Drug Development & Delivery

March 2014 Vol 14 No 2

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Solubilization Insights

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

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"This analysis covers the drugs that have been approved, and the data suggests a strong and increasing adoption of various technologies - especially throughout the past 15 years. What lies ahead for the rest of the current decade? The combination of three key factors....."

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Cell Therapy Challenges

"These technologies are evolving from tissue culture dishes and flasks to high-end, fully controlled bioreactor systems, which will allow production of large quantities of cells under cGMP. The challenge becomes even bigger when looking at off-the-shelf allogeneic therapy. When mature, the industry will face an even larger challenge of downstream processing of the cell products."

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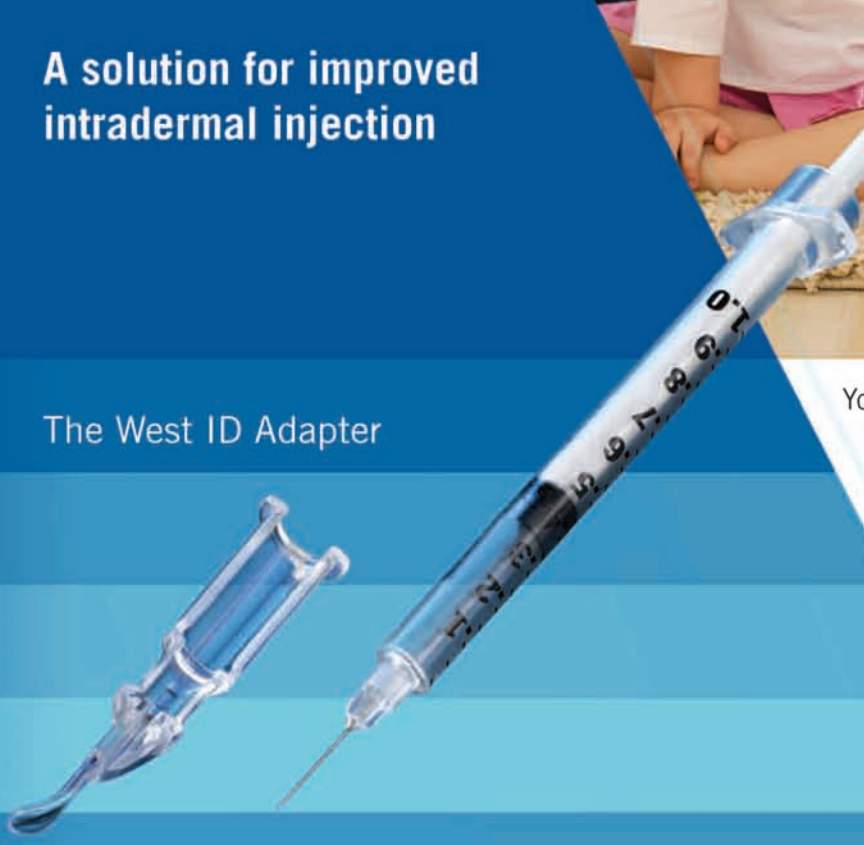

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Horizon Discovery Signs Major Agreements; Launches GENASSIST Line of Kits & Reagents

Horizon Discovery recently announced it has signed a worldwide distribution agreement with Haplogen GmbH, with immediate effect. Under the terms of the agreement, customers can now access, directly from Horizon, Haplogen's Haploid Gene Trap Mutant Collection of isogenic human cell lines deficient for the expression of single genes. This agreement represents the first time Horizon will be distributing another company's products, recognizing Horizon's past success in penetrating the global model cell lines market.

Haploid cellular models offer a biologically relevant system for in vitro genetic analyses of molecular, cellular, and developmental events in various cell lineages. Haplogen's Haploid Gene Trap Mutant Collection is the largest haploid cell line bank available, and comprises over 9,400 mutant clones, affecting over 3,700 human genes and an additional 1,600 inducible clones covering 1,100 genes. For-profit customers will be able to access the cell-line bank by signing an annual limited-use label license, whilst academic customers will be able to access an unlimited term license and will receive a greater than 90% discount.

"Horizon's mission is to give scientists access to high-value products and services that address their research needs," commented Dr. Darrin Disley, CEO, Horizon. "The addition of the Haplogen cell line products to our offering supports our growth strategy and is highly complementary to our current product portfolio, including our X-MAN range of diploid isogenic cell lines. We anticipate announcing further partnerships in the future as we continue to broaden our product offering to meet the needs of our customers."

Horizon Discovery also announced it has signed a supply and distribution agreement with Sirion Biotech GmbH. Under the terms of this agreement, Horizon's customers can now access Sirion's highly efficient RNAiONE custom shRNA development services, as well as Sirion's off-the-shelf validated shRNA and cDNA over-expression reagents. Through this partnership, Horizon now offers a broad spectrum of gene modulation technologies ranging from stable shRNA knockdown and cDNA overexpression systems to the ability to edit endogenous genes via rAAV, ZFN, and CRISPR platforms.

Short hairpin RNA (shRNA) has become a staple of the research community for silencing genes, but identifying the most effective shRNA sequence to provide the greatest level of gene suppression often presents a problem. Sirion's RNAiONE platform is a validation system that reliably produces shRNAs with a gene-silencing efficiency often greater than 90%.

The platform is being made available through Horizon as a custom service that delivers a shRNA sequence, transduction-ready lentivirus, or a treated knock-down cell pool. Inducible knock-down and over-expression systems are also available, offering a valuable tool for functional gene analysis and to help deal with the adaptive capacity of cells. Horizon will also be making available over 125 off-the-shelf RNAiONE-validated shRNAs and over 70 cDNA overexpression constructs. These will be available as transduction ready lentivirus particles or as plasmids.

"Gene over-expression and knockdown studies are important to both basic and preclinical research, helping to determine the specific roles of genes and potentially leading to the discovery of novel targets for new drugs," said Dr. Jon Moore, VP, Oncology, Horizon Discovery. "Issues surrounding knock-down efficiency and the associated phenotypic variation have led to inconsistent results. The high silencing efficiency ensured by RNAiONE gives researchers confidence in their functional genomics investigations."

Lastly, Horizon Discovery announced it has launched the first products and services from its new GENASSIST range of gene editing kits and reagents that enable easier, robust implementation of CRISPR and rAAV gene editing experiments.

The current GENASSIST offering comprises both off-the-shelf reagents for using CRISPR editing technology and a unique kit combination of these reagents to allow customers to generate their own CRISPR-ready cell lines that constitutively express Cas9-nickase. Using such cell lines provides a quick start for customers, enabling them to make further modifications to the cell line more efficiently than if they were starting fresh each time. Horizon is also launching a new service for the design, manufacture, and most importantly, validation of CRISPR RNA guides, in order to maximize the likelihood that gene editing will occur as expected.

"The launch of our first CRISPR kits mark the next stage in Horizon establishing itself as the leader in the gene editing field. Recent advances in gene editing technology, with techniques, such as rAAV, ZFN, and CRISPR, have had a revolutionary effect on translational genomics. Horizon's goal is to make these developments accessible to the wider scientific audience, through contract manufacturing, do-it-yourself products, and high-end technical support services. As the only company who can offer all of these techniques singularly or in combination, we can ensure that researchers, on their own or with our advice, can make an informed choice of which technology or combination of technologies to deploy to gain the correct answer to the biological question being asked," said Dr. Disley.

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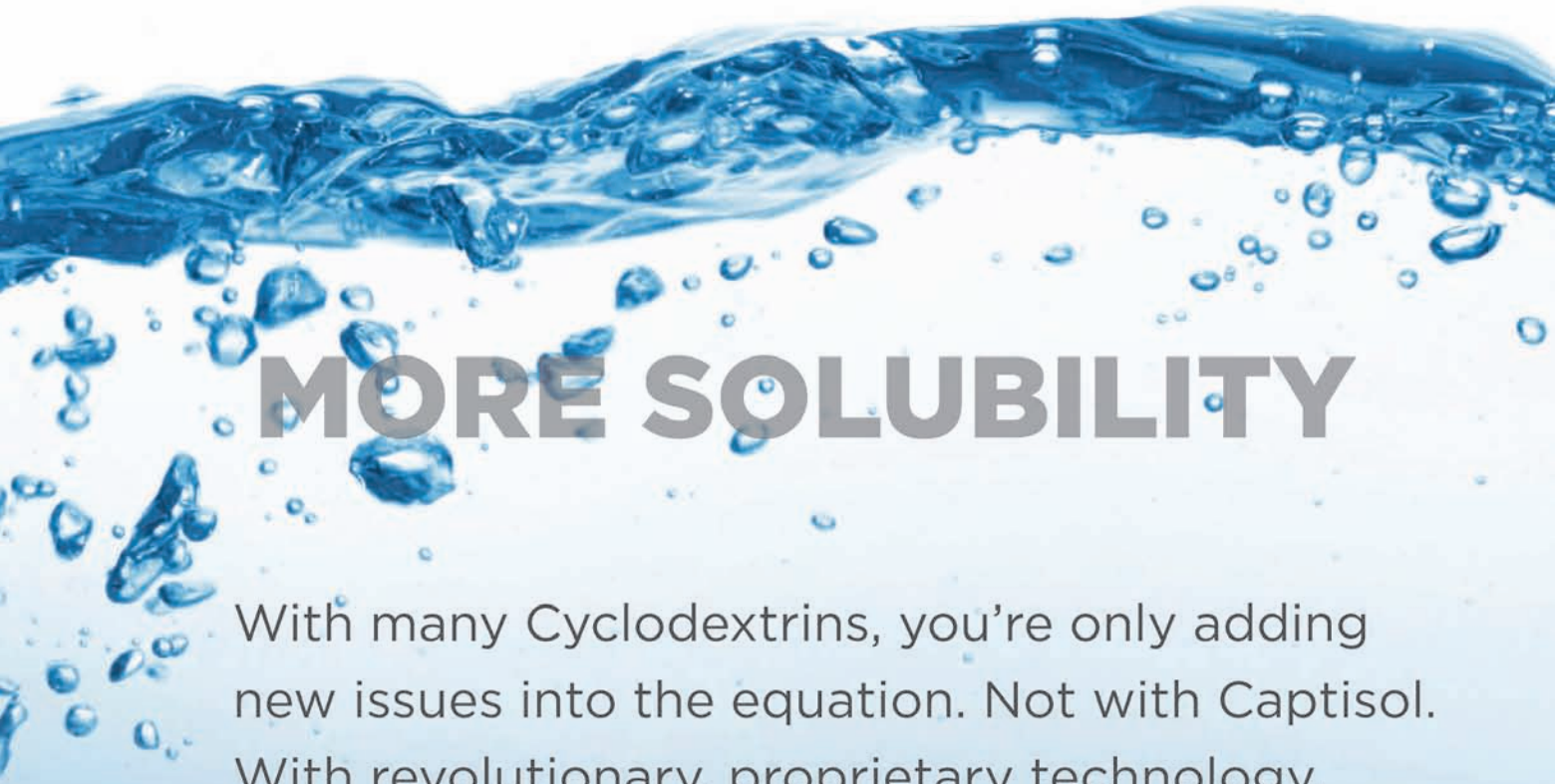

