. Therefore, a non-protic, aqueous-free ocular delivery system has the potential to provide an alternative approach in particular for poorly soluble drugs.

TABLE 1

	CyclASol™	Oil-in-Water Emulsion
Applied Dose	0.1 mg	0.1 mg
Cmax Cornea	1326 ng/g	633 ng/g
Cmax Lacrimal Gland	169 ng/g	11.9 ng/g

Comparison of Cmax and Tmax between CyclASol™ and Oil-in-Water emulsion after application of an equivalent dose on rabbit eye.

EYESOL™ OCULAR DRUG DELIVERY PLATFORM

EyeSol™, Novaliq's proprietary ocular drug delivery technology, offers such an alternative. EyeSol™ is based on Semi−Fluorinated Alkanes (SFAs), which are a special class of fluorocarbon compounds that have been thoroughly investigated and have gained increasing interest in the biomedical field throughout the past 20 years.

These compounds have a characteristic linear or branched molecular structure consisting of a fluorocarbon segment $(CF_2)_nF$ (RF) linked to a hydrocarbon segment $H(CH_2)_n$ as a diblock (RH). In the

FIGURE 2

Substance	Surface Tension (mN/m)
F6H8	19,65
F4H5	17,43
Water	72

Excellent wetting and spreading properties of SFAs in comparison to water. Water (left), plain surface, two SFAs.

case of triblock compounds (RFRHRF), a $(CH_2)_m$ spacer is linked symmetrically to two fluorocarbon segments $F(CF_2)_n$. The molecular structures are hence $F(CF_2)_n (CH_2)_m H$ and $F(CF_2)_n (CH_2)_m (CF_2)_n F$ with $_n$ and $_m$ = 2 to 20

Liquid, water-insoluble SFAs are physically, chemically, and physiologically inert. They are colorless, laser-stable compounds with densities of 1.1 to 1.7 g/cm^3.[7] Despite the intramolecular CF_2-CH_2 bond, SFAs are very stable compounds biochemically and biologically because the RH segment with its electron density has a bond-stabilizing effect on the overall molecule. The use of SFAs in the field of ophthalmology has mainly been focused in the past on the treatment of disorders in the posterior segment of the eye. For the treatment of complicated retinal detachment, these compounds have been injected intraocularly as temporary endotamponades for more than 10 years (eg, Densiron® 68, Vitreous Substitute®). They are very well tolerated and have shown an excellent safety profile. SFAs are chemically and biologically inert and thus do not cause ocular tissue irritation.

The use of SFAs in the anterior segment of the eye is currently a promising field of research. Recently, these compounds have been investigated by Novaliq regarding the major requirements for an anterior ocular drug delivery system safety/tolerability, drug stability, and bioavailability with favorable results.

EXCELLENT SAFETY PROFILE

The EVEIT test is an excellent ex vivo test to evaluate and compare the tolerability of different eye drops in a standardized setting. After placing artificial lesions on the cornea, the corneas were treated with EyeSol™, Hyaluronic acid 0.1% (HA, gold standard), and Benzalconium chloride (common preservative) solutions as comparators. Eight drops each of the three formulations were administered continuously every hour for 72 hours. After 3 days of treatment, the endothelia recovered under both EyeSol™ and the current gold standard HA therapies, in contrast to the preservative compound, benzalconium chloride which resulted in extensive, irreversible damage.[8]

The local tolerability of EyeSol™ was confirmed in another sensitive eye irritation test, the Hen's Egg Test Chorioallantoic Membrane (HET-CAM) assay. In the HET-Cam assay, chemicals are placed in direct contact with chorioallantoic membrane of the hen's egg. The occurrence of vascular injury or coagulation is an indication for the damage of mucus membranes (especially the eye) in vivo.[9,10]

Microbiological testing has clearly demonstrated that this water-free preparation does not require preservatives. Therefore, it is provided preservative-free even in multi-dose units. Lacking preservatives, most of them with irritating potential, have clearly demonstrated that the formulation will not cause cornea damage, as frequently reported from using other substances upon prolonged use and demonstrated in the EVEIT study with the Benzalconium chloride, for example. Furthermore, as a multi-dose unit, cost of goods will be substantially reduced, and the manufacturing process will be substantially simplified.

The extraordinary spreading properties support the drug distribution on the corneal surface. In addition, their low viscosity and low surface tension result in much smaller droplet size compared to water with 15 microliters instead of 40 to 50 microliters for a conventional aqueous drop. Thus, spill over and the immediate loss of the majority of the administered dose are avoided. The implication of the avoidance of the spill over on the bioavailability is obvious. It

should also be noted that the refractive index of SFAs is similar to water so that vision is not impaired in contrast to emulsions and oily drops.

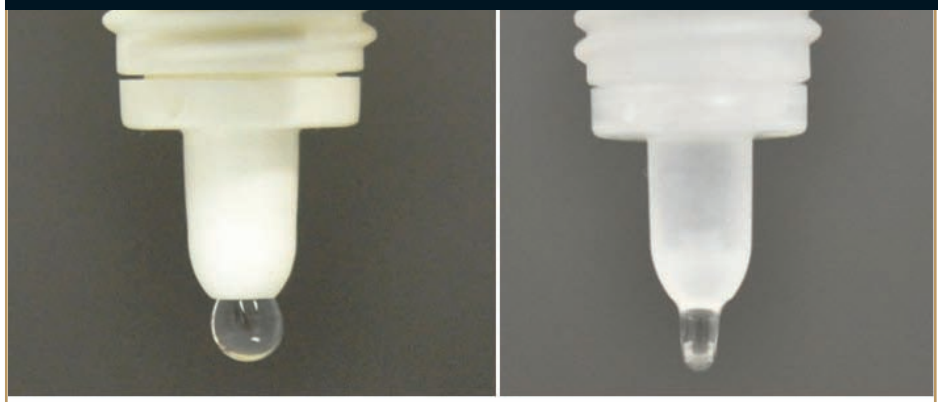
Due to their amphiphilic nature, SFAs can also dissolve a variety of therapeutically relevant poorly water-soluble compounds, such as cyclosporine A and tacrolimus. For other compounds, the free base may be used instead of a salt, for example lodocaine. It is obviously very advantageous to present the drug in an uncharged form to facilitate penetration into the cornea. This is a big step forward for the delivery of poorly soluble drugs, as it offers a new approach delivering such compounds as a solution instead of an emulsion.

Obviously, one of the main degradation pathways for aqueous-based formulations is hydrolysis. By using a non-aqueous environment, compounds such as tacrolimus, which have hydrolysable bonds such as a lactone, will demonstrate a superior stability profile compared to aqueous-based formulations. In summary, it can be stated that SFAs resemble many requirements for a "perfect carrier."

PENETRATION PROFILE OF CYCLASOLTM INTO THE LACRIMAL GLAND

The lacrimal gland is regarded a relevant target organ for cyclosporine A. In a pharmacokinetic study in rabbits, CyclASol™ applied on top of the rabbit's eye was compared with an oil-in-water emulsion (current gold standard). A major difference of C_{max} (14-fold increase in favour of CyclASol™) and between the two formulations was detected in the lacrimal gland. Regarding the cornea the difference of C_{max} was two fold in favor of CyclASol™. The spreading properties of the SFAs in the EyeSol™ technology may be responsible for the altered pharmacokinetics compared to a standard aqueous formulation.

FIGURE 3



Comparison of the size of an aqueous drop (left) and a SFA drop (right).

SUMMARY

Despite the relatively recent emergence of SFAs in the pharmaceutical field, they have already demonstrated outstanding potential as novel drug-carrier solvents.

In addition, the unique combination of physico-chemical properties, including the excellent spreading behavior, the physical and chemical inertness, the solubility of poorly water-soluble compounds, together with the reduced drop volume, thus avoiding blinking, makes SFAs excellent candidates to overcome most of the challenges facing the drug delivery industry today. CyclASol™ is the first cyclosporine A solution for dry eye disease. This proprietary product is based on the EyeSol technology. So it is provided preservative free in multi-dose units. The absence of surfactants, irritating preservatives, and the avoidance of blurry vision associated with emulsions leads to improved tolerability and convenience of this non-aqueous product. ◆

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BIOGRAPHIES

Dr. Dieter Scherer joined Novaliq in April 2009 as its Chief Business Officer. His 20 years of experience covers the gamut from business development and licensing to product development in the field of drug delivery. His experience covers a wide variety of dosage forms, with his speciality in working with the delivery of poorly soluble drugs. After filling various staff and line functions with increasing responsibilities at LTS Lohmann in Germany and SkyePharma in Switzerland, he set up his own consultancy (Apis Pharma AG) in 2003 advising drug delivery companies throughout Europe. Dr. Scherer graduated as a Pharmacist at the J.W. Goethe University in Frankfurt and later earned his PhD in Pharmaceutical Technology from the same faculty.

Dr. Eva Alvarez-Gonzalez started her professional research activity 2 years ago at the Strathclyde Institute of Pharmacy and Biomedical Science (SIPBS) with Dr. Chris van der Walle in the formulation of bacteriophage-coated microcrystals. She is currently a Research Associate at SIPBS working with Professor Clive Wilson in the study of protein stability under novel solvents working closely with Novaliq GmbH. She graduated with a first class Master degree in Chemical Engineering from the University of Oviedo (Spain) in 2007. She was awarded an Erasmus grant to finalize her undergraduate studies at the Chemical and Process Engineering Department at the University of Strathclyde. At the end for her undergraduate studies, she was awarded with the prize to the best MEng. graduate at the University of Oviedo. She then moved to Glasgow (UK), where she earned her PhD in Chemical and Process Engineering from the University of Strathclyde. Her thesis *Nucleation of Beta-Lactoglobulin Clusters in Solvent-Induced Denaturation* introduced her in the pharmaceutical field, gaining experience in protein handling, formulation, and characterization.

Tony Pettigrew joined Novaliq GmbH in 2012 as Chief Protein Chemist. Within this role, he works on Novaliq's proprietary drug delivery technology based on Semi Fluorinated Alkanes (SFA) particularly in the area of biopharmaceutical formulation. Prior to his role at Novaliq, he has built up a solid background in the biotech field, his previous positions including being at a Manager in the Biopharma Application Development group at Novozymes Biopharma DK A/S and in the AD/QC group at Veloxis A/S DK (formerly LifeCycle Pharma A/S DK). Mr. Pettigrew graduated as a chemist at Liverpool John Moores University (1993) and later earned his MSc in Analytical Chemistry (1995) from the University of Huddersfield.

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Phil Hodges
President,
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"This sale positions both Metrics and Mayne for significant additional growth in contract, proprietary, and generic pharmaceuticals. By bringing Mayne and Metrics together, both companies benefit."

When Phil Hodges co-founded Metrics Inc. in 1994 - with just three other employees on payroll - he set out to build a different kind of contract analytical laboratory. One that was dedicated to scientific excellence, doing the job right, and forming long-term relationships with clients based on mutual trust. Today, with just over 300 employees, Metrics Inc. hasn't changed its focus from trust and strong science, even though its services and capabilities have grown exponentially. Metrics now offers a broad range of contract pharmaceutical development services, including formulation, clinical material manufacturing for Phase I, II, and III trials, commercial manufacturing, and analytical method development and validation services. The company has consistently experienced double-digit revenue growth annually. This past October, Metrics announced it had agreed to be acquired by Mayne Pharma Group Limited, a publicly traded pharmaceutical company based in Melbourne, Australia. Metrics will operate as a subsidiary of Mayne. Drug Development & Delivery recently interviewed Mr. Hodges, who will continue to serve as President of Metrics, to discuss how he will guide the company's future direction and growth, and what the transaction means for Metrics, Mayne, and their customers. Mr. Hodges also has been appointed to Mayne's Board of Directors. Before starting Metrics, he worked for 11 years at Burroughs Wellcome Co. in the field of developing and validating analytical methods. (Burroughs Wellcome eventually became part of GlaxoSmithKline).