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Metrics, Inc. Expands With Fast-Track Product Development Laboratory

Metrics Inc. is making significant investments in its facilities and equipment for the benefit of contract services clients by opening a new laboratory to better support fast-track development of pharmaceutical products.

Also in its Greenville facility, the company is adding to its equipment portfolio a Gerteis Mini-Pactor, a high pressure-precise roller compactor that provides Metrics' formulation development scientists even greater flexibility in batch sizes and throughput.

The fast-track development laboratory and Gerteis Mini-Pactor represent continuing investment efforts at Metrics to support the changing needs of its contract services clients, said Stefan Cross, President of Mayne Pharma USA, the parent company of Metrics.

The $1.6 million, 4,524-sq-ft facility, located on the company's main campus in Greenville, NC, provides maximum flexibility for early formulation and analytical method development. The facility is designed for preclinical development of early formulation prototypes and related analytical methods. In this laboratory setting, formulators and chemists will have significant autonomy to conduct development activities more quickly, explained Dr. Brad Gold, Vice President of Pharmaceutical Development.

Segregated from the main Metrics operations and containing fully dedicated equipment, these new processing suites have independent HVAC systems and state-of-the-art engineering controls, such as interlocking airlock doors, room air pressure differentials, high-volume room air turnover, and 100-percent HEPA air filtration.

"These suites offer our scientists tremendous flexibility, which will support the fast-track development of drug products," Mr. Gold said. "Prototype formulations and methods developed in this lab will be transferred to the adjacent facility for further development and manufacture of clinical trial materials and registration batches. There, they will be manufactured under the exacting auspices of current Good Manufacturing Practice so that Metrics will continue to deliver proven scientific and operational excellence in oral solid dosage forms."

The ground floor of the new facility consists of five processing rooms and one analytical laboratory. The second floor consists of workstations, office space, and a conference room. This project increases to 16 the total number of processing rooms, which are in addition to the extensive analytical laboratories and large-scale manufacturing and packaging operations that Metrics has available. The new facility is expected to be fully operational by mid-February.

Housed within Metrics' main facility, the company's new Gerteis Mini-Pactor has capacity ranging from 10 grams for pilot projects to 100 kilograms per hour for small-scale production, making it especially useful in a formulation development laboratory setting.

"While big pharma companies may already be familiar with this particular roller compactor, Metrics can be considered an early adopter among pharmaceutical contract development and manufacturing organizations," said Mr. Gold. "This equipment investment reflects Metrics' ongoing commitment to operational excellence and to conducting science that is most meaningful to our clients and the patients we collectively serve."

Nuvilex Announces $27-Million Funding to Advance Late-Phase Clinical Trials

Nuvilex, Inc. recently announced it has entered into a stock purchase agreement with Lincoln Park Capital Fund, LLC, a Chicago-based institutional investor. Lincoln Park initially purchased 8 million shares of Nuvilex's common stock at $0.25 per share for $2 million and has committed to invest, at the sole option of Nuvilex, up to an additional $25 million of equity capital over the term of the purchase agreement. The proceeds from this investment will be used for Nuvilex's late-stage clinical trials in advanced inoperable pancreatic cancer, for research into the use of constituents of marijuana in the emerging medical marijuana arena, and for general operating purposes.

"Our stock purchase agreement with Lincoln Park gives Nuvilex the flexibility to access capital over time at prevailing market prices and as our needs arise," said Kenneth L. Waggoner, CEO and President of Nuvilex. "The initial funding helps us to proceed with our planned late-stage pancreatic cancer clinical trials. The $2-million initial investment also reflects the commitment to Nuvilex and our live-cell encapsulation platform for developing treatments for cancer and diabetes."

During the 36-month term of the stock purchase agreement, Nuvilex, at its sole discretion, has the right to sell Lincoln Park up to an additional $25 million of Nuvilex common stock in amounts as described in the agreement and subject to certain conditions, which include the effectiveness of a registration statement with the US SEC, covering the sale of the shares that may be issued to Lincoln Park. Nuvilex controls the timing and amount of any future investment. Lincoln Park is obligated to make purchases if and when Nuvilex decides.

Under the terms of the stock purchase agreement, there are no upper limits on the price Lincoln Park may pay to purchase Nuvilex's common stock. The purchase price of the shares related to any future investments will be based on the prevailing market prices of Nuvilex's shares immediately preceding a notice of sale to Lincoln Park. Lincoln Park has agreed not to cause or engage in any direct or indirect short selling or hedging of Nuvilex's common stock. The stock purchase agreement may be terminated by Nuvilex at any time at its sole discretion and without any monetary cost to Nuvilex.

Nuvilex is a biotechnology company focused on developing and preparing to commercialize treatments for cancer and diabetes based upon a proprietary cellulose-based live-cell encapsulation technology called Cell-in-a-Box. This unique technology will be used as a platform upon which treatments for several types of cancer, including advanced, inoperable pancreatic cancer, and diabetes are being built.

Roche Signs Licensing Agreement With Sysmex Inostics GmbH

Roche recently announced a licensing agreement with Sysmex Inostics GmbH for its emPCR portfolio of patents. Under the terms of the licensing agreement, Roche grants Sysmex Inostics GmbH a worldwide, non-exclusive, royalty-bearing license.

Through emulsion PCR (emPCR), each DNA molecule is individually isolated within its own bubble in a water/oil emulsion, which includes a capture bead and PCR amplification reagents. As a result, even though about a million molecules are prepared simultaneously, each molecule is individually amplified to one single bead, the equivalent of having a million separate PCR reactions. This technique allows for massive parallelization (high throughput) that results in a significant cost advantage over Sanger sequencing.

Sysmex Inostics GmbH is primarily a clinical service lab providing analysis of free circulating tumor-DNA in plasma for prediction of drug response and for monitoring of cancer by quantifying the amount of tumor DNA to detect relapse and to detect resistance mutations, utilizing emPCR technology. Actual Sysmex Inostics GmbH customers are pharmaceutical companies and academic and medical centers who use Sysmex Inostics services in clinical trials in which tissue collection is a problem.

"Roche has an active out-licensing program for its emPCR-based intellectual property portfolio," said Dan Zabrowski, Head of Roche Sequencing Unit. "By continuing to out-license this technology, we contribute to the development of well-validated techniques within the molecular diagnostics field."

Sysmex Inostics, a subsidiary of Sysmex Corporation, is a molecular diagnostic company whose core competency is mutation detection utilizing highly sensitive technologies, such as Plasma-Sequencing and BEAMing. With BEAMing being one of the most sensitive and quantitative technologies available today for the detection of tumor-specific somatic mutations in blood samples, Sysmex Inostics' BEAMing services are readily available to support clinical trials and research in oncology. Furthermore, Sysmex Inostics companion diagnostics (CDx) team offers services for the development of non-invasive plasma DNA-based IVD tests supported by a growing network of partners to cover the entire IVD development process. In addition, BEAMing tests (OncoBEAM) are available through a CLIA certified laboratory for routine clinical analysis. Sysmex Inostics' headquarters are located in Hamburg, Germany, and Sysmex Inostics' Clinical Laboratory is located in Baltimore, MD.

Nuevolution Announces Exclusive License Agreement

Nuevolution A/S recently announced that it has entered an exclusive license agreement with a subsidiary of Merck & Co., Inc., known as MSD outside the US and Canada, for small molecule compounds targeting an undisclosed intracellular target for use as leads in Merck's drug discovery and development.

Under terms of the agreement, Merck will gain exclusive rights for the further development and commercialization of the compounds. This is the second agreement between Nuevolution and Merck. Nuevolution will receive an undisclosed upfront payment and milestone payments for certain preclinical, clinical, and agreed upon commercial milestones. In addition, Nuevolution is eligible to receive royalties on the commercial sales of approved products. Further financial details were not disclosed.

With this agreement, Nuevolution delivers on its new strategy to transform from a technology platform biotech company to a lead compound development company, providing novel products to improve future health treatments for patients.

Nuevolution applies its Chemetics platform to identify small molecule drug candidates for therapeutically important targets. Chemetics uses proprietary innovative DNA labelling to allow small molecule screening at an unprecedented scale for lead discovery. The technology allows efficient screening of billions of molecules against biological targets. Nuevolution has patented its Chemetics technology and holds a strong validated patent portfolio within the technology field. In its existing collaborations and internal pipeline development, Nuevolution has successfully addressed several challenging targets, including protein-protein interactions by the identification of drug-like small molecules.