Q: For our readers who may not be familiar, can you please provide some background?

A: For 18 years, Metrics has operated as a contract partner to pharmaceutical companies worldwide. Metrics really consists of two separate businesses - there's our contract formulation development and manufacturing business, and then there's our generics business.

Both businesses have been successful because of our core analytical expertise. When it comes to analytical scientists, Metrics has a drawer full of sharp knives. Our scientists can take any unique compound and figure out the best, fastest, and safest way to get it into clinical trial. Likewise, for our generics business, our scientists can reverse-engineer pharmaceutical

products whose patents are expiring and figure out exactly what is in innovator products. Both businesses have been successful and profitable.

Q: So why sell Metrics and why now?

A: In 2004, when we first started the generic business, we raised $4.3 million from investors, and we promised we'd look for an acquisition within 5 or 6 years so we could return their investments to them. So there was never any question about an eventual sale; the only questions involved how and when that sale would happen, and how it would leave the state of the company.

After spending 18 years of my life building this company, I wanted to make sure Metrics was left in the right hands - that Metrics would continue to prosper financially and support the local economy. Metrics is an important part of the economy in Pitt County (North Carolina) - our salaries are among the highest here, and we do a lot for East Carolina University, an investment the university has more than returned to us. I wanted those local investments and benefits to continue.

Metrics has grown like crazy in recent years - our sales for the fiscal year that ended in June were nearly $52 million. You should sell when you're on a steep slope up, which we have been and believe we will continue to be. Our business model is successful and attractive, making it a good time to attract the right buyer. Plus, we had to look at tax ramifications. There's a chance the Bush-era tax cuts would expire, which could make the transaction much more expensive for investors in 2013, so this provided additional incentive to close the deal in 2012.

Q: How did Mayne emerge as the right buyer?

A: It was a long process. One company we worked with made an early bid, but that didn't pan out. Then another company came in, but those talks didn't progress either. At that point, we realized we needed folks experienced with such deals. I've known Neal McCarthy at Fairmount Partners for years, so he came in and Fairmount put together a book on Metrics and sent it out in March 2012.

Twenty-eight companies signed confidentiality agreements, which gave them access to more details; most of them were private equity firms. Nine companies ended up coming to Metrics and getting the full dog-and-pony show. From there, we narrowed the choices down to four - two were private equity firms and two were strategic partners. I just couldn't get excited about a private equity firm taking over Metrics, so Mayne ended up being the best strategic fit.

I really like Mayne for several reasons. When it comes to our clients, their projects will continue to get the same expertise and personal attention they've come to expect from Metrics. When it comes to our community, we will continue to recruit new employees and pursue new contracts. This sale does not reduce our workforce in Greenville; indeed, we anticipate growing our workforce under Mayne's leadership. And the senior management team at Metrics remains the same.

This sale positions both Metrics and Mayne for significant additional growth in contract, proprietary, and generic pharmaceuticals. By bringing Mayne and Metrics together, both companies benefit.

Q: Can you expand on how both companies benefit?

A: Well, from the perspective of Metrics, Mayne has a strong track record of developing proprietary pharmaceuticals. A deliberate part of their business strategy has been to offer products with proprietary improvements in safety and efficacy, which helps ensure optimum pricing and market exclusivity. So when it comes to proprietary products and technologies, we can tap Mayne's expertise for our clients' needs, as well as our own generics business.

Metrics also will benefit by gaining access to Mayne's more sophisticated

infrastructure in back-office organizational support areas as accounting and information technology - as well as Mayne's expertise in intellectual property.

I really like what Mayne brings from a synergistic point of view, and I don't believe they will change our business model very much. They obviously value both the formulation development and generic aspects of our business. This sale isn't about changing Metrics; it's about strengthening Metrics and positioning it for additional growth.

Q: And how does the sale benefit Mayne?

A: Metrics has particular expertise in formulating complex oral products, including highly potent and unstable compounds, controlled substances, and products with poor bioequivalence. These products are sold through exclusive partnerships or through our wholesale distributor, Midlothian Laboratories. So with our large and veteran staff of formulating scientists and technicians, Metrics has knowledge and expertise to share with Mayne.

Mayne also benefits by gaining access to the pharmaceutical market in the United States. In pharmaceuticals, Australia represents 1% of the global market, whereas the United States represents 35%. This sale gives Mayne real access to its most relevant market, expands its capabilities, and accelerates its development and commercialization operations.

Q: What can you tell us about Mayne Pharma that we don't know?

A: Mayne is a specialty pharmaceutical company with an intellectual property portfolio built around the optimization and delivery of oral dosage drugs. Mayne has a long and successful history of modifying existing drugs in order to advance their safety, efficacy, or ease of administration. The company is very technologically driven and has a significant product portfolio and pipeline.

Q: Are there downsides to your new partnership?

A: Truth be told, the most challenging part of this sale has been working around the 15-hour time difference between Greenville, NC, and Melbourne, Australia. Thank goodness for modern technology.

Q: What immediate changes do you anticipate?

A: The next year or so represents a transition period, and I honestly don't foresee a lot of changes. I plan to stay on as President for next 13 months or so, and will continue to serve as a member of Mayne's board of directors after that. The senior leadership team at Metrics is intact and will remain in place, and many of the investors that provided the capital that started Metrics have invested in Mayne, which I believe speaks volumes about their confidence about the sale and what it means for Metrics and our community.
Ultimately, the sale of Metrics means that clients at both companies can access more options and more resources that advance their own research and work.

Q: What parting thoughts would you offer clients?

A: I'd offer the assurance that the honorable way Metrics has always worked with clients will never change. Clients will continue to work directly with a Metrics scientist - like they always have - and we remain committed to conducting excellent science and keeping their projects on track. ◆

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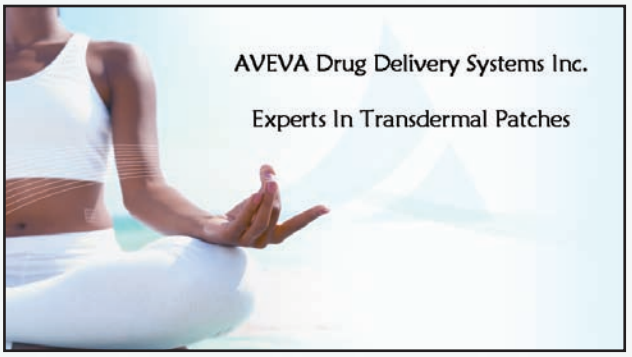
Licensing & Capabilities



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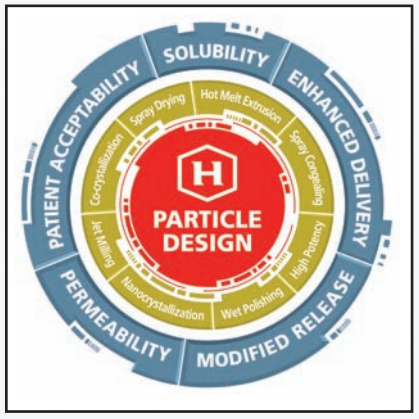

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DRUG DEVELOPMENT Executive

APTALIS™ | Pharmaceutical Technologies

APTALIS PHARMACEUTICAL TECHNOLOGIES: PATIENT CENTRIC DRUG DELIVERY

Robert Becker, PhD
Chief Research Officer,
Aptalis Pharma

Aptalis Pharmaceutical Technologies offers a broad portfolio of oral drug delivery technology platforms, including Taste-Masking, Bioavailability Enhancement, and Customized Drug Release. Together, these flexible technology platforms combined with the company's licensing, manufacturing, and R & D capabilities enable Aptalis Pharmaceutical Technologies and its partners to produce customized drug formulation solutions across a range of dosage forms and therapies with high patient acceptability. Drug Development & Delivery recently interviewed Robert Becker, PhD, Chief Research Officer at Aptalis Pharma, to discuss Patient Centric Drug Delivery and the company's role in supporting patient compliance and driving commercial value through new drug formulations.

"Aptalis Pharmaceutical Technologies aims to differentiate its services by offering partners multiple components in the drug development process to create a pathway to commercialization, including 1) formulation expertise to target novel clinical outcomes and 2) a combination of product-related and technology patents offering market protection and support to regulatory filings, all building a foundation for the goal of providing regulatory approval and market exclusivity for the partner once the product reaches the market."

Q: What is patient centric drug delivery?

A: Patient centric drug delivery is the development of drug products that address unmet needs within specific target populations. These target populations include geriatric, pediatric, and dysphagic patients - as well as patients suffering from debilitating mental illness. Due to increasing focus given to the overall therapeutic outcomes of drug therapy, the prescription and consumer health industry is seeking drug delivery technology solutions that can be applied to improve the clinical benefits of drugs for these target populations by enhancing patient acceptance and adherence via improved side-effect profiles, taste-masking of bitter ingredients, or dosing convenience through ease of administration. Controlling these factors can also extend product life cycle and, in some cases, expand the market for a given drug.

Q: For patient centricity in target populations such as pediatrics and geriatrics, what are some of the factors pharma needs to consider to support medication adherence?

A: Very young and old patients are often unable to consume conventional solid dosage forms, such as tablets and capsules. Elderly patients often suffer a higher burden to take multiple medications several times a day. For elderly patients, the pill size, shape, color, and packaging configuration has to be considered to accommodate common limitations in vision and coordination. Adolescents and teenagers lead active lifestyles that are conducive to creating convenient dosage forms. Younger individuals may experience embarrassment regarding their medical condition (eg, acne) and desire a dosage form that can be administered discretely. Patients with dysphagia due to causes such as stroke and Parkinson's disease and patients with mental illness, who are unwilling or unable to take their medications, also are prime target populations for patient centric drug delivery. By giving focus to these patient characteristics and developing products with features that meet their needs, pharma can enhance patient adherence, which is fundamental to the successful medical management of diagnosed illness.

Q: What solutions can Aptalis Pharmaceutical Technologies provide to meet the needs of these patient populations?

A: We offer a broad portfolio of oral drug delivery technology platforms, including customized oral drug-release technologies, bioavailability enhancement technology, and taste-masking and ODT (orally disintegrating tablet) formulation technologies. In fact, our ability to utilize our technologies separately or in combination makes our company's taste-masking platform an industry-leading offering.

For example, our AdvaTab® ODT Technology is capable of high drug loading and is compatible with Microcaps® taste/odor-masking technology - a combination offering patients a pleasant taste experience with a smooth and creamy mouth feel in an easy-to-swallow, fast-dissolving dosage form. By making drugs more palatable, taste-masking can improve compliance and extends product reach to patients who are more taste-sensitive, such as geriatric and pediatric patients.

Our Biorise® technology enhances bioavailability of poorly water-soluble and readily permeable drug molecules by breaking down crystalline forms into nanocrystals and/or amorhpous (noncrystalline) drug. The drug is then stabilized in a carrier system that increases intrinsic solubility and dissolution rate of the drug to enhance rate and extent of absorption for a faster onset of action, equivalent therapy at lower doses, and/or oral dosing of poorly soluble drugs. Through our Biorise® technology, drug developers of an NCE (New Chemical Entity) can advance poorly soluble compounds that otherwise may be discontinued. For commercialized drugs, this technology can reduce dosage amounts and frequency of administration, thereby enhancing compliance, convenience, and above all, patient safety - a prominent concern among pediatric and geriatric patients due to age-dependent variability in pharmacokinetics and pharmacodynamics.

Within our customized drug-release platform, our range of technologies enables customized release profiles that can be tailored to optimize a drug's therapeutic performance and reduce the potential for overmedication. For example, a time-modified release profile can be developed for drugs requiring rapid onset of action followed by maintenance of the therapeutic plasma level within a single dosage unit. Alternatively, time pulsatile release may be optimal for compounds needing rapid escalation of physiological drug levels after a defined delay. In contrast, combination products may require different release profiles for each active ingredient, particularly relevant for geriatric patients in reducing the pill burden associated with multiple-drug use.

Together, our technology platforms combined with our licensing,

manufacturing, and R&D capabilities, enable us to produce customized drug formulation solutions for partners across a range of multiple therapeutic classes, such as GI, cardiovascular, pain, nutrition, respiratory, and CNS.

Q: What are the benefits of incorporating drug delivery early in the product development cycle?

A: Technology advances and increasing regulatory demand for safer and more efficacious drugs have enhanced their applications, and now drug delivery technologies are used throughout the drug development process. Traditionally, patent expirations have led pharmaceutical companies to seek adoption of new drug delivery systems for marketed products, potentially adding years of additional patent protection and enhanced market longevity. Today, however, drug delivery technologies are significant in many stages of the product life cycle. For example, pharmaceutical companies use drug delivery technologies to optimize returns on R&D investment by reformulating existing products and/or creating effective formulations for promising, but difficult to deliver molecules that may have been halted in clinical development.

Early application of drug technologies can strengthen market adoption by creating a more differentiated, attractive product upon market entry. This type of approach can add further market protection to the brand by establishing a broader IP estate to challenge generic entry through the creation of new patentable material and extended patent expiry dating.

By moving away from the traditional business model that has shaped the pharmaceutical industry in the past, pharmaceutical companies can look to drug delivery companies as full strategic partners. These partnerships can enable increased R&D productivity, improved drugs, extension of product life cycles, and strengthened offerings resulting in clinical relevance that reshapes healthcare.

Q: How can Aptalis Pharmaceutical Technologies create a pathway to market access for its partners?

A: Aptalis Pharmaceutical Technologies aims to differentiate its services by offering partners multiple components in the drug development process to create a pathway to commercialization, including 1) formulation expertise to target novel clinical outcomes and 2) a combination of product-related and technology patents offering market protection and support to regulatory filings, all building a foundation for the goal of providing regulatory approval and market exclusivity for the partner once the product reaches the market.

To meet our partners' business needs, we offer resources for the development of new product formulations, as well as licensing of existing product formulations. We have increased the flexibility of our business model in response to partners' needs, and in select cases, may also invest resources into the development of the product.

Our R&D and manufacturing processes are physically integrated within our facilities to enhance the flow of product development from formulation through scale-up and commercial manufacturing. This turnkey approach enables our partners to maintain the consistency associated with a single partner relationship, eliminating the need to work with multiple vendors during product development, which can lead to repeated quality validations. We manufacture all of the products that we develop for our licensees with facilities owned and operated by Aptalis. These high-quality cGMP facilities in the United States and Europe are approved to handle controlled substances and the use of solvents. Our positive history of cooperative collaboration with the US FDA and regulatory agencies and licensees in Europe, Asia, and the Middle East have resulted in highly successful quality inspections and international audits with multiple audits

conducted annually.

Our use of best-practice alliance and project management teams enable pharmaceutical companies to work with us in collaborative partnerships with common expectations and goals. This model promotes quality partnerships and enables shared expertise, information, and workflow optimization across all functions and stages of the product development cycle. Given our fully integrated development and management model, we can leverage efficiencies across all stages of development to provide our partners with a more cost- and time-effective path to approval and to market compared to various contract manufacturing scenarios.

Aptalis Pharmaceutical Technologies endeavors to offer partners the most effective patent protection possible from the company's broad and diversified portfolio. This portfolio comprises patents with claims directed to the company's formulation technologies and related materials, processes, equipment, and methods of manufacture. Additionally, there are many product-related patents, which contain more specific claims directed to particular drugs or classes of drugs in combination with formulation technology. Currently, the company-owned and in-licensed patent portfolio contains more than 475 active granted patents, with more than 300 patent applications pending.

Q: Can you provide an example of one such pathway to market access?

A: Our company's formulation expertise was evidenced in January 2012 with the FDA approval of an NDA for an oral powder formulation of Gilead's Viread®. The company used its Microcaps® proprietary technology to co-develop Viread® (tenofovir disoproxil fumarate) oral powder in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients aged 2 to 5. Co-developed by Aptalis Pharmaceutical Technologies and Gilead, the oral powder formulation of Viread® uses the Microcaps® taste-masking technology. The market launch of Viread began in February 2012. Gilead will be responsible for the product commercialization, while our company will manufacture and supply the oral powder to Gilead.

The microencapsulation technology, known as Microcaps®, employs versatile and precise coating techniques to encapsulate individual drug particles using solvent- and aqueous-based coacervation. This includes taste- and odor-masking, customized release profiles, conversion of liquids to solids and the separation of incompatible materials. Microcaps® can also be combined with the company's AdvaTab® technology to provide an orally disintegrating tablet with superior mouth-feel attributes.

In summary, Aptalis Pharmaceutical Technologies develops and manufactures enhanced pharmaceutical oral products, applying this expertise to product development for partners who wish to provide innovative, effective patient-centric therapeutics for unmet medical needs. ◆

Late Breaking News

In November 2012, the European Commission granted marketing authorization for a new pediatric indication of a new oral granule formulation of Gilead Sciences, Inc.'s Viread® (tenofovir disoproxil fumarate) for HIV-1 infected children aged 2 to less than 6 years, and for HIV-1 infected children above 6 years of age for whom a solid dosage form is not appropriate. This authorization, which covers all 27 countries of the European Union (EU), follows the January 2012 U.S. Food and Drug Administration's (FDA) New Drug Application (NDA) approval of Viread® oral powder in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients ages 2-5. Aptalis Pharmaceutical Technologies is the manufacturer and supplier of Gilead Sciences, Inc.'s Viread® (tenofovir disoproxil fumarate). To learn more, visit the Aptalis Pharmaceutical Technologies website at http://AptalisPharmaTech.com/.

Analysis & Materials Characterization

Surface Characterization of Pharmaceuticals by X-Ray Photoelectron Spectroscopy

By: Jeffrey Shallenberger, MS; and Robert W. Lee, PhD

Introduction

There is an interest in controlling and understanding the concentration of APIs and excipients on pharmaceutical powder surfaces for a host of reasons. Some of this interest is driven by decreasing particle size for aerosols or nanomedicine applications, in which the atoms in the near-surface make up a significant fraction of the total atoms as the size decreases into the sub-micron range. Roughly 5% of the atoms are present within the outer 10 nm of a 1-micrometer particle. This percentage rises to nearly 20% for a 0.25-micrometer particle (Figure 1).

In addition to concerns based purely on size, the outer surface of pharmaceutical particles is often chemically quite different from the bulk. Processing can result in the segregation or coating of one component relative to others at the surface of a particle. This, in turn, affects a host of performance parameters, including solubility, dissolution rates, stability, flowability, agglomeration, and crystallinity.

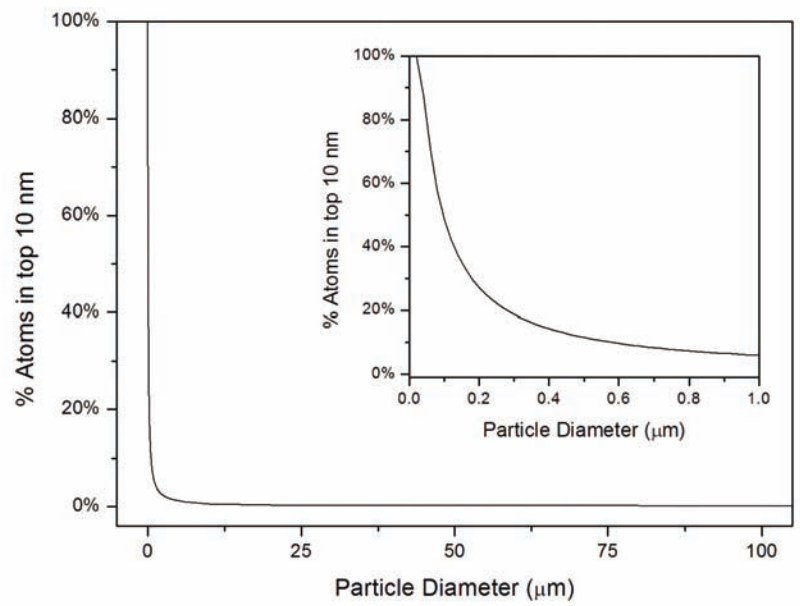

Figure 1.
Percentage of atoms present at the surface (outer 10 nm) of spherical particles as a function of particle diameter. Inset highlights exponentially increasing fraction for nano-sized particles.

Analytical tools exist to characterize the surface area (BET), particle size (light scattering), surface charge (zeta potential), morphology (SEM, AFM), crystalline phase (XRD, DSC), bulk chemical environment (NMR, Raman, FTIR, NIR), and trace constituents (ICP-MS, HPLC, LC/MS, GC/MS). The analytical options for studying surface chemistry are fewer and less well-known in the pharmaceutical industry. This paper will discuss one of the two most powerful tools from probing surface chemistry of pharmaceuticals: x-ray photoelectron spectroscopy (XPS). The other

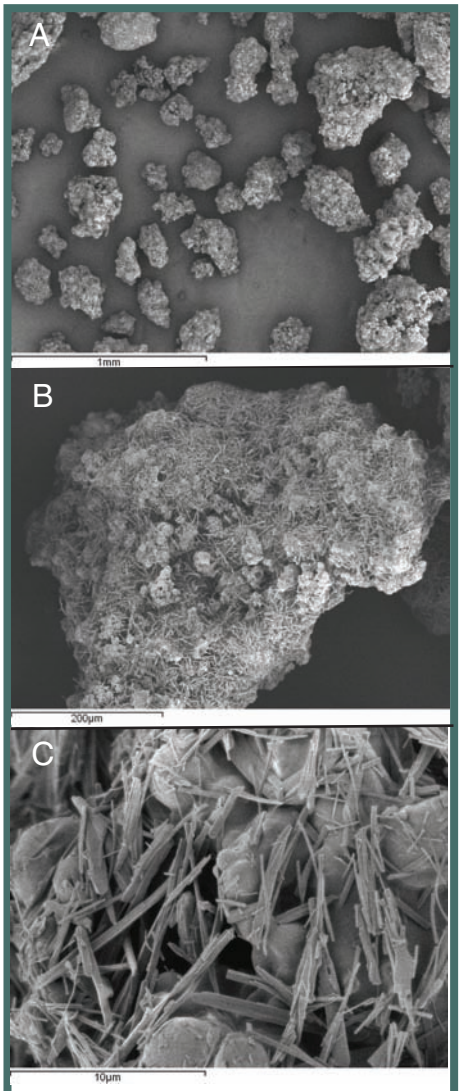

Figure 2 A, B & C.
Scanning electron micrograph (SEM) of spray dried powders at 50X (A), 200X (B), and 5,000X (C). Note that the fine, needle-like features are believed to be indomethacin crystals.

surface chemical tool - Time-of-Flight secondary ion mass spectrometry (TOF-SIMS) - will be the subject of a future article.

Principle of Technique

X-ray photoelectron spectroscopy was developed in the 1950s and 60s due largely to the pioneering work of Kai Siegbahn at Uppsala University in Sweden.[1] He was awarded the Nobel Prize in Physics in 1981 for his contributions. XPS has been used widely since the early 1970s, when the instruments became commercially available to study surface chemical phenomenon in catalysts, metals, surface modified polymers, nanomaterials, biomedical devices, and semiconductors.