"This agreement is the first preclinical compound out-licensing agreement for Nuevolution. It marks the immediate realization of our chosen strategy to both offer access to our technology as well as out-license leads identified by the use of the Chemetics platform," said Alex Gouliaev, CEO of Nuevolution A/S. "We are very pleased to see that the compounds will be developed further by Merck."

"Looking at our deal track record, Chemetics has provided us with a commercially proven lead discovery engine," added Stig Løkke Pedersen, Chairman of Nuevolution A/S. "The out-licensing of compounds represents the best future source of sustainable growth for the company. It is very encouraging to see existing partnerships develop into long term relationships."

Nuevolution is a leading small molecule lead discovery company founded in 2001 and based in Copenhagen, Denmark. The company has developed Chemetics, a unique, patent-protected hybrid of proven wet chemistry and molecular biology, which represents the ultimate fragment-based drug discovery technology.

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Sonrgy Secures Exclusive License to Commercialize Drug Delivery Nanotechnology

Sonrgy, Inc. recently announced it has entered into an exclusive license agreement with the University of California for the company's core technology, an ultrasound-sensitive drug delivery platform.

The agreement grants the company the sole rights to develop and market the technology worldwide. Protecting the fundamental enabling technology establishes a significant barrier to potential competitors, and is a vital step toward bringing the platform to the clinic.

Based on research conducted in the lab of Prof. Sadik Esener at the UC San Diego Moores Cancer Center, "the SonRx technology addresses long-standing challenges related to stability and controlled release in nano-scale drug delivery," stated Dr. Michael Benchimol, Sonrgy's Chief Technology Officer. "We are excited to initiate the next steps of its commercial development."

Sonrgy is a preclinical stage biotechnology company based in San Diego, CA, that is developing a targeted chemotherapy delivery platform to improve survival and quality of life for millions of cancer patients. Sonrgy's tiny nanocarriers safely transport potent chemotherapy drugs to cancer tumors and release high doses on command in response to a focused beam of ultrasound.

These carriers deposit drugs directly at the tumor cell sites, avoiding the many serious side effects of toxic chemotherapy circulating in the blood stream. Nanocarriers can deliver chemotherapy before surgery to reduce tumor size, after surgery to prevent recurrence and in situations when surgery is not possible to arrest tumor growth. This distinctive approach to delivering chemotherapy can be applied to many cancer tumors and enables more intensive treatment of the cancer, potentially improving effectiveness while reducing harmful effects on the rest of the body.

Management Insight

In Pursuit of Ethics: Reflections On Why We Do What We Do

By: Derek Hennecke, CEO & President, Xcelience LLC

In January, the FDA banned imports from a fourth Ranbaxy plant in India after an unscheduled inspection revealed a lab littered with flies, a leaking refrigerator for drug samples, and evidence that laboratory technicians were altering data to improve test results.

The company once again expressed Shock! Outrage! And, of course, Regret! Much as it did in previous years, upon several similar infractions, which have happened year after year since 2005, culminating last year when Ranbaxy paid a record $500 million in fines and penalties and pled guilty to seven criminal counts related to egregiously falsifying laboratory data.

Our industry is not supposed to be like Big Steel, or Big Auto. We are not motivated by profit. We have a higher purpose; saving lives and improving quality of life. Don't we?

And yet, here we are again. A few years ago, it was J&J, once a paragon of pharmaceutical virtue, that underwent a massive shattering of public confidence as a series of quality breaches led to recalls of products from Tylenol to Rolaids to Sudafed to Motrin to contact lenses and hip implants. Merck fell from grace earlier this decade with its shameless promotion of Vioxx, when it knew of clear risks but buried the facts.

In this week's *Wall Street Journal*, Johns Hopkins' Dr. Victor Serebruany alleges that the results of AstraZeneca's studies for the anti-clotting drug Brilinta were significantly skewed to minimize deaths. The FDA review team leader, Thomas Marciniak, claims that trial records were so sloppy as to actually assert that 12 patients reported their own deaths by phone. AstraZeneca continues to defend both the trial and the efficacy of the drug.

My point is not to wag a righteous finger. True, in the case of Ranbaxy there was undoubtedly unconscionable greed at the heart of the matter. Greed is a businessperson's usual motive. There are others. In the scientific crowd, similar crimes are more often committed in the pursuit of reputation, such as the 1998 British vaccination study by Dr. Andrew Wakefield in England, which linked autism to vaccines, famously leading thousands of parents to shun vaccinations for their children and giving Dr. Wakefield fleeting status as a medical hero. This study has since been broadly scorned as complete fabrication, but in many ways, the revelation comes too late. The "facts" of the study had already become common knowledge, touted on Oprah and lauded by the likes of Jenny McCarthy, who has since been reported quietly announcing that - Oops! - her son didn't have autism after all; it was a misdiagnosis. She has since denounced her announcement, so it is becoming somewhat hard to follow.

Any individual who purposely sets out to game the FDA or to falsify scientific findings is unabashedly evil. There are people like this, though I don't think a lot. What concerns me is the vast number of people who surround these individuals. In every one of these situations, from Ranbaxy to Vioxx to Dr. Wakefield, there were dozens, if not hundreds, of people who were privy to what was going on, in whole or in part, and who went along with it.

Did they behave unethically in staying quiet? Most of us would say they did. And yet the evidence suggests that, in the same position, most of us would also stay quiet. Why?

I can think of any number of reasons. Fear is a big one. Picture the young professional trying to get ahead, full of ambition and zeal, ready to make a mark. His mentor brings him in on a big business deal in a third-world country, and the young man learns his mentor and all those at the table are engaged in behavior his MBA textbooks soundly discourage.

This happened to a close friend of mine, many years ago. I'd venture to say he was/is a good man. What did he do? Nothing. He knew intuitively his career prospects would dim if he spoke up. I suspect, however, he may also have enjoyed the warm glow of being initiated into part of this elite circle. The fact that corruption only took place in the third world and not at company headquarters lent a sort of moral exceptionality to it. They were good men, most of the time.

I think of my friend when I hear of the bribery allegations of China's pharmaceutical trials. I wonder how many employees of these US firms went along with things, because that's the way things are done in China.

Conformity is another reason people can head down the wrong path. At Ranbaxy, former employees told *Fortune* back in 2010 that executives there approached the regulatory system as an obstacle to be gamed, boasting about their cleverness in deceiving regulators. The newspapers raged about this revelation, but no one ever asked the employees about their own complicity through silence. Their sharp outrage came only after the debacle unfolded. While the gig was still on, they did like everyone else: they fit in.

A strong ethical culture within a company is the best inoculation against unethical behavior, but such cultures can be fragile and must be regularly reinforced. J&J's downfall may be just such a case. Certain stressors can bring down a wall of corporate values like a brick through the glass conference room door. Rapid organic growth, mergers and acquisitions, decentralized management, rapid reaction to regulatory findings, quality systems that aren't part of the enterprise IT architecture; these are just a few changes that can cause employees to put ethics on the back burner in favor of more immediate issues.

Here's another conundrum. The first Ranbaxy plant closure took place in 2005. In the following 9 years, the company was plagued by criminal investigations and plant closures. And yet in 2011, the FDA awarded Ranbaxy the right to produce a generic Lipitor. Does this seem odd? But wait. In May 2013, Ranbaxy paid the largest fine in history for criminal negligence in deceiving and falsifying records for the FDA. Yet, only this January did someone actually go in and take a peek inside the Indian plant in Toansa that does most of the production for generic Lipitor. Did no one consider that there might be quality issues at this Ranbaxy plant between 2011 and 2014? No one at all?

Often, it just takes one person to put a stop to unethical behavior. Blowing the whistle on an entire organization is one of the hardest things an individual can do. Hats off to the FDA official David Graham who spoke out against his organization's handling of the heart attack side effects of the arthritis drug Vioxx in 2005. It must have been a tough decision; the pressure to conform must have been enormous. I'd wager he still doesn't feel welcome at company picnics.

How far would *you* go to do things right? UK management guru Charles Handy opines heavily on such matters in his recent memoir, *Myself & Other More Important Matters*. What is refreshing about Mr. Handy's works is his promotion of the manager-philosopher; a thinking being who balances life and work, morals, and ethics, as well as ledgers, columns, and marketing strategies.

In his business study curriculum, he presents students with the Greek tragedy, *Antigone*. In this play, Antigone's brother Polyneices dies on the battlefield of a civil war. When the dust settles, the new ruler of Thebes decrees that her brother's body be left to rot on the field of battle, to be preyed upon by carrion. This is the worst fate anyone in those times could imagine, as their religion dictated that, without burial, the soul would never rest. Antigone defies the edict and buries her brother, knowing that she will be put to death for her act.

How far would you go to stand up for what is right? What beliefs, if any, do you hold so dear that you would defy anyone to uphold them? Could you stand on your principles against legitimate authority? Should a good person obey a bad order? These are questions often ignored in modern business schools and, perhaps as a result, in modern businesses, where the ends are often deemed to justify the means, within the boundaries of legality, or at least, detectability.

It's easy to overlook such questions and focus on the day-to-day business of 100 new emails requiring response, and three projects due by Friday. And yet, when you reach the end of your career and look back on it, the emails will be forgotten, and the way you answered those questions will have defined your life.

Voltaire wrote, "How infinitesimal is the importance of anything I do, but how infinitely important it is that I do it." Thank you Charles Handy for this much-needed reminder of why we do what we do. ◆

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

BIOGRAPHY

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

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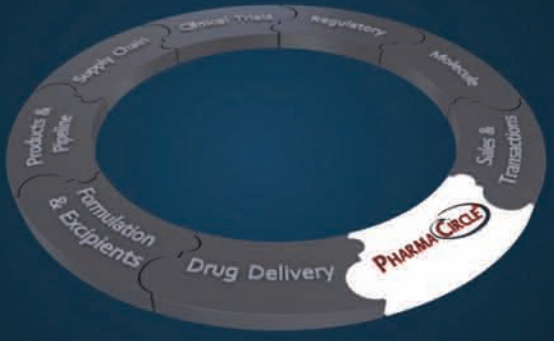

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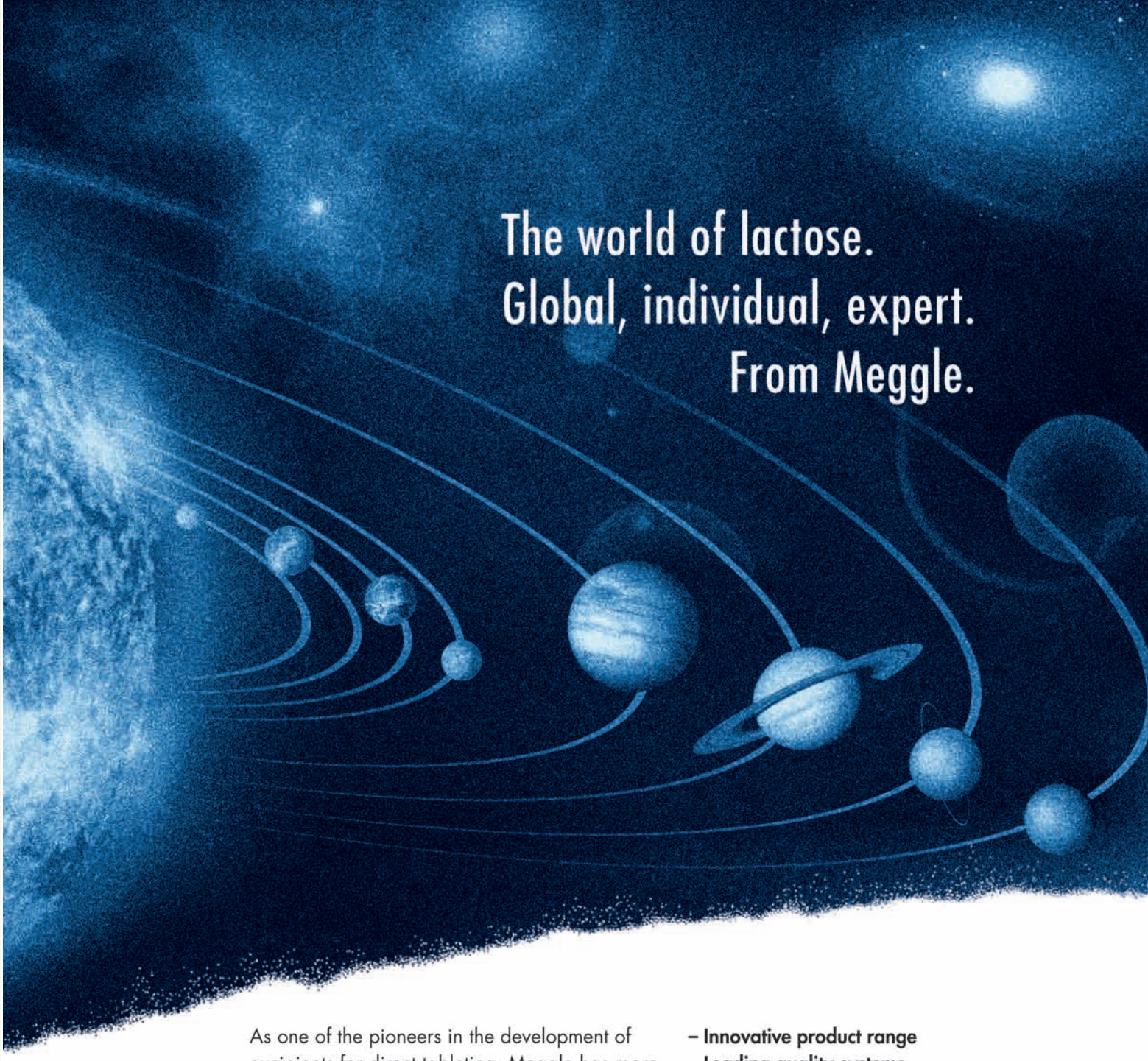
The Second Quadrant

Analysis of the Historical Use of Solubilization Technologies

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

In 2013, contributors to *The Second Quadrant* gave insights into how to decide what solubilization technologies might be most appropriate based on the API's characteristics and dosage form requirements for the drug product. Pharmaceutical companies are increasingly focusing on the use of solubilization to advance their most promising compounds to the marketplace. The Developability Classification System (DCS) further refines the FDA Biopharmaceutics Classification System (BCS), overlaying dissolution rate onto solubility and permeability and providing a third dimension to assist in categorizing an API and understanding what type of solubilization strategy is most likely to succeed.



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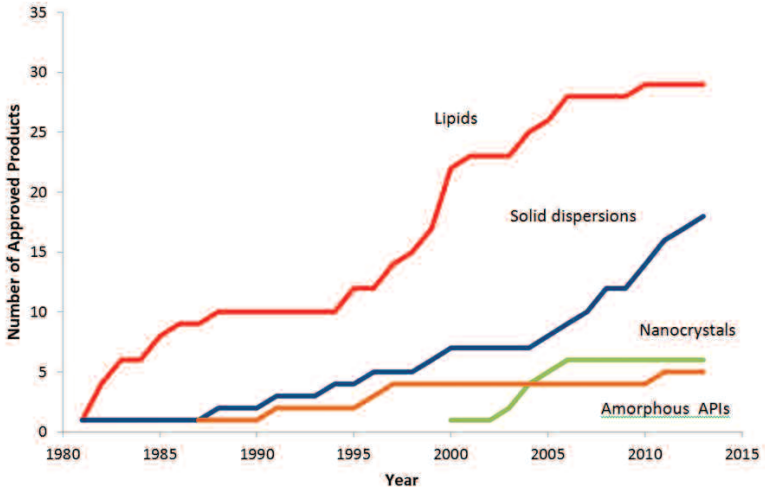
EXCIPIENTS & TECHNOLOGY

The progress being made in the knowledge base around addressing BCS Type II compounds has been significant in the past decade, and appears to be accelerating. In this month's column, we take a historical look at the marketed drugs that have been solubilized, the technologies used, and the therapeutic areas these drugs address. The goal of this analysis is to gain better insight into the commercial use of solubilization and its impact on the pharmaceutical industry.

THE GROWING USE SOLUBILIZATION TECHNOLOGIES SINCE 1975

Since 1975, we have found that approximately 60 marketed drugs have leveraged solubilization technologies to enhance oral bioavailability. In the preceding 36 years, from the time the FDA required submission of an NDA in 1938, solubilization technology was virtually unused on a regular basis. Apparently, the disease areas focus, drug discovery methodologies, and the lack of mature solubilization platforms restricted the use prior to the 1970s. In comparison, the past nearly 4 decades have shown robust growth in the reliance on solubilization platforms, accounting on average for around 6% of all NMEs approved from 1975 through 2013, and more than 10% in the past decade (Table 1).[1-7] Some years stand out to validate the need and use of solubilization platforms. For example, in 2005, 20% of NMEs approved used technologies including solid dispersion, lipid, and nanocrystal platforms. The data for the most recent 4-year period (2010-2013) seems to represent a slight decline in growth, but it is still early in the decade, and the data set is relatively small.

FIGURE 1



Approved Drugs: Use of Solubilization Technologies Since the 1980s

Based on the trends throughout the past 4 decades and the changing chemical space in drug development, we expect the decade will show additional and significant current growth in use of solubilization technologies once we have visibility into the full 10-year period.

SOLUBILIZATION TECHNOLOGIES: BY MARKETED DRUG APPROVALS BY DECADE

The popularity, utilization, and success of the diverse technologies throughout the past 6 decades is reflected in changing landscape of approved drugs applying solubilization approaches since the 1970s. In order to gain a quantitative understanding of the historical role of solubilization, we have compiled a comprehensive database of approved drugs that are formulated using a variety of solubilization technologies and delivered orally. In addition, we further filtered the dataset to only include formulations delivered as tablets or capsules (excluding solution and suspension vehicles). The technologies that have been used were divided into four classes: solid dispersions, pure amorphous APIs, lipids, and nanocrystals.

From our analysis, we confirm that lipid technologies have the most widespread use in terms of drug approvals in the years prior to 2005. The use of solid dispersion technologies has also seen strong growth but has lagged lipids by approximately 5 to 7 years. However, it appears that throughout the past decade, the growth rate of solid dispersions has been twice that of the lipid formulations. While it is not possible to determine the reasons in the available data, the more rapid adoption of solid dispersions may be a result of many factors,

TABLE 1

Decade*	NMEs Approved[1,2]	Using Solubilization Technologies[3,4,5,6]
1940-1969	543	NA
1970-1979	170	0.6%
1980-1989	217	4.1%
1990-1999	311	5.1%
2000-2009	235	10.2%
2010-2013	109	6.4%

FDA Drug Approvals Since 1970 & Percentage of Solubilized Drugs by Decade & Showing Drugs that Used Oral Solubilization Technologies

***The 30-year period of 1940-1969 is included to show the lack of solubilization technology utilization prior to the 1970s. 2010-2013 is included to reflect the data available to date for the current decade.**

TABLE 2

	Lipids	Solid dispersions Amorphous	Nanocrystals	Cyclodextrins	Totals by Area
Anti-infectives	6	7	3	1	17
Immune/Inflammatory	4	4	1	1	10
Cardiovascular	6	4	1	2	13
CNS	2	1	2		5
Dermatology	3				3
Endocrinology	3				3
Urology	2				2
Oncology	2	1			3
Musculoskeletal	1				1
Respiratory			1		1
Totals by Technology	29	17	5	5	2

Therapeutic Areas of Approved Drugs & Solubilization Technologies Applied[3-7]

including the attractiveness of a tablet dosage form (and conventional processing equipment), generally higher unit dose achievable, the widespread availability of manufacturing capabilities (HME and spray-drying), and the exponential growth in scientific knowledge of solid dispersions in the past decade as reported in last month's column.[3-6]

TECHNOLOGIES USED & THERAPEUTIC AREAS ADDRESSED

The PhrMA 2013 Profile of the Biopharmaceutical Industry points to a study finding that since 1975, medicines have contributed to a 60% increase in survival rates of cancer patients, and that research done by the American Heart Association has found that in the 10-year period of 1999-2009, death rates due to cardiovascular disease have dropped by 33%. Even more dramatically, since the approval of antiretroviral treatments in 1995 the HIV/AIDS death-rate has dropped by 85%.