In XPS, which is also known as Electron Spectroscopy for Chemical Analysis (ESCA), a photon ionizes an atom resulting in the ejection of a core electron. The kinetic energy, KE, of these photo-electrons is related to the x-ray energy, hν, by the photoelectric effect:

Equation 1.

$$KE = h\nu - BE$$

Where BE is the binding energy of the core electron. Because each element in the periodic table has a different electronic configuration, XPS can be used to identify what elements are present in a sample. The number of emitted photoelectrons is proportional the concentration of that element present within the sample by way of near-universal sensitivity factors, making the technique quantitative without standards. Most commercial instruments use soft x-ray sources with $h\nu < 1500$ eV, resulting in photoelectrons with kinetic energies in the 200- to 1400-eV range. Low-energy electrons travel only a very short distance through solids, making the technique inherently surface sensitive; virtually all the signal originates from the outer 5 to 10 nm of the sample. Somewhat analogous to NMR, XPS has the ability to determine the nearest neighbor chemical environment in many organic and inorganic materials by way of small changes (termed chemical shifts) in the energy of the photoelectrons.

These four attributes (surface sensitivity, element and chemical state specificity, and standardless quantification) combine to make XPS an extremely powerful tool for studying various surface chemical phenomena in the pharmaceutical and biotech industries. These include identification of surface contaminants and degradation products on APIs, understanding lubricant thickness and coverage, quantifying protein adsorption on surfaces, evaluating surface contamination of packaging and delivery components, and even identification of API co-crystals.[2-5] The focus of this paper is quantification of APIs and excipients on engineered powder surfaces.

Experimental Approach

Materials & Methods: Solumer Technology, a proprietary drug delivery technology that consists of spray drying an API with a combination of amphiphilic and hydrophilic polymers, was used to prepare the drug product.[6,7] This technology is characterized by modified thermal behavior exhibiting a depressed melting temperature and enthalpy of melting of the drug, spontaneous formation of colloidal dispersions upon reconstitution with aqueous media, and enhanced dissolution rate/solubility of the drug as well as the ability to achieve prolonged supersaturation in dissolution media. The API was indomethacin (25% w/w loading in the final formulation), which is a COX inhibitor with empirical formula, $C_{19}H_{16}ClNO_4$. The amphiphilic polymer was Poloxamer 407, which is a triblock co-polymer of polyethylene glycol - polypropylene glycol -

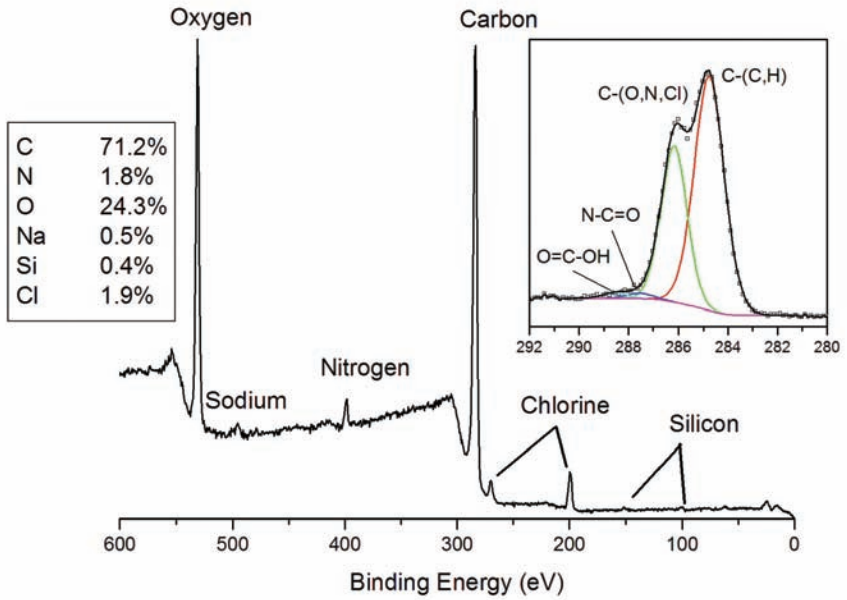

Figure 3.
Low and high energy resolution (inset) photoemission spectra from spray dried powder. Note the presence of Cl and N from the indomethacin. The accompanying table shows the atom% of elements detected on this surface.

polyethylene glycol. The PEG blocks are 101 units long, and a PPG central block is 56 units long. The hydrophilic polymer was sodium carboxymethylcellulose (CMC).

The formulation was prepared by mixing the excipients with solubilized API using a combination of water and ethanol then spray drying with a Mini Spray Dryer B-290 (Buchi Labortechnik AG). Representative scanning electron micrograph acquired at 50X, 200X, and 5,000X are provided in Figures 2A-2C. Indomethacin is the fine needle-like material. The average particle size was 100 to 200 micrometers. The powder was gently packed into a sample cup, and the XPS analysis was performed using a 2-mm X 1 mm x-ray beam simultaneously sampling several dozen particles.

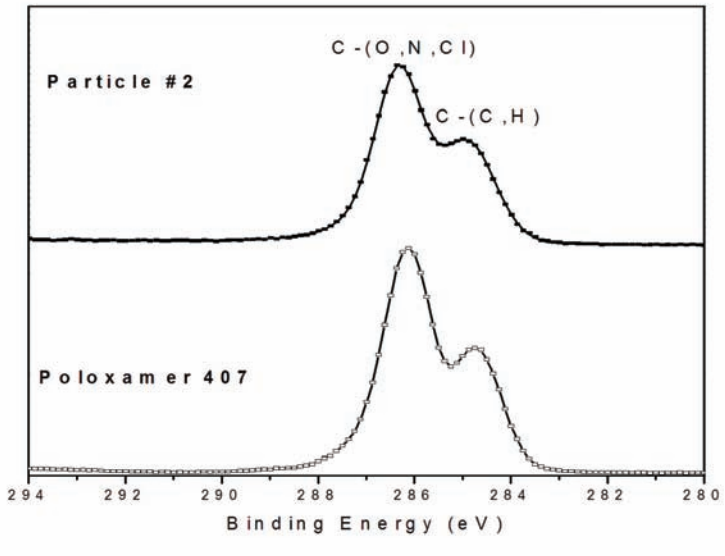

Figure 4.
High-energy resolution photoelectron spectra from pure Poloxamer 407 (bottom) and particle No. 2 showing similar shape and peak intensities.

The photoelectron spectrum (Figure 3) shows distinct peaks for the elements expected in the sample (C, O, N, Cl, and Na) as well as minor amount of Si from an unknown source (XPS does not detect hydrogen). The inset shows the carbon high-energy resolution spectrum. Four different bands are detected in carbon spectrum. The lowest binding energy band (284.8 eV) is from -CH_3 and carbon in the aromatic ring structure of indomethacin. The large peak at 286.3 eV is due to C-O, C-Cl, and C-N bonds present in the API and/or the excipients. The weak peak at ~287.7 eV is due to N-C = O, and the other weak peak at ~288.5 eV is due to COOH.

Quantification: By integrating the area under the peaks and applying relative sensitivity factors, the intensity can be converted into atom percent of elements. The composition for the aforementioned sample is included in the box inset in Figure 3.

To convert the elemental composition of multi-component pharmaceutical sample to a more useful measure of the amount of the individual components, one needs a unique element or functional group for each component. For indomethacin, we may use nitrogen or chlorine, neither of which is present in the excipients. Sodium will serve as a tag for sodium carboxymethylcellulose. Poloxamer 407 contains no unique elements

or functional groups. It will be quantified by difference. The general equation for converting the elemental concentration to mole percent is shown in Equation 2.

Equation 2.

$$\%Component\ A = \frac{[x_A]^{exp}}{[x_A]^{\infty}}$$

Where $[X_A]^{exp}$ is the experimentally measured atom% of the unique element or functional group present in component A and $[X_A]\infty$ is the atom% measured on the pure material. If pure materials are unavailable, an acceptable alternative is to derive $[X_A]\infty$ from the empirical formula of the material in question.

For the sample in Figure 3, [N] exp was 1.8 atom% and compared with [N]∞ = 4.0% expected for pure indomethacin. Thus, the atom fraction of indomethacin on the surface of this sample is 1.8/4.0 = 0.45 or 45%. A similar approach was done using Na to quantify the surface concentration of CMC. The pure sodium CMC (data not shown) sample was found to have 9.2 atom% Na. The low Na concentration on the powder confirms that there is ~5% CMC on the surface.

Knowing the chemical structure of the Poloxamer (PEG101-PPG56-PEG101), we can compare the residual (non-indomethacin and non-CMC) material with that expected for Poloxamer. Bulk Poloxamer 407 contains ~12 carbon atoms bonded to O (C-O) for every -CH_3 due to the high PEG fraction. After accounting for the indomethacin contribution, the surface C-O/CH_3 ratio of the residual material is close to 2.0. This large discrepancy could indicate that the residual is something other than Poloxamer. However, analysis of the pure Poloxamer 407 also reveals a carbon spectrum also with a C-O/CH_3 ratio close to 2. This indicates that Poloxamer present on the surface of the particles has the more hydrophobic PPG block oriented to the outer surface and the hydrophilic PEG end groups buried below the surface.

Micro Focused XPS

While not generally considered a microanalysis tool, modern XPS instruments can acquire data on areas as small as 10 micrometers. In this study, there was an interest in checking the homogeneity of the product. Figure 5 shows an x-ray-induced electron micrograph acquired in the XPS. The image is formed much like in a scanning electron microscope in which a focused electron beam is rastered across a sample surface while secondary electrons are collected. In this case, we rastered a ~5-micrometer x-ray beam across the surface while collecting secondary electrons. The image quality and resolution are not as good as in the SEM micrograph (Figure 2), but clearly permit identification and subsequent selection of an individual particle for analysis. In this example, microfocused XPS was done to assess the uniformity of the Indomethacin-Poloxamer distribution at five different ~150-micrometer agglomerates. The results are summarized in Figure 6. The drug surface concentration varied by more than

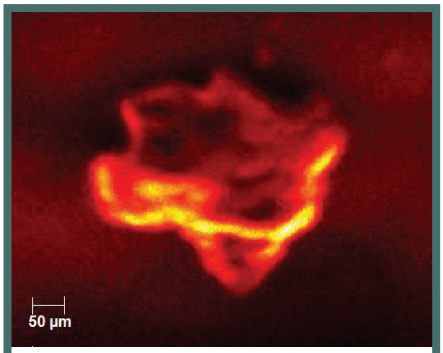

Figure 5.
XPS micrograph acquired showing single drug particle.

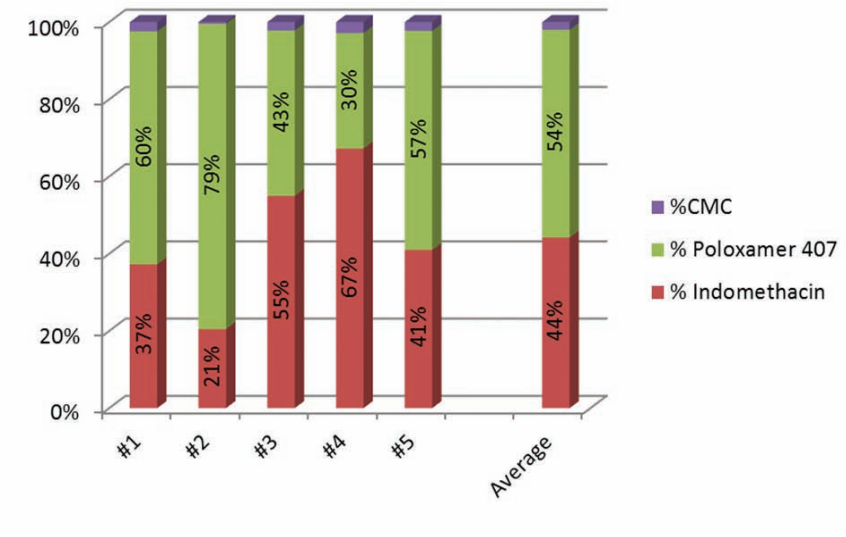

Figure 6.
Results of microfocused XPS to assess the uniformity of the Indomethacin-Poloxamer distribution at five different ~150-micrometer agglomerates.