We performed a study to evaluate the role solubilization technologies play to support drug success in the various therapeutic areas, and the findings were surprising. Table 2 shows the number of commercial products that are in the various delivery platforms and in each therapeutic area. The industry has long been aware that there's a strong need for solubilization in the drugs addressing the therapeutic areas of anti-infectives, cardiovascular, and immune/inflammatory. One surprising observation that this analysis reveals is the relatively few applications of solubilization to oncology. This is surprising to us at Agere since a large proportion of the compounds in our development portfolio are in oncology. One explanation for this may be that the approach to treating cancer has shifted from cytotoxic agents to targeted therapies, and these compounds, which are largely still in development, have lower solubility in general. In addition, many oncology drugs in the past have been dosed using methods other than oral delivery and as solubilization technologies have improved significantly, more therapeutic agents are now being developed for oral use.

CONCLUSIONS

This analysis covers the drugs that have been approved, and the data suggests a strong and increasing adoption of various technologies - especially throughout the past 15 years. What lies ahead for the rest of the current decade? The combination of three key factors – the complexity of diseases being addressed, that modern drug targets favor compounds with poor solubility and today's methods for designing, synthesizing and optimizing chemical libraries – promise to increase the reliance on solubilization technologies to realize the potential of promising drugs in development. It's a safe prediction that the utilization of bioavailability-enhancing platforms will rapidly accelerate before the end of the decade.◆

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REFERENCES/NOTES

1. FDA, Summary of NDA Approvals and Receipts.1938-present.
2. FDA New Molecular Entity Approvals. 2012-2013.
3. Knox C, Law V, Jewison T, Liu P, Ly S, Frolkis A, Pon A, Banco K, Mak C, Neveu V, Djoumbou Y, Eisner R, Guo AC, Wishart DS. DrugBank 3.0: a comprehensive resource for 'omics' research on drugs. Nucleic Acids Res. 2011;Jan;39(Database issue):D1035-41. PMID: 21059682.
4. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, Gautam B, Hassanali M. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res. 2008;Jan;36(Database issue):D901-6. PMID: 18048412.
5. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006;Jan 1;34(Database issue):D668-72. PMID: 16381955.
6. Agere analysis.
7. This estimate is thought to be conservative, as drugs thought to have used solubilization technologies but that were not yet verified were not included in this calculation.

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New Drug Delivery & Stabilization Platforms Gaining Global Interest

By: Sam de Costa, PhD

The launch by Nova of two stabilization and drug delivery platforms that have the potential to revolutionize the delivery of vaccines, therapeutics, and diagnostics, while significantly cutting costs, has attracted sharp interest from pharmaceutical and biotech companies around the world.

Both the patented Hypodermic Rehydration Injection System (HydRIS) and Vitrified Readily Injectable Suspension (VitRIS) are aimed at entirely removing the need for cold storage, achieving faster dissolution and providing aseptic-grade pharmaceutical products, and are now available for clinical evaluation following efficacy trials.

Created to complement Nova's advances in aseptic processing, they are genuinely novel, ground-breaking technologies that provide a truly viable response to the significant challenges faced by those trying to solve the world's vaccination problems, where vaccine delivery and drug stability are among the many obstacles for some developing countries.

It is for this reason in particular that we have been receiving such a great deal of interest from pharma and biotech companies seeking to solve many of the issues they have around stabilizing the medicines of tomorrow, including vaccination efforts in regions and countries where infectious diseases affect millions every year.

HYDRIS

HydRIS is a drug delivery device that has been developed to stabilize vaccines in a ready-to-inject-format with the particular aim of eliminating the necessity to refrigerate vaccines, and as such, has far-reaching applications in therapeutics, field medicine, bio-defense, and diagnostics.

It works by drying a mixture of active ingredients and a blend of amorphous, glass forming sugars on to a filter paper-like membrane, which is then enclosed in a plastic casing. The casing has ports at either end for a needle and syringe, allowing liquid from the syringe to flood the device and instantly reconstitute the dried material before its injection into the patient.

We have tested the device with conventional vaccines, labile products, and highly sensitive live virus and bacterial vectors, which were kept stable for prolonged periods at elevated temperatures as high as 45°C without any product degradation.

The potential of HydRIS to meet global healthcare challenges related to storage and stability has been underlined by a successful proof-of-concept study by scientists at Oxford University, UK.

We know that a significant proportion of vaccines across the world are destroyed because of improper storage, and we set out with the focused aim of creating solutions that allow products to be kept at ambient temperatures wherever in the world they may be.

As well as enabling a marked reduction in costs, the

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benefits for human health are significant when we bearing in mind that the device's ready portability significantly simplifies logistics, a crucial element when delivering vaccines that are thermo-stable at tropical temperatures to people in developing countries.

The HydRIS device is small, lightweight, and especially robust, making it suitable for a very wide range of possible applications - whether that is a mass vaccination program in developing country, battlefield applications, or preparing for possible pandemics.

VITRIS & AEROSPHERES

Our second stabilization platform, VitRIS, is currently being evaluated by a number of global pharma firms who are making early feasibility enquires, and we are currently evaluating a project to produce a pentavalent vaccine against childhood diseases.

The process provides a stable, ready-to-inject suspension, which can be used without any additional reconstitution steps at the point of administration using nothing more than a standard syringe and a needle. Even highly unstable products are then able to be stored for long periods without the need for refrigeration.

VitRIS technology, which is based on an aseptic spray-drying process, can produce stabilized product in dry powder format that can be instantly dissolved upon reconstitution. This platform, known as AeroSpheres, is now available to pharma and biotech companies as a viable alternative to lyophilisation.

Based on the well-established industrial spray-drying process, APIs are mixed with water-soluble glass formers and aseptically spray-dried as solid, non-crystalline glass, thus producing a highly polished microsphere in which the product is immobilized and stabilized.

The stabilized powders can be suspended in a non-aqueous liquid, matching the density of the powder with the density of the liquid, to prevent the powder from floating or sinking. What we have managed to do at Nova is master this challenging density-balancing process, with the result that we are now able to offer it as a service to our clients.

FIGURE 1

Nova's Aseptic Spray-Dryer

In a further development to the technology, we have acquired the expertise to manufacture patented Aerospheres, which, during spray-drying, creates hollow microspheres with a thin shell wall around the API. Thermo-stable, Aerosphere dry powder can cut dissolution rates by a factor of 10 in comparison with conventionally spray-dried powder.

Trials have shown that the VitRIS and Aerosphere technologies can be successfully applied to a large number of pharmaceutical preparations, including vaccines, insulin, monoclonal antibodies, recombinant growth hormones, proteins, enzymes, and nucleic acids and live biologics.

ASEPTIC SPRAY-DRYING

Fundamental to Nova's innovative platforms are its aseptic processing capabilities. We have had aseptic lyophilization

FIGURE 2

capabilities for a number of years and continues to offer the service to a wide range of clients, from large pharma to small biotech. Increasingly though, clients began began to seek an alternative to lyophilization to reduce costs and address other, associated problems.

As a result, we concentrated on pioneering aseptic spray-drying in clinical manufacture, and have experienced such significant demand that we are currently planning substantially increased capacity to allow commercial manufacture of spray-dried powder. We predict that the next 5 years will see greater uptake of the process as a more viable alternative to traditional lyophilization.

We are not surprised by the call for it. Although, as we know, spray-drying has been used by the pharmaceutical industry for some time, notably in API manufacture, it has not been available for manufacturing injectable-grade products, for example, vaccines, under truly aseptic conditions.

At Nova, we have found the technology fundamental in creating novel pharmaceutical products - indeed, VitRIS has been developed to complement Nova's marked advances in aseptic spray-drying, a truly enabling technology whose tight control over particle characteristics leaves open all avenues for drug delivery and presentation.

Where new drug development is concerned, we are witnessing a markedly increased demand in therapeutic areas, such as oncology, especially when clinical trials demand repeat dosing. Spray-drying will offer pharma and biotech companies greater efficiencies, quicker processing, and greater flexibility.

We have recently undertaken a number of projects for which the use of spray- drying, under truly aseptic conditions, has not only been beneficial, but in some cases, has been essential in order to meet certain criteria for quality and delivery.

One of the primary benefits of aseptic spray-drying over lyophilization is that it subjects the product to gentler processing conditions. A major drawback to lyophilization is that it does expose active ingredients to freezing temperatures, which can cause irreversible damage to their composition. During spray-drying processes, sensitive "actives" within the product are not subject to high temperatures for any prolonged period of time, which minimizes in-process damage to the product. The evaporative cooling effect during drying further minimizes any potential damage to the product by heat, which means that even highly labile products are compatible with the technology.

One of our largest current spray-drying customers is the Dutch company The Medicines Company, formerly Profibrix B.V, which has developed a new haemostat product based on a blend of spray-dried microparticles containing the clotting factors Fibrinogen and Thrombin. Essential to this product is the fact that the spray-dried active clotting proteins can be mixed in the final presentation and stored at room temperature without initiating coagulation, an outcome not possible if the product is formulated as a liquid.

We have manufactured late-stage clinical trial material at commercial scale to supply the ProFibrix pivotal trial FINISH-3 and are preparing for commercial supplies in the future that require kilogram quantities of powder. When we note the volumes required, the high-capacity spray-drying capability is essential for product realization.

From an economic standpoint, spray-drying requires less financial investment and operational time compared to a similar-scale lyophilization plant, with the efficiencies it generates benefiting clients in a number of ways.

When high throughput is required, a significant cost reduction is achieved as aseptic spray-drying is a reliable continuous process that facilitates high-volume manufacture.

There are various situations in which this is crucial to pharmaceutical firms, such as when large quantities of a vaccine or drugs are required for stock-piling under emergency situations.

Lyophilization's ability to meet such demands is highly limited because it is a batch process, meaning the quantity of product that can be manufactured is, naturally, restricted to the size of the lyophilizer. Up to now, we have aseptically spray-dried pharmaceutical biologics continuously for up to 5 days to manufacture large, kilogram quantities of power. Generally, lyophilization cycles take a number of days, and in some cases, weeks, to finish, but equivalent quantities can be manufactured using spray-drying within a shorter period, due to high-volume capacity, which at the same time, uses less energy in the process.

Once spray-dried, the product can be filled aseptically into various presentations, including vials, syringes, medical devices, and capsules. We have been able to extend cost-savings for clients using this process as the spray-dried powder can be aseptically blended, filled, and finished under the same roof.

The impact spray-drying has on product quality renders it essential for certain drug preparations. Through particle engineering, spray-drying enables further development of the product, offering improved characteristics that can result in greater bioavailability, rapid dissolution, or improved flowability.

Pharmaceutical firms have increasingly sought Nova's expertise when it comes to producing heat-stable multivalent vaccines in a spray-dried format. Many of these companies have approached us to enquire about proof-of-concept trials to demonstrate compatibility.

Using aseptic spray-drying, the separate components of the vaccine can be jointly or individually spray-dried (under conditions unique to each separate element) before being combined in the final delivery method. Such a process would not be possible using traditional lyophilization techniques.

To meet the increased demand from around the world for large-scale production, Nova is currently drawing up plans to expand our manufacturing capabilities to cater for full-scale commercial manufacturing volumes. Conversely, we have also experienced an equally global demand for much smaller

FIGURE 3

HydRIS Device: Vaccines are dried on a fibrous membrane and stabilized

volumes of powder, often from start-ups, in the very early stages of drug development. In instances like these, it is not economically viable to produce using our main manufacturing facilities. To meet this increasing demand for smaller test batches of aseptically manufactured powder, we have recently installed a series of scale-down spray-dryers operating under aseptic conditions. Our hope is that this capability will enable smaller companies, who work hard to secure sponsorship and funding for new drug candidates, to undertake feasibility studies that previously would have been beyond their financial reach.

So we are happy to say that, in combination with our ability to undertake large- scale aseptic spray-drying, we have become a one-stop facility for early stage developments to commercial supply of aseptically spray-dried pharmaceutical products.

Our prediction is that the adoption of aseptic spray-drying

by the global pharmaceutical industry will increase exponentially. When it comes to manufacturing innovative drugs using novel platforms, such as VitRIS, we have shown that it is not only more effective than lyophilisation, but may prove to be the only process capable of doing the job.

NOVEL DRUG DELIVERY

We are also witnessing particular interest from pharmaceutical companies in another of our capabilities. A number of customers currently testing vialled powders are making serious enquiries around prefilled syringe delivery, as later-stage trials bring a new focus on effective presentations.

The driver behind this particular trend is a clinical one. As we are aware, when products are contained in vials, administrators have to open packaging and draw up the dose manually, which not only takes up valuable time but creates a risk that the dosage will be inaccurate or, worse, that an incorrect product could be administered. Prefilled syringes remove this risk and significantly boost patient safety.

Nova has experienced an encouragingly high demand for this presentation method as a component of diagnostic kits, and also from biotechs manufacturing antibodies, but their potential also spans liquid protein formulations and biosimilars.

Clinical factors are not the only consideration, however. Commercial drivers are also contributing to a greater interest, as firms seek to extend lucrative patents on drug blockbusters. This patent cliff has undoubtedly been greatly influential in altering the composition of the global pharma industry and contributed to some degree of fragmentation. Against its negative effects, however, should be the fact that it also presents exciting new opportunities. Those firms willing to embrace the latest technologies in drug delivery can reinvigorate existing drugs and conceive exciting new ones, thus leading the way in helping to meet the needs of a rapidly changing global healthcare landscape. ◆

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

BIOGRAPHY

Dr. Sam de Costa is the Programme Manager for Thermo-Stabilisation & Aseptic Spray-Drying projects at Nova Bio Pharma Group. He is an experienced project manager with over 10 years of pharmaceutical R&D and medical device development expertise. He has been responsible for the development of HydRIS and VitRIS stabilisation platforms and was a principle inventor for the HydRIS medical device. At Nova, he also heads the team responsible for R&D of pharmaceutical aseptic spray-drying. He can be reached at +44 116 2230100 or at sam.decosta@novalabs.co.uk.

FIXED-DOSE COMBINATIONS

Fixed-Dose Combination Products – A Review (Part 1 – Introduction)

By: Tugrul T. Kararli, PhD, MBA; Kurt Sedo; and Josef Bossart PhD

INTRODUCTION

The pharmaceutical industry has being paying increasing attention to the potential of Fixed-Dose Combination (FDC) products. In a series of three articles, we will examine the past, present, and future of these products with the intent of understanding their whats and whys. We may even identify a few areas ripe for new product concepts.

The US pharmaceutical business has seen a number of combination products approved throughout the past 2 decades. Every year, it seems there are another half-dozen or so FDC products approved by the FDA. This number does not include combination product approvals that represent new dosage strengths, new manufacturers, or generic products. If we were to include these products, the annual total would be even higher. But, as we will see, even "novel" FDC products are often "variations on a well-worn theme."

Let's start by explaining why we are using the term Fixed-Dose Combination (FDC) rather than Combination. While both types of products suggest the use of more than one active ingredient, the FDC designation implies that these actives are incorporated into a single dosage presentation. So an FDC product might have two actives in a single tablet, capsule, patch, or vial. It's like a martini; the formulator, in this case, a bartender combines gin and vermouth in a single, inseparable "dose." The customer cannot in any practical sense separate these two ingredients. A Combination though might mean two actives taken together or separately, and in proportions that are infinitely variable. Instead of a martini, you take a sip of gin and a drop of vermouth, or two sips of gin and one of vermouth. FDC products can be thought of as a subset of Combination products. They are similar but not the same. It's easy to think of therapeutically and commercially important FDC combination products, a beta-blocker and diuretic combination, or an estrogen and progestin female hormone product.

So a product like Advair, a combination of fluticasone and salbutamol in an integral inhaled dosage form is an FDC, while a combination of injectable interferon and oral ribavirin is not. To put practical boundaries on this review, products such as multi-vitamins, electrolyte solutions, pancreatic enzyme replacements, purgatives, and insulin combinations, are not included. The overriding principle is whether the product contains two or more actives that provide a defined additive or synergistic therapeutic benefit in a dosage form that does not permit the user to adjust the proportion of the actives. Doses can be increased or decreased, but their ratio cannot be altered in the normal course of dosing.

FIXED-DOSE COMBINATION PRODUCTS – THE BENEFITS

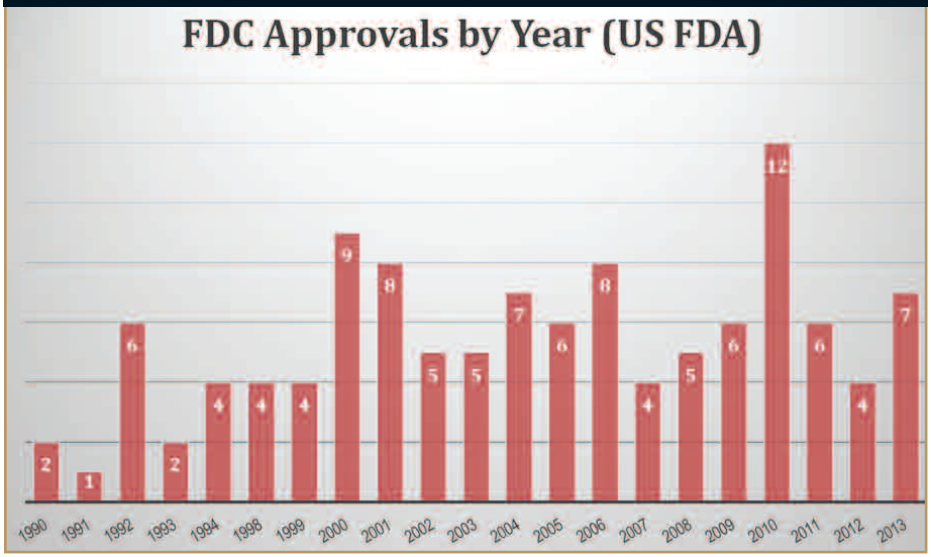
Efficacy & Safety

There is little question that many patients benefit from receiving more than one pharmaceutical active to treat a medical condition when their actions are synergistic, or at least additive. Often, efficacy can be significantly improved with minimal impact on the combination product's safety and tolerability. The combination of a beta-blocker with a diuretic has a well-established safety and efficacy profile as an antihypertensive. Raise the dose of the beta-blocker, and you start to have tolerability and safety issues, yet the diuretic alone has limited efficacy by itself. Put them together, and you have a much better balance of efficacy and safety.

Compliance

It's easier to remember to take one medication rather than two. This is particularly the case if the two products are dosed on different schedules, for example, once and twice a day. Combine them in a single dosage form, adjust the formulation to permit once-daily dosing, or if necessary twice-daily dosing, and it becomes much easier for patients to be compliant, especially if they are taking medications for other indications. This has the net effect of improving efficacy by ensuring more consistent dosing. The results reported in most clinical trials are dependent upon consistent dosing. Making it easier to take and remember a prescription product makes it more likely that an individual will follow the clinically validated dosing pattern. It's not only easier, it's better when you can combine two actives in a single product and improve compliance.