3X among the five particles analyzed. The average indomethacin concentration detected on the five particles (44%) agreed well with the 45% found on the large area analysis of several dozen particles. It was considerably higher than the 25% w/w loading in the final formulation.

Summary

This article introduced an important analytical tool for quantitatively probing the chemistry of the outer few nanometers of pharmaceutical materials. X-ray photoelectron spectroscopy (XPS) is a quantitative, surface-sensitive spectroscopy capable of probing the local chemical bonding of inorganic and organic materials. In this study, we use XPS to quantify the amount of an API (indomethacin) and two excipients (sodium carboxymethylcellulose and Poloxamer 407) present on the outer surface of individual particles. Analyses were done both in aggregate (to provide a snapshot of the average surface composition) as well as on individual particles (to assess surface chemical uniformity). Understanding the surface concentration of various components in pharmaceutical powders is critical for controlling performance parameters, such as solubility, dissolution, stability, flowability, agglomeration, and crystallinity. ■

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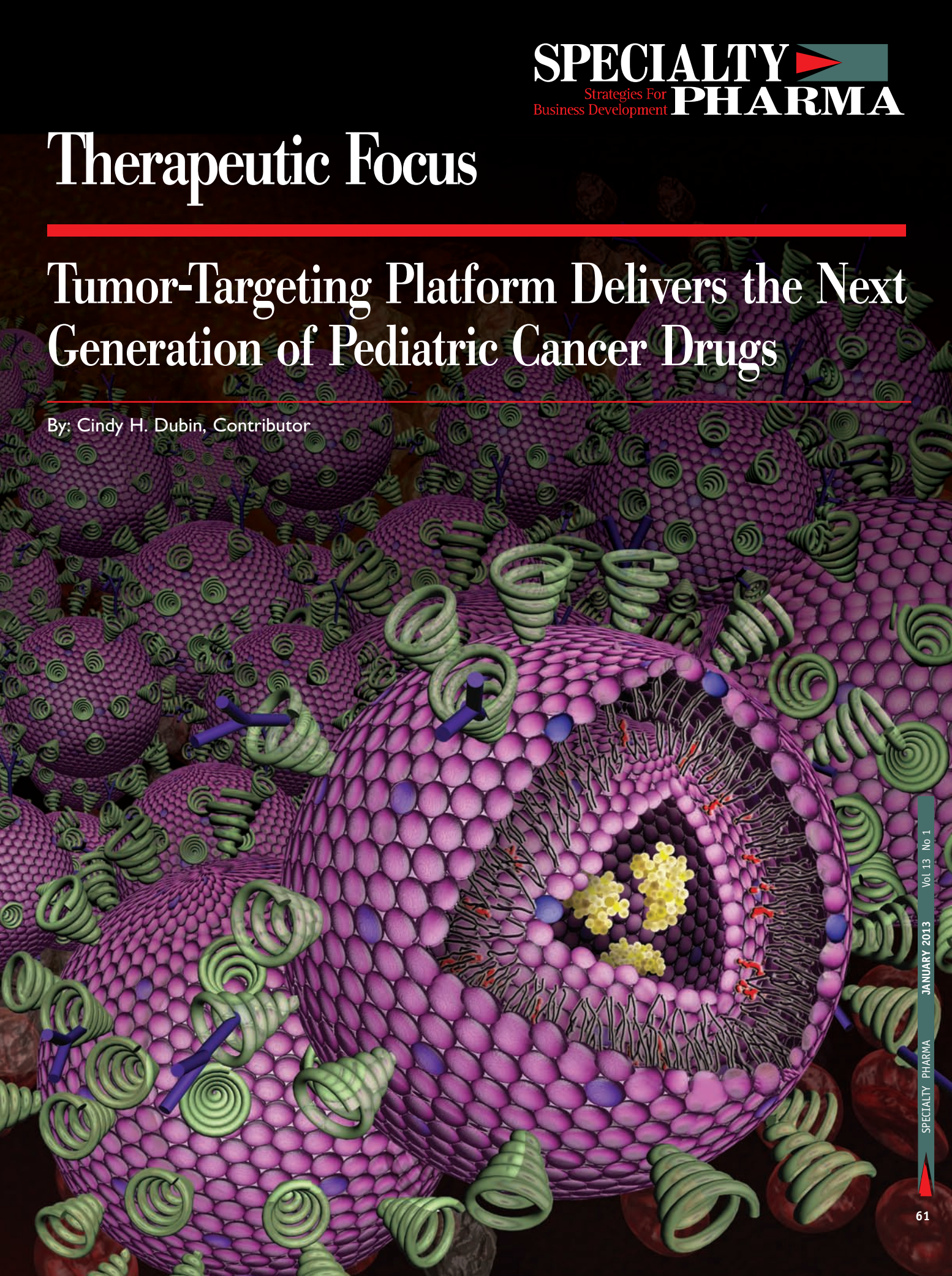
SPECIALTY PHARMA
Strategies For Business Development

Therapeutic Focus

Tumor-Targeting Platform Delivers the Next Generation of Pediatric Cancer Drugs

By: Cindy H. Dubin, Contributor



Introduction

It's no secret that cancer continues to be a huge problem in our society. Despite clear progress in cancer treatments throughout the past 40 years, as evidenced by significantly increased survival rates, current cancer treatments remain inherently toxic and have potentially severe short- and long-term side effects that can complicate care, diminish quality of life, and can be fatal. Academic researchers and private companies pour billions of dollars every year into developing better treatment options, yet safer and more effective therapies continue to elude us. Despite all the effort and resources deployed, the pace of improving cancer treatments is in fact slowing.

Furthermore, small cancer markets like pediatric sarcomas, which affect about 1,700 children per year, have not been given priority in drug development pipelines. Every year, nearly one-third of children diagnosed with pediatric sarcoma die. While overall mortality rates have decreased over time, they continue to be extremely high for recurrent or metastatic cancers. There is still a desperate need for therapies that can address underserved populations, eradicate the cancer state without severe complications, and prolong the lifespan of the patient after diagnosis. NanoSmart Pharmaceuticals has taken on that challenge.

The Problem with Today's Cancer Drugs

Many of the cancer drugs in use today are non-specific mitotic poisons that inhibit tumor growth by killing cells that are rapidly dividing. Unfortunately, mitotic poisons can also kill any normal cells that are dividing. This is because the drugs have difficulty differentiating between the patient's normal cells and the cancer cells. The inevitable non-specific destruction of healthy cells results in serious acute side effects and complications, such as vomiting, hair loss, anemia, and immune suppression.

Despite the inability to discriminate between cancerous and healthy tissues, the current strategy for cancer treatment is to aggressively administer these drugs with the hope that the cancer can be eradicated before too many healthy cells are destroyed. While this approach has improved overall treatment outcomes, it still subjects the patient to very harsh treatments with potentially life-threatening complications because the toxic drug levels are often very close to effective drug levels. In order to mitigate the severity of side effects, patients are usually placed on a therapeutic regimen that provides for the staggered administration of several different drugs with intermittent recovery periods. As a result, any strategies that improve the safety and effectiveness of individual drug products are greatly desired.

One way scientists have tried to enhance cancer therapies is by developing antitumor antibodies that can directly target the tumor. Typically, these are monoclonal antibodies that target certain kinds of growth receptors that are over-expressed on tumor cells. By binding to the growth receptors these antibodies can inhibit tumor growth. The initial monoclonal antibodies that were developed were made using

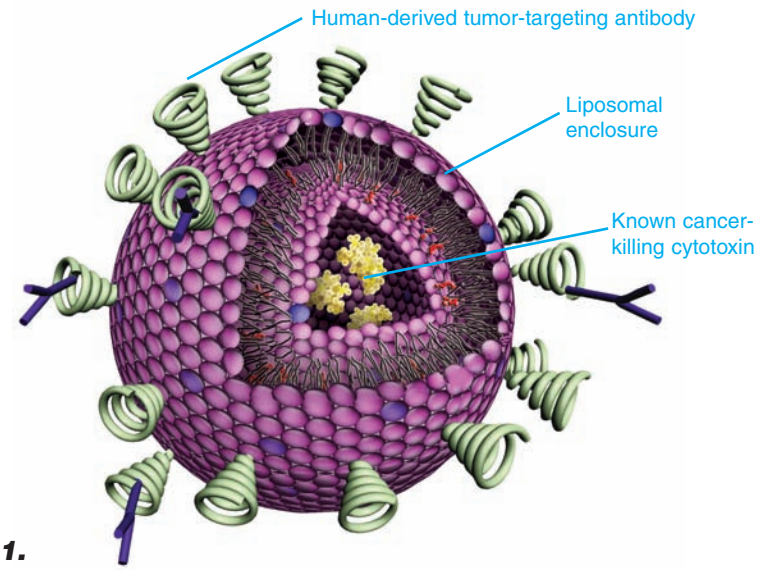


Figure 1.

NanoSmart's Tumor-Targeting Immunoliposome.

A phospholipid bilayer (liposome) encapsulates an anti-cancer agent (FDA-approved drug) and is coated with NanoSmart's patented antibodies. The drug formulation is administered intravenously and travels in the blood to the tumor sites. Once the immunoliposomes reach areas of necrosis within and around tumors, they bind there and slowly release the anti-cancer agent, eliminating the tumor while protecting healthy cells.

mouse hybridomas. More recently, fully human monoclonal antibodies have been developed using phage display and genetic engineering technology.

However, despite the extensive research into developing antitumor antibodies, less than a dozen antibody-targeted drugs have been approved by the FDA for cancer treatment. Those that have been approved are only able to treat a small portion of the patient population due to genetic variability within cancers. Specifically, the tumor markers that the antibody targets are not universally over-expressed, and thus, the antibody-targeted drug is only effective in small subsets of the intended cancer population. This problem is so prevalent in drug development that the current trend in the pharmaceutical industry is to develop highly specific markers that are effective for only small sub-populations. It is thus a very costly approach with increasingly limited applicability in the market.

Another method scientists have tried is to enhance cancer therapies by enclosing the cancer drug in liposomes, which are nanoparticles consisting mainly of lipid molecules. Formulating cancer drugs in liposomes has the following three beneficial effects on safety and efficacy:

(1) protecting healthy cells by sequestering the toxic drugs within a physical barrier as it travels to the target site;

(2) increasing bioavailability of the drug by delaying degradation of the drug by the liver, more than doubling the half-life of the original drug; and

(3) passive targeting of the tumor site through "leaky" blood vessels that are characteristic of tumor vasculature.