FIGURE 1



Value

What is the value proposition for fixed-dose combination products? In short, that depends what product(s) you are looking at and with respect to whom. From the pharmaceutical company perspective, an FDC product can extend market exclusivity with a resulting improvement in sales and profits. In some cases, it may even permit higher prices. From the patient perspective, a combination product can reduce co-payments costs by half. Rather than two prescriptions, there is only one. Providers, governments, and insurance companies can also benefit if the FDC product results in better efficacy through a therapeutic benefit, reduced side effects, or just better compliance.

This can of course be turned on its head in some situations. An originator can find that a competitor has incorporated his off-patent active into a combination product with a resulting loss in sales to the originator. The patient can find that the FDC product is priced such that it falls into a higher co-pay tier. The provider may find an increased price is not offset by a reduction in disease complications sufficient to warrant the increased cost. It all depends.

THE REGULATORY SITUATION

A therapeutic is developed through a standard series of steps, from preclinical through clinical with many other activities,

including supporting toxicology, formulation development, and manufacturing developed in parallel. In the case of a novel single-entity product, the process is reasonably well understood and developed, though not without surprises when it comes to safety and efficacy. In the case of fixed-dose products, the situation is a little different. While the same steps are involved, the inclusion of two separate actives creates additional issues ranging from the basic toxicology of two separate molecules, interactions between these two drugs, creating a stable formulation of the two or more actives, and the more basic issues of the efficacy and safety of combining these drugs. And there is also the issue of dose-ranging studies to determine their best ratios.

In practice this has meant that the vast majority of FDC products have been developed using previously approved actives. The developer can start with a good sense of how the two or more actives behave independently, and in some cases, in combination if the products have been used in ad hoc combinations, for example, estrogens and progestins. The challenges then are largely related to formulation, dose-ranging, and assessing drug-drug interactions. Challenging to be sure, but much less so than starting with two, or even one, new chemical entity (NCE). About 99% of FDC products approved in the past 2 decades include at least one previously approved active.

The development and approval of FDC products with one or more NCE is largely confined to indications in which there are pressing clinical needs and good, rather than perfect, is an acceptable outcome. It should also be mentioned that in many cases, the development of a combination product is relatively trivial because although the actives may be unique, the pharmacological combination of the agents is often well understood and considered to be safe. Examples would include combinations of an antihypertensive agent with hydrochlorothiazide, and an antihistamine agent with pseudoephedrine.

REVIEW METHODOLOGY

This review is restricted to products approved in the US from 1990 through the end of 2013 and were sourced using the PharmaCircle Product & Pipeline and FDA Products modules. These modules have FDC product-specific search capabilities. The results were then manually reviewed and edited to eliminate duplicates and products that did not meet the review's product scope as discussed earlier. The use of US data provides a more comprehensive and consistent collection of products. To be included in the analysis, each product was required to have a unique FDA Application Number. Unless otherwise noted, a single Application Number was associated with a single entry. In the case where a new formulation for an FDC product was approved at a later date, it was not considered to be a new product if it was approved under an earlier Application Number. Similar products approved with new/different Application Numbers were generally considered to be new FDC products. An example would be Suboxone (Application Number 20733) approved in 2002 as a sublingual tablet formulation, and then approved in 2012 (Application Number 22410) as a sublingual film. If the FDA deemed this to be a new combination, we won't argue. But new indications, even with a new Application Number, were not included if they involved the same actives and the same formulation as the original approval. Combination products that involved two separate dosage components were not included. Generic [505 (j)] and OTC FDC products were similarly excluded.

FDC PRODUCTS 1990 TO 2013, CURRENT SITUATION

For the period 1990 through 2013, the FDA approved a total of 131 prescription FDC products. This amounts to an average of 5.5 FDC products per year. The peak year for

FDA approvals was 2012, with 12 FDC products approved. The low point was 1991 when only a single FDC product was approved. Figure 1 provides a summary of approvals by year.

Of the 131 approved prescription FDC products approved in this period, a total of 13 have been discontinued. In some cases, the products were withdrawn because of poor commercial performance, while in other cases, the products were superseded by improved presentations. Two active FDC products accounted for 117 of the FDC products, while there were 12 products with three actives and only 2 with four actives.

Digging a little deeper, we find that for 21 of the 131 FDC products, the approval of the FDC product was the first approval for at least one the actives. In one case, Coartem (Application Number 22268), the FDC product approval represented the first approval for both of the actives in the product.

In the next article in this three-part series, we'll dissect these numbers and examine FDC product approvals by therapeutic area, corporate sponsor, dosage form, as well as a number of other parameters. ◆

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BIOGRAPHIES

Dr. Tugrul T. Kararli earned his PhD in Pharmacology from the University of Florida and his MBA from DePaul University. Dr. Kararli worked at Searle/Pharmacia for 18 years and held various positions and responsibilities within the Pharmaceutical Sciences department, participating in pharmaceutics, product development, and drug delivery activities. As the Chairman of the Global Drug Delivery Technology Team at Pharmacia, he was responsible for identifying, planning, and executing the drug delivery technology strategies for marketed and development products. Dr. Kararli has authored numerous articles on various aspects of pharmaceutics and drug delivery and holds more than a dozen US and international patents. Currently, he is the Founder and President of PharmaCircle LLC, a knowledge management service company in the drug delivery and pharmaceutical/biotechnology fields.

Mr. Kurt Sedo is Vice President of Operations at PharmaCircle LLC. He earned his BS in Chemistry and Mathematics from the University of Wisconsin Stevens Point. Prior to joining PharmaCircle in 2003, he held various R&D Scientist positions within Searle/Pharmacia's Pharmaceutical Sciences Department in Analytical Development and Drug Delivery.

Dr. Josef Bossart is Managing Director of The Pharmanumbers Group, a boutique research and consulting group providing the biopharmaceutical industry with analysis and insights that improve business outcomes. He has more than 3 decades of experience in the biopharmaceutical sector, including senior sales, marketing, business development, and management positions within Big Pharma, Specialty Pharma, and Emerging Pharma companies. He earned his PhD in Medicinal Chemistry from The Ohio State University, College of Pharmacy.

Repurposing Drugs to Transform Lives

By: Roger Garceau, MD, FAAP

INTRODUCTION

Every year, drug companies large and small make the tough decision to stop developing a promising molecule based on mixed signals from the US Food & Drug Administration. To my knowledge, no one has ever tallied the number of development projects that have been shelved in the wake of such setbacks. But there's an even more intriguing statistic that market analysts might try to uncover. It's the number of projects that are suspended after a disappointment, then resurrected to treat an entirely different illness. I'd like to describe one such treatment - a drug that might have slipped into obscurity if the team at NPS Pharmaceuticals had accepted defeat. Instead, the medicine has received an extraordinary second chance to address a different, and significant, unmet medical need.

The drug, Natpara, is a bioengineered version of human parathyroid hormone (PTH) that closely mimics the action of the natural hormone. In the body, PTH is the principal regulator of calcium and phosphorous. People with hypoparathyroidism have lost the ability to produce this molecule in adequate amounts - or at all - either due to a surgical mishap or because of an autoimmune condition. They often suffer a litany of woes ranging from acute fatigue and muscle pain to cognitive impairment and depression. Some go on to develop more chronic problems of renal calcifications and stones, seizure disorders, and bone abnormalities.

Of all the classic endocrine disorders, hypoparathyroidism is the only one for which there is no approved replacement therapy, nor is there a national or international consensus on how to manage the illness. Indeed, the current standard of care - large daily doses of calcium and vitamin D - brings risks of adverse events, such as renal failure, that can be far worse than the deficiency itself.

We believe this gap may soon be filled. Phase III clinical data on Natpara, some of which were released at ENDO, the Endocrine Society's annual meeting in mid-June 2013, strongly suggest that the bioengineered hormone is well tolerated and significantly reduces the need for supplementation, while maintaining or normalizing serum calcium. Our presentations at ENDO 2013 also included data from the largest and most comprehensive research thus far analyzing the burden of illness for hypoparathyroidism. We filed a Biologic License Application (BLA) with the FDA in October 2013.

HYPOPARATHYROIDISM

By any measure, hypoparathyroidism is a miserable state of being - one that afflicts approximately 50,000 people in the US. It's a rare disease, but like so many illnesses in that class, the frequency with which it strikes is a poor yardstick for the suffering it causes. As the patient's serum calcium levels plummet, there are burning sensations in the extremities, muscle aches, cramps, anxiety, depression, seizures, and sometimes heart failure and other long-term complications.

We documented this progression at the ENDO 2013 meeting in a survey called PARADOX that assessed the ailment's clinical, social and economic impact on patients.[1]The research, which NPS carried out in collaboration with the Mayo Clinic and the Hypoparathyroidism Association, involved surveying 374 patients with the illness over a period of several weeks. Nearly every patient (99%) reported experiencing multiple symptoms despite taking medications like calcium and vitamin D supplementations. Some 82% of patients reported experiencing fatigue. More than three-quarters noted muscle pain, spasms, and some version of pins-and-needles, which is also known as paresthesia. Cognitive and emotional symptoms plagued the majority of patients with 72% of patients reporting brain fog or mental lethargy.

PARADOX further proved what many of us have suspected: The current "management" can be worse than the disease. The oral calcium doses can become a torment: one patient noted taking upward of 48 pills every day in order to raise serum calcium levels. Long-

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term treatment with such a course can lead to organ calcification and renal failure - and may not relieve the disease symptoms. In our research, nearly 70% of patients suffered comorbid conditions, including heart arrhythmias and kidney stones.