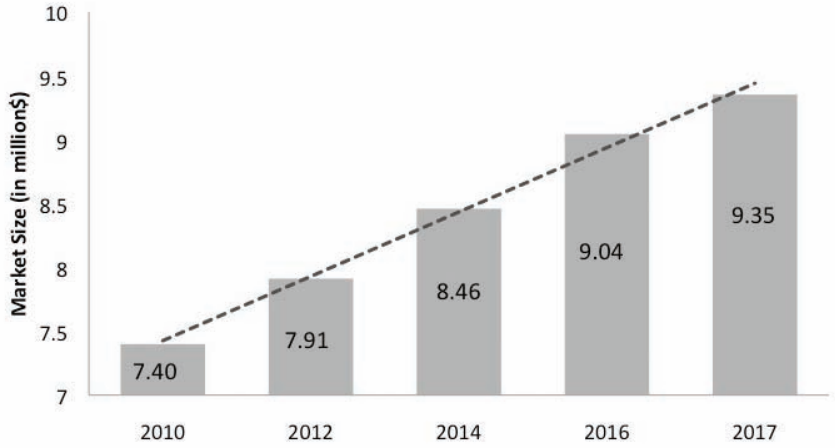


Figure 2.

Ewing's Sarcoma Market Data.

Despite substantial growth over time, the Ewing's sarcoma market is projected to remain under $10 million per year in the near future. This is a very small amount compared to the lung and breast cancer markets, which are in the billions. (Source: Ewing's Sarcoma Therapeutics - Pipeline Assessment and Market Forecasts to 2017).[1]

While this is certainly an improvement, it is not enough. According to Dr. Noah Federman, MD, Director of the Pediatric Bone & Soft Tissue Sarcoma Program at UCLA's Jonsson Comprehensive Cancer Center and Mattel Children's Hospital at UCLA, "The mere feat of achieving passive targeting of a liposome to a tumor does not necessarily mean that the particle will enter the cancer cell, nor that it will deliver its cytotoxic payload." So while the safety profile of these drugs is indeed improved, optimal effectiveness and targeting ability continues to be elusive. Scientists attempt to address this problem by coating drug-filled liposomes with monoclonal antibodies (immunoliposomes). But unfortunately, the immunoliposomes developed thus far suffer from the same limitations of monoclonal antibodies alone (i.e., the limited ability for therapy to be effective in the entire patient population due to limited expression of the targeted tumor markers).

The idea of improving cancer drugs using immunoliposomes has been around for decades, but to date, no immunoliposomes for the treatment of cancer have been successfully commercialized. The reason is that there is a lack of truly effective tumor-targeting antibodies being utilized to carry sufficient payloads of drug to the tumor site. Only a handful of antitumor antibodies have been developed so far, and it will take some time before they are successfully used to prepare immunoliposomes.

The Next Generation of Immunoliposomal Drugs

The task of finding a specific cancer tumor marker that is ubiquitously expressed in the entire patient population is extremely difficult. While most cancer research has focused on developing antibodies that target specific tumor markers, NanoSmart is taking a different approach: localized targeting of the tumor with human-derived anti-nuclear antibodies.

NanoSmart's targeted drug delivery system targets areas of necrosis that are found in and around solid tumors (Figure 1). The antibody is collected and purified from patients that have an autoimmune disease called Systemic Lupus Erythematosis (SLE). The SLE antibody targets the nuclear material (DNA) found within all human cells. And because the antibodies are harvested from humans, the patient's immune response limiting bioavailability of the drug is no longer an issue.

As solid tumors grow, they cut off their own blood supply to the tumor core, causing the inside tumor cells to rupture and release nuclear material. The tumor also ruptures normal healthy cells that surround the tumor site, causing those healthy cells to also release their nuclear material. NanoSmart's patented SLE-antibody attaches to the nuclear material of these ruptured/dead cells found in the center of, and on the outside of, cancerous tumors. Because it is not specific for a particular cancer marker, the SLE antibody has the potential to target many different types of solid tumors, including prostate cancer, breast cancer, lung cancer, liver cancer, and rare pediatric cancers, such as Ewing's sarcoma and osteosarcoma.

Active tumor targeting is the ultimate goal of cancer drug development, and localized targeting of solid cancer tumors allows for virtually universal treatment. "We have taken an approach to targeting tumors that is different from other companies," explains Dr. James Smith, President of NanoSmart. "We are treating cancer by targeting normal cellular material that is inappropriately expressed within, and near, the tumor mass." Other regional targets that are currently being researched for the treatment of cancer include sites of angiogenesis and different pH levels of tumor tissues.

A Focus on Pediatric Sarcomas

NanoSmart elected to focus on pediatric cancers, specifically pediatric sarcomas, for its initial pipeline of products. Pediatric sarcomas are rare malignancies that typically present solid tumors in bones or soft tissues, such as muscles and fat. Some common pediatric sarcomas include osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and synovial sarcoma. Sarcomas account for approximately 13% of all cancers affecting patients who are younger than 20 years old, are the fourth most common pediatric cancer, and one of the most deadly. Whereas the 5-year survival for all pediatric cancers approaches 80%, the survival for all non-metastatic bone and soft tissue sarcoma is approximately 60% to 70%. The outcome for children with metastatic, refractory, or recurrent sarcomas is dismal with about a 20% to 30% survival overall. Furthermore, for those patients fortunate to be long-term survivors from pediatric sarcomas, the late effects of therapy are considerable and can be life-threatening. "Despite significant early incremental improvements in outcomes of children with sarcomas, the survival curves have been stagnant in the past decade," says Dr. Federman. "We are desperately in need of novel targeted therapeutics to these highly aggressive cancers in children."

NanoSmart has completed its initial immunoliposomal drug formulations of dactinomycin and vincristine, both of which are used to treat rhabdomyosarcoma and Ewing's sarcoma. In fact, both vincristine and dactinomycin are part of the standard backbone therapy for rhabdomyosarcoma and are responsible for many of the dose-limiting toxicities, such as peripheral neuropathy and myelosuppression, respectively. Because of the small patient population and low incidence of the disease, the Ewing's and rhabdomyosarcoma therapeutics market is relatively small compared to other cancers (Figure 2), and untapped opportunity exists for companies with better disease cures and therapies with improved toxicity profiles.

NanoSmart's immunoliposome is capable of targeting multiple types of pediatric cancer. However, it is not limited to just pediatric cancers. Vincristine, for

example, is currently indicated for Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor. Using NanoSmart's platform to reformulate vincristine into a safer and more effective drug has the potential to improve the existing therapy for many different patients with a variety of different cancers.

NanoSmart has entered into several research collaboration agreements with Children's Hospital Los Angeles (CHLA) and University of California Los Angeles (UCLA) Sarcoma Program in an effort to optimize drug formulations utilizing dactinomycin and to extend its indications for other pediatric sarcomas, such as rhabdomyosarcoma, Wilms' tumor, and osteosarcoma. These entities are dedicated to finding solutions for these underserved patients, and are able to deploy significant resources to expedite NanoSmart's drug development. In theory, validating NanoSmart's drug delivery platform with just one drug would open the door for the creation of a broad platform of novel biopharmaceuticals, just by switching out the active pharmaceutical ingredient within the liposome.

Summary

NanoSmart Pharmaceuticals is developing the next generation of targeted drug liposomes that target cancers by binding to areas of necrosis, which are present in and around many different types of tumors. The wide applicability of the platform to multiple cancer types has enabled NanoSmart to pursue the underserved, pediatric patient population that is in dire need of safer and more effective therapies.

Despite the slowing trend of newly-developed therapeutic options, interest in pediatric and rare cancer is growing among both large and small pharma companies, government and regulatory agencies, and patient advocacy groups. NanoSmart is ideally positioned to leverage this intensifying focus to develop a new generation of safer and more effective drug products. "Children with cancer need the industry to focus on innovative drug formulations that can be efficiently commercialized," says Dr. Smith, "We have an extraordinary opportunity to develop a novel drug pipeline that can make a profound impact on the lives of these most-vulnerable patients." ■

Reference

1. Darling, Joan. A different View of Sarcoma Statistics. ESUN. 4(6). Revised October 2007. Website visited: http://sarcomahelp.org/articles/sarcoma-statistics.html.

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Drug Development & Delivery

Cindy H. Dubin has been a professional journalist since 1988. She is currently a Contributing Editor to Drug Development & Delivery. Prior to this position, she spent several years focusing her writing on pharmaceutical formulation and development. She has been recognized by the American Society of Business Press Editors for her work on nanotechnology, and her writing has been awarded by the prestigious Neal Award Committee for Journalistic Excellence. Ms. Dubin earned her BA in Journalism from Temple University in Philadelphia and her certificate in Business Logistics from Pennsylvania State University.

Executive Summary

Steve Orndorff
President & CEO
Ariel Pharmaceuticals, Inc.

Ariel Pharmaceuticals, Inc: Reducing Shareholder Risk Through Expedited Clinical Development

Ariel Pharmaceuticals, Inc. is a private, specialty pharmaceutical company focused on the development and commercialization of drugs that improve quality of life for patients with acute neurological disorders. Ariel's first product is intended to address unmet needs in acute migraine. Ariel's strategy is to in-license drugs in development for CNS in which there are hard clinical endpoints that can be demonstrated in clinical trials of relatively short duration. *Specialty Pharma* recently interviewed Steve Orndorff, President and CEO of Ariel, to discuss the company's drugs in development and plans for the future.

Q: ***Can you provide our readers with an overview of Ariel's lead program in development?***

A: We in-licensed our lead product, AP-1531, from BTG International Ltd. in September 2011. This compound is a first-in-class, orally available, potent, and selective EP4 receptor agonist intended for the treatment of acute migraine. It has a unique dual mechanism-of-action that works locally to suppress the release of CGRP neuropeptide and inhibit cerebrovascular dilation. AP-1531 specifically targets PGE2 - EP4 signaling, which is believed to provide a superior safety profile compared to triptans and non-steroidal anti-inflammatory drugs (NSAIDs), the most commonly prescribed treatments for this condition. In six Phase I clinical trials, AP-1531 has been shown to be well tolerated at doses that provide analgesic effects.

AP-1531 is protected by 65 issued US patents and their foreign equivalents in the major world markets that extend through 2024 and relate to composition-of-matter, use of EP4 receptor antagonists, and screening tools.

Q: ***What role does PGE2 - EP4 signaling play in migraine?***

A: Despite decades of research, the cause of migraines is not well understood. Migraines appear to involve activation of the trigeminovascular system in the brain stem, with release of inflammatory neuropeptides and dilation of cranial blood vessels. Prostaglandin PGE2 interacting with the EP4 receptor has been shown to cause vasodilation and the release of inflammatory neuropeptides, particularly CGRP and Substance P. EP4 receptors are concentrated in the cerebral vasculature and are scarce in coronary and pulmonary vasculature, so EP4 receptors are an excellent target for directing a therapeutic to the source of migraines and minimizing disruptive impacts on other critical organs. AP-1531 has been shown to be a highly specific EP4 receptor antagonist that effectively blocks PGE2 - EP4 signaling. We believe that because of this specificity for EP4 and EP4's localization in cerebral vessels, AP-1531 will have a much better safety profile than current migraine therapeutics.

Q: ***What is your development plan for AP-1531?***

A: We plan to initiate Phase II studies in patients with migraine headaches in 2012, with study completion expected in approximately 1 year. We strongly believe AP-1531 has the potential to effectively treat patients who are non-responsive to triptans or are at risk due to the cardiovascular side effects of triptans. Ariel may also eventually explore additional indications, including acute pain and cancer in which EP4 signalling plays a role in these diseases.

Q: ***What's the market for acute migraine products and what makes AP-1531 superior to other currently available treatments?***

A: According to the World Health Organization (WHO), episodic migraine headaches affect 11% of the world population and are among the top four disabling neurological conditions. Migraine headaches account for an estimated 30 million days of lost productivity at a cost of up to $17 billion per year in the US, and approximately half of migraine patients suffer severe pain and require bed rest.

Currently, the most common migraine therapies are NSAIDs and triptans; however, shortcomings of currently available drugs include slow speed of activity (up to 90 minutes for market leader Imitrex), recurrence of pain, and debilitating side effects, including cardiovascular and gastrointestinal toxicity. We believe that given the dual mode of action, selectivity and fast onset of AP-1531, we will be able to provide patients with faster relief with less side effects than the currently available treatments.

Q: ***Does Ariel have other products in its pipeline?***

A: The EP4 receptor has been shown to play a significant role in a number of diseases where prostaglandin E2 is involved. These range from orphan diseases like Familial Adenomatous Polyposis (FAP) to neurodegenerative diseases like Multiple Sclerosis and to major diseases involving pain and/or inflammation. We are developing AP-1531 and a related library of EP4 ligands as a therapeutic platform and our first therapeutic applications are osteoarthritis pain and colorectal cancer.

Q: ***Could you provide us with an overview of Ariel's business and funding strategies?***

A: Ariel's goal is to reduce shareholder risk and accelerate time-to-value inflection. Our strategy is in-licensing drugs that are already in human testing for clinical indications that have short development timelines, well-defined endpoints for efficacy with limited or no Competition, and established mechanism-of-action to ensure predictability and cost efficiency.

We are currently raising a Series A financing that we anticipate will take our product development through completion of Phase II trials. Our plan is for a shareholder exit in less than 5 years.

Q: ***Can you tell us more about yourself and how you started Ariel?***

A: Ariel was founded in January 2011 and is structured to in-license clinic-ready drugs in acute care clinical indications that have no or limited competition. We strongly believe our licensed products are first-in-class, revolutionary therapeutic approaches with clinical indications that have great market opportunity and limited competition.

I've been in the biotechnology industry for more than 30 years and have been the founder of three biotech companies in Colorado throughout the past 15 years. Before founding Ariel, I launched Accera, Inc., where I oversaw research, development, and the commercial launch of Axona®, a prescription-only medical food intended for the clinical dietary management of mild-to-moderate Alzheimer's disease. I also founded Univera Pharmaceuticals, Inc., a drug discovery company focused on diseases of inflammation and the immune response. Throughout my career, I've had responsibilities in a wide range of disciplines, including basic research, manufacturing, product development, and business development at various biotechnology companies. ■

Therapeutic Focus

Peptide-Based Cancer Therapeutics

By: Jyothi Thundimadathil, PhD, American Peptide Company Inc.

Introduction

Over the years, peptides have been evolved as promising therapeutic agents in the treatment of cancer, diabetes, and cardiovascular diseases - and application of peptides in a variety of other therapeutic areas are growing rapidly. Currently, there are about 60 approved peptide drugs in the market generating an annual sale of more than $13 billion. Out of four peptides drugs in the market that have reached global sales over $1 billion, three peptides are used in treating cancer directly or in the treatment of episodes associated with certain tumors (leuprolide, goserelin, and octreotide).The number of peptide drugs entering clinical trials is increasing steadily; it was 1.2 per year in the 1970s, 4.6 per year in the 1980s, 9.7 per year in the 1990s and 16.8 per in 2000s. There are several hundred peptide candidates in the clinic and pre-clinic development. From 2000 onward, peptides entering clinical study were most frequently for indications of cancer (18%) and metabolic disorders (17%).

In conventional chemotherapy, the cancer cell-specific delivery of cytotoxic agents is difficult without affecting normal cells, which leads to systemic toxicity, causing undesirable severe side effects. "Molecularly targeted cancer therapies" using proteins, peptides, and related biomolecules are gaining momentum due to the possibility of improved drug potency and efficiency and minimal side effects. Peptides can be used as: direct anti-cancer drugs, cytotoxic drug carriers, vaccines, hormones, radio-nuclide carriers, and drug targets. Though shorter *in vivo* half-life of peptides is a concern, recent advances in drug delivery systems and peptide modification are expected to override those difficulties.

Peptide	Sequence comparison	Indications
	LHRH (GnRH) agonists	
Buserelin	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-NHEt	Prostate cancer
Gonadorelin	Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2	Cystic ovarian disease, Induce ovulation etc.
Goserelin	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-AzGly-NH_2	Prostate cancer; Breast cancer
Histrelin	Pyr-His-Trp-Ser-Tyr-D-His(N-benzyl)-Leu-Arg-Pro-NHEt	Prostate cancer; Breast cancer
Leuprolide	Pyr-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt	Prostate cancer; Breast cancer
Nafarelin	Pyr-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH_2	Endometriosis symptoms, Central precocious puberty
Triptorelin	Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2	Prostate cancer; breast cancer
	LHRH (GnRH) antagonists	
Abarelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3´-pyridyl)Ala-Ser-(N-Me)Tyr-D-Asn-Leu-isopropylLys-Pro-DAla-NH_2	Prostate cancer
Cetrorelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3´-pyridyl)Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2	Prostate cancer; Breast cancer
Degarelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3´-pyridyl)Ala-Ser-4-aminoPhe(L-hydroorotyl)-D-4-aminoPhe(carbamoyl)-Leu-isopropylLys-Pro-D-Ala-NH_2	Prostate cancer
Ganirelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3´-pyridyl)Ala-Ser-Tyr-D-(N9,N10-diethyl)-homoArg-Leu-(N9,N10-diethyl)-homoArg-Pro-D-Ala-NH_2	Fertility treatment

Table 1.
LHRH agonists and new-generation antagonists available in the market.

Emergence of Biologics in Cancer Treatment

Mortality from cancer is about to surpass that from cardiovascular diseases in the near future. About 7 million people die from cancer-related cases per year, and it is estimated there will be more than 16 million new cancer cases every year by 2020. Cancer is characterized by uncontrolled division of cells and the ability of these cells to invade other tissues leading to the formation of tumor mass, vascularization, and metastasis (spread of cancer to other parts of the body). Though angiogenesis (growth of new blood vessels from pre-existing vessels) is a normal and vital process in growth and development, it is also a fundamental step in the transition of tumors from a dormant state to a malignant one. So, angiogenesis inhibitors have been used to suppress tumor cell growth. Chemotherapy is one of the major approaches to treat cancer by delivering a cytotoxic agent to the cancer cells. The main problem with the conventional chemotherapy is the inability to deliver the correct amount of drug directly to cancer cells without affecting normal cells. Drug resistance, altered biodistribution, biotransformation, and drug clearance are also common problems. Targeted chemotherapy and drug delivery techniques are emerging as a powerful method to circumvent such problems. This will allow the selective and effective localization of drugs at predefined targets (eg, overexpressed receptors in cancer) while restricting its access to normal cells, thus maximizing therapeutic index and reducing toxicity. Discovery of several protein/peptide receptors and tumor-related peptides and proteins is expected to create a new wave of more effective and selective anti-cancer drugs in the future, capturing the large share of the cancer therapeutic market. The "biologics" treatment option against cancer includes the use of proteins, monoclonal antibodies, and peptides. The monoclonal antibodies (mAbs) and large protein ligands have two major limitations compared to peptides; poor delivery to tumors due to their large size and dose-limiting toxicity to the liver and bone marrow due to nonspecific uptake into the reticulo-endothelial system. The use of such macromolecules has therefore been restricted to either vascular targets present on the luminal side of tumor vessel endothelium or hematological malignancies. Peptides possess many advantages, such as small size, ease of synthesis and modification, tumor-penetrating ability, and good biocompatibility. Peptide degradation by proteolysis can be prevented by chemical modifications, such as incorporation of D-amino acids or cyclization.

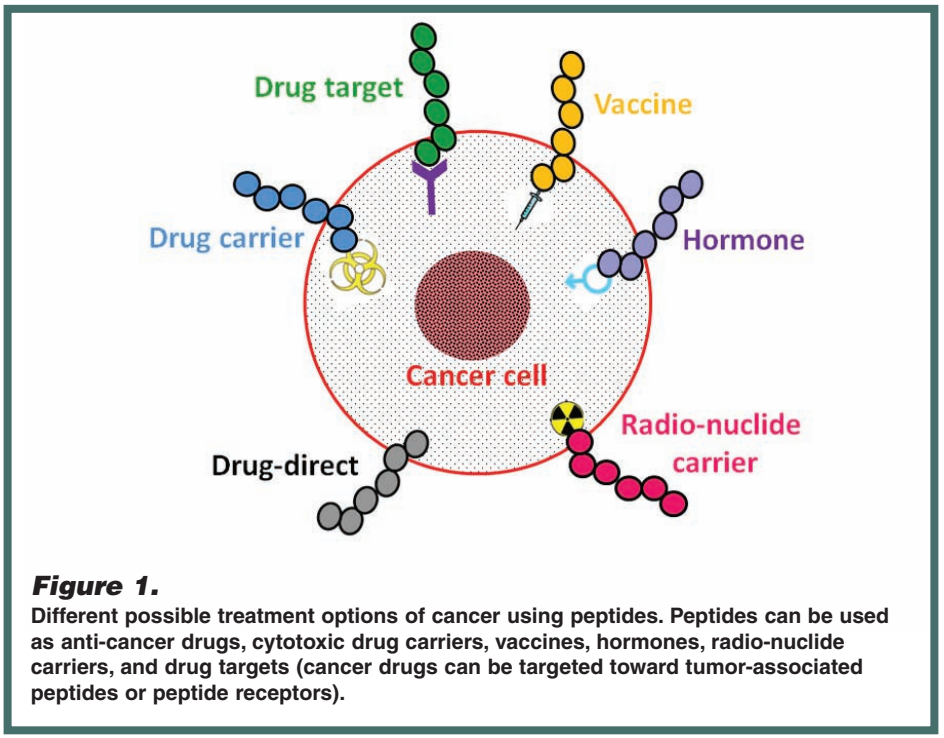

Figure 1.
Different possible treatment options of cancer using peptides. Peptides can be used as anti-cancer drugs, cytotoxic drug carriers, vaccines, hormones, radio-nuclide carriers, and drug targets (cancer drugs can be targeted toward tumor-associated peptides or peptide receptors).

LHRH Agonists & Antagonists

The best classical example of the application of peptides in cancer treatment is the use of LHRH (luteinising hormone-releasing hormone) agonists introduced by Schally et al as a therapy for prostate cancer. Since then, depot formulations of LHRH agonists such as buserelin, leuprolide, goserelin, and triptorelin have been developed for more efficacious and more convenient treatment of patients with prostate cancer. Administration of these peptides causes down-regulation of LHRH receptors in the pituitary, leading to an inhibition of follicle-stimulating hormone

(FSH) and LH release, and a concomitant decrease in testosterone production. This offered a new method for androgen deprivation therapy in prostate cancer patients. Discovery of LHRH antagonists resulted in therapeutic improvement over agonists as they cause an immediate and dose-related inhibition of LH and FSH by competitive blockade of the LHRH receptors. To date, many potent LHRH antagonists are available for the clinical use in patients. Cetrorelix was the first LHRH antagonist given marketing approval and, thus, became the first LHRH antagonist available clinically. Subsequently, new-generation LHRH antagonists, such as abarelix and degarelix, have been approved for human use. A list of LHRH agonists and antagonists available in the market are shown in Table 1.

Somatostatin Analogues in Cancer Therapy

Apart from the use of peptide-based LHRH agonists and antagonists for treating cancer, somatostatin analogues are the only approved cancer therapeutic peptides in the market. Potent analogues of somatostatin (peptide hormone consisting of 14 amino acids, found in delta cells of the pancreas as well as in hypothalamic and other gastrointestinal cells), including octreotide (sandostatin), has been developed for the treatment of acromegaly, gigantism, thyrotropinoma, diarrhea, and flushing episodes associated with carcinoid syndrome, and diarrhea in patients with vasoactive intestinal peptide-secreting tumors (VIPomas). Similarly, another long-acting analogue of somatostatin, lanreotide (somatuline), is used in the management of acromegaly and symptoms caused by neuroendocrine tumors, most notably carcinoid syndrome and VIPomas.

Most neuroendocrine tumors (NETs) feature a strong overexpression of somatostatin receptors, mainly of subtype 2 (sst2). Currently, five somatostatin receptor subtypes (sst) are known (sst1-5). The density of these receptors is vastly higher than on non-tumor tissues. Therefore, sst are attractive targets for delivery of radioactivity via radiolabeled somatostatin analogs. The sst2 has been shown to internalize into the cell in a fast, efficient, and reversible manner after specific binding of a receptor agonist. This molecular process is likely to be responsible for the high and long-lasting uptake of radioactivity in the target cell after binding of the radiolabeled somatostatin analog. Introduced in the late 1980s, [111In-DTPA0]-octreotide (Octreoscan), the first available radiolabeled somatostatin analog, rapidly became the gold standard for diagnosis of sst-positive NETs. Numerous peptide-based tracers targeting sst have been developed over the past decade. Octreoscan and Neotect (tc-99m depreotide) are the only radiopeptide tracers on the market approved by the Food and Drug Administration. An octreotide scan or octreoscan is a type of scintigraphy used to find carcinoid and other types of tumors and to localize sarcoidosis. Octreotide, a drug similar to somatostatin, is radiolabeled with indium-111 and is injected into a vein and travels through the bloodstream. The radioactive octreotide attaches to tumor cells that have receptors for somatostatin. A radiation-measuring device detects the radioactive octreotide, and makes pictures showing where the tumor cells are in the body.

Current Status & Future of Peptide Based Anti-Cancer Agents

The application of peptides as a direct therapeutic agent, in targeted drug delivery and as a diagnostic tool in cancer biology, is growing. Drug targeting exploits differences in the nature of normal and cancer cells and their microenvironment. To establish efficient and reliable therapeutic delivery into cancer cells, a number of delivery agents and concepts have been investigated in the recent years. Among many improvements in targeted and controlled delivery of therapeutics, cell-targeting peptides have emerged as the most valuable non-immunogenic approach to target cancer cells. Peptides can be incorporated into multicomponent gene-delivery complexes for cell-specific targeting. In contrast to larger molecules, such as monoclonal antibodies, peptides have excellent tumor penetration, which make them ideal carriers of therapeutics to the site of primary tumor and the distant metastatic sites. Different possible cancer treatment options using peptides are summarized in Figure 1.

A recently identified peptide called iRGD is able to specifically recognize and penetrate cancerous tumors but not normal

tissues. Discovery of such peptides having extraordinary tumor-penetrating properties will definitely make substantial improvements in cancer treatment in the future. Chlorotoxin (a 36 amino acid peptide derived from scorpion venom) binds preferentially to glioma cells compared with non-neoplastic cells or normal brain has allowed the development of new methods for the treatment and diagnosis of cancer.

BN/GRP (bombesin/gastrin-releasing peptide) peptides were shown to bind selectively to the G-protein-coupled receptors on the cell surface, stimulating the growth of various malignancies in murine and human cancer models. Thus, it has been proposed that the secretion of BN/GRP by neuroendocrine cells might be responsible for the development and progression of prostate cancer to androgen independence. GRP is widely distributed in lung and gastrointestinal tracts. It is produced in small cell lung cancer (SCLC), breast, prostatic, and pancreatic cancer, and functions as a growth factor. The involvement of bombesin-like peptides in the pathogenesis of a wide range of human tumors, their function as autocrine/paracrine tumoural growth factors, and the high incidence of BN/GRP receptors in various human cancers prompted the design and synthesis of BN/GRP receptor (GRPR) antagonists, such as RC-3095, RC-3940-II, and RC-3950.

Peptide receptor radionuclide therapy (PRRT) combines octreotide with a radionuclide (a radioactive substance) to form highly specialized molecules called radiolabeled somatostatin analogues or radiopeptides. These radiopeptides can be injected into a patient and will travel throughout the body binding to carcinoid tumor cells that have receptors for them. Once bound, these radiopeptides emit radiation and kill the tumor cells they are bound to.

Recently, many researchers are focusing on the development of GHRH (growth hormone releasing hormone - a hypothalamic polypeptide) antagonists as potential anti-cancer therapeutics because the GHRH is produced by various human tumors, including prostate cancer, and seems to exert an autocrine/paracrine stimulatory effect on tumors. Another promising and emerging approach for the therapy of prostate cancer consists of the use of cytotoxic analogues of LHRH, bombesin, and somatostatin, which can be targeted to receptors for these peptides in prostate cancers and their metastases. For example, a potential drug candidate, AEZS-108 couples a peptide, LHRH, with the chemotherapeutic agent doxorubicin to directly target cells that express LH-RH receptors-specifically, prostate cancer cells.

There is a tremendous effort to discover angiogenesis inhibitors, based on polypeptides as the safest and least toxic therapy for diseases associated with abnormal angiogenesis. A number of ongoing clinical trials in this area focus on peptides derived from extracellular matrix proteins, growth factors and growth factor receptors, coagulation cascade proteins, chemokines, Type I Thrombospondin domain-containing proteins, and serpins. Recently, it was found that angiotensin-(1-7) can stop lung cancer tumor growth in mice. Also, peptides that can inhibit cell growth in drug-resistant ovarian cancer have been identified. Stapled peptides are showing promise for treating colon cancer and other forms of cancerous growth.

Peptide Vaccines

Active immunization seems to be the most promising strategy to treat cancer, though many approaches based on the employment of immune cells or immune molecules have been studied. Researchers have studied and debated the possibility of vaccinating against cancer for decades. Only in recent years has the debate changed from being focused on preclinical proof-of- principle to discussions on what defines a tumor antigen and how best to optimally deliver vaccines based on defined antigens to induce anti-cancer immunity. This new method of treating cancerous cells relies on vaccines consisting of peptides derived from the protein sequence of candidate tumor-associated or specific antigens. Tumor cells express antigens known as tumor-associated antigens (TAAs) that can be recognized by the host's immune system (T-cells). Many TAAs have recently been identified and molecularly characterized. These TAAs can be injected into cancer patients in an attempt to induce a systemic immune response that may result in the destruction of the cancer growing in different body tissues. This procedure is defined as active immunotherapy or vaccination as the host's immune system is

either activated de novo or re-stimulated to mount an effective, tumor-specific immune reaction that may ultimately lead to tumor regression. Any protein/peptide produced in a tumor cell that has an abnormal structure due to mutation can act as a tumor antigen. Such abnormal proteins are produced due to mutation of the concerned gene. Clinical studies have therefore been initiated to assess the therapeutic potential of active immunization or vaccination with TAA peptides in patients with metastatic cancer. So far, only a limited number of TAA peptides, mostly those recognized by CD8 (+) T cells in melanoma patients, have been clinically tested. Several melanoma TAAs have been identified and are being evaluated as peptide-based cancer vaccines in clinical trials around the world. Recent advances in the field of molecular biology have enabled the rapid identification of dozens of candidate TAAs for several important human cancers. The challenges for future studies are to determine the most efficient means of administering the vaccine and to develop methods to determine if the vaccine is effective.

Summary

In summary, peptides are poised to make a significant impact in the near future in the area of cancer treatment and diagnosis. A number of peptide-based therapies, such as cancer vaccines, tumor targeting with cytotoxic drugs and radioisotopes, anti-angiogenic peptides, etc. are currently in clinical trials and expected to yield positive results. Stimuvax (palmitoylated peptide vaccine against non-small lung cancer, Merck), Primovax (peptide cancer vaccine, Pharmexa), Melanotan (pre-cancerous actinic keratosis-Clinuvel) and Cilengitide (Glioblastoma-Merck) are some examples of potential peptides in late clinical trials. Due to the tremendous advancement in the large-scale synthesis of peptides, it will be possible to cut down the manufacturing costs, thereby making peptide-based anti-cancer drugs more affordable. ■

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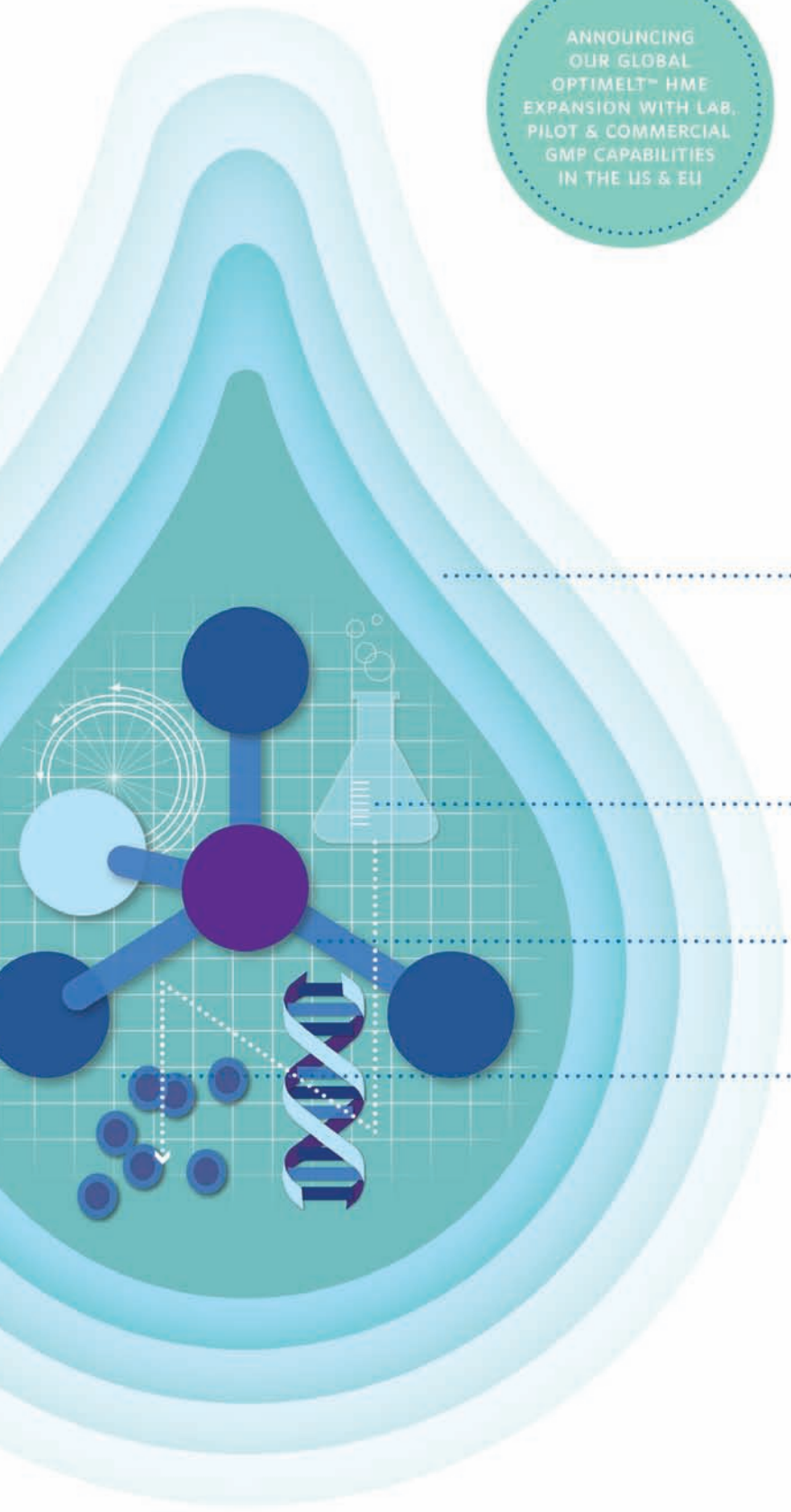

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