ETIOLOGY

Researchers generally point to two disruptive events connecting the lack of sufficient PTH to calcium deficiency. Shortage of the hormone leads to a renal malfunction that makes it hard for the body to produce active vitamin D and absorb dietary calcium. At the same time, loss of PTH results in excessive calcium excretion through the kidneys.[2] The imbalance in the metabolism of phosphate and calcium leads to dire reduction in the rate of bone turnover, as well as soft tissue calcification. In the most detailed survey of the subject to date, researchers described how the disruption in mineral homeostasis leads to an increase in bone mass in the cancellous and cortical compartments.[3]

INTERVENTION

In addition to sharing the results of the PARADOX study at ENDO 13, researchers involved in the Natpara clinical trials provided an update on a study called REPLACE, a Phase III registration trial examining the drug's safety and efficacy. Dolores M. Shoback, MD, a professor in residence at the University of California, San Francisco School of Medicine, presented a poster showing that at the end of a 24-week treatment period, 43% of patients on the drug (36 out of 84) were able to reduce or halt vitamin D therapy and significantly curb calcium supplementation.[4] The ratio of patients on placebo who achieved similar reductions was just 5% (two out of 37). And the rate of adverse events in the two arms of the trial, Natpara and placebo, were comparable. These encouraging results are broadly comparable to what we are seeing in an open-label extension trial in the US called RACE, in which some 50 patients are taking Natpara every day - some of them for as long as 2 years.

THE BIRTH OF PTH

The curious history of recombinant human PTH holds lessons for biotech companies that find themselves at a drug-development crossroad. NPS acquired the molecule in 1999 when it bought a Toronto-based company, Allelix Bioharmaceuticals. At the time, we had an internal team that was investigating calcium receptors. The acquisition strengthened that effort by adding a group of talented scientists who were starting to develop PTH as an osteoporosis treatment.

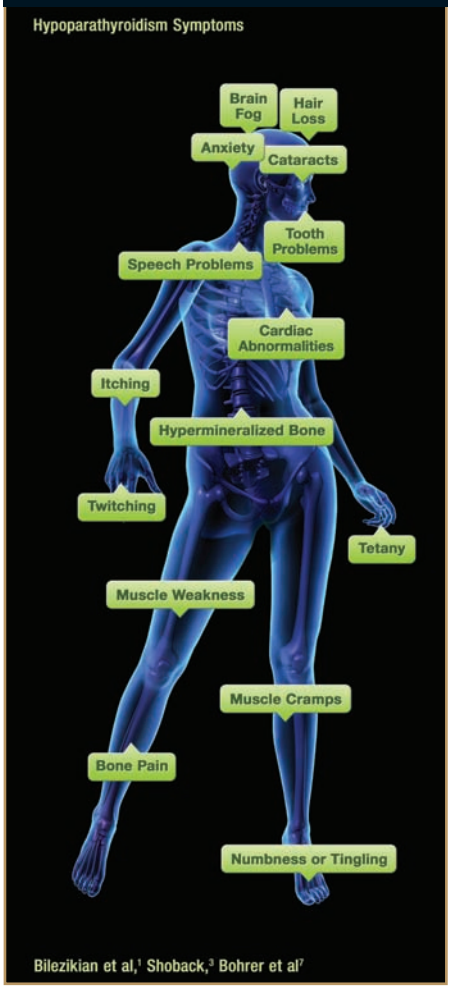
The program got off to a good start in the US and Europe. By 2004, we'd formed a collaboration with Nycomed, a Danish pharmaceutical company later acquired by Takeda Pharmaceutical of Japan. This gave NPS a development and commercial partner in Europe and other markets. In 2005, we filed an NDA for osteoporosis in the US and Nycomed filed in Europe. A year later, the molecule was approved and launched in Europe as Preotact, at 100-microgram dose, to treat osteoporosis in postmenopausal women.

Just as Preotact went on sale in Europe, however, the FDA came back with an approvable letter requesting an additional trial. The panel was concerned that too high a dose of the drug could lead to hypercalcemia and requested additional Phase III data. A new Phase III trial would consume scarce funds. Worse, it would place us several years behind a competitor - a major drug company that had just begun selling a therapy for osteoporosis that, superficially, resembled ours. While our version of PTH is a replica of human PTH and contains the entire chain of 84 amino acids, the rival drug was a fragment just 34 amino acids in length. Our opponent's head start was a crippling competitive blow. Our only course was to retrench and consider fresh options.

"AHA" MOMENT

The new path we took, focused on hypoparathyroidism, owes a great debt to the work of John P. Bilezikian, MD, Associate Chair of the Department of Medicine at Columbia University's College of Physicians and Surgeons, and a leading expert in metabolic bone diseases. In 2004, he and his

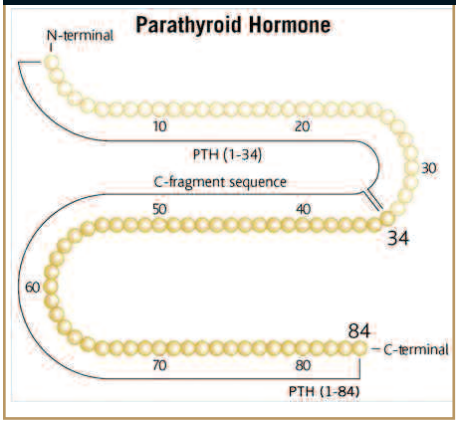
FIGURE 1



colleagues began dosing hypoparathyroid patients every other day with 100 micrograms of our whole PTH molecule. In 2007, just as NPS was shifting its strategic focus toward the orphan drug space, Dr. Bilezikian shared results showing that hypoparathyroidism patients on PTH had significant improvement (even on every-other-day therapy) though it was clear the dose and frequency might need to be adjusted.

This development presented a welcome opportunity that fit with the company's redefined strategy. With no replacement therapy available, hypoparathyroidism was the very definition of an unmet medical need. It's hard to imagine a patient choosing a daily course of many pills several times per day to treat only a portion of the symptoms, while remaining exposed to all of the associated risks. How would such a regimen ever be preferable to a single daily injection in the thigh that could restore hormone balance? In 2007, we went back to the FDA with a program to test PTH, which we have since

FIGURE 2



renamed Natpara. The response was very supportive. We wrote the protocol and enrolled the first patient in our pivotal REPLACE study at the end of 2008.

DELIVERY

In Europe, patients inject Preotact with a pen that holds 14 once-a-day 100-microgram doses. In the US, we used the same system in initial trials, but we have now switched all patients over to an entirely new pen system, which is the basis for the drug/device BLA we put before the FDA. The pen has proved highly versatile in our trials, which had an adaptive structure that conforms to the FDA's concept of small-and-flexible trial designs. Because not all patients require the same dose of PTH, we developed four dosing strengths, allowing for individual titration. In most cases, we would start the patient at 50-micrograms a day, then up-titrate as the patient gradually achieved normal serum calcium levels while reducing dependence on calcium and vitamin D. Patients have tolerated the transition well, compliance has been excellent, and dropout rates were very low.

KNOWN UNKNOWNS

As Dr. Bilezikian and others have pointed out, trials of PTH replacement therapy have not answered every functional and morphologic question a scientist might ponder. We can't say how the therapy changes skeletal microstructure and qualities of bone mineral in patients with the deficiency. Our ability to precisely correlate markers of bone turnover with biopsy readouts is still cursory. And what about long-term use? Does PTH therapy protect the kidney over time? And what quality-of-life improvements might we see in five years, or in 10?

CONCLUSION

I believe these important puzzles will be resolved over time. Meanwhile, the merits of a therapy that replaces a missing biologic component over perpetual dosing with calcium and vitamin D supplements seem incontrovertible. In trials connected to NPS, and in others I've observed, replacement therapy not only lowers the risk of hypocalcemia and hypercalciuria, but also may have the potential to reduce the likelihood of calcium deposition in the kidneys and other soft tissues.

As this narrative portrays, our hopes at the beginning of our journey were quite different from the hopes we hold for Natpara today. We learned, at an early point, that recombinant PTH was unlikely to play a role in curing osteoporosis. On the other hand, I believe we've demonstrated that science sometimes offers up a second chance - the opportunity to aim a powerful medicine at an entirely different population of patients from those originally identified. In the orphan drug business, seizing such opportunities can deliver the greatest rewards. ◆

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REFERENCES

1. Initial findings from PARADOX presented at ENDO 13. Website visited: http://www.npsp.com/media?trxml_v=nrd&trxml_nr_id=1830235.
2. Horwitz M, Stewart A. Hypoparathyroidism: is it time for replacement therapy? J Clin Endocrinol Metab. 2008;93(9):3307-3309.
3. Bilezikian JP, Khan A, Potts JT Jr., Brandi ML, Clarke BL, Shoback D, Jüppner H, D'Amour P, Fox J, Rejnmark L, Mosekilde L, Rubin MR, Dempster D, Gafni R, Collins MT, Sliney J, Sanders J. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target organ involvement, treatment, and challenges for future. Research J Bone Miner Res. 2011;26(10):2317-2337.
4. Shoback DM, Mannstadt M, Clarke BL, Vokes TJ, Lagast H, Bilezikian JP. The effect of recombinant human parathyroid hormone (rhPTH [1-84]) on vitamin D metabolism: results from phase III REPLACE and phase I clinical studies. Website visited: https://endo.confex.com/endo/2013endo/webprogram/Paper7502.html.

BIOGRAPHY

Dr. Roger Garceau is the Executive Vice President and Chief Medical Officer for NPS Pharmaceuticals, joining the company in December 2008 and bringing over 20 years of broad pharmaceutical industry experience to his position. From 2002 to December 2008, Dr. Garceau served in a number of senior leadership positions at sanofi-aventis and most recently was Vice President of the New Products group. Previously, Dr. Garceau held various positions, including Vice President of Clinical Operations, Interim Head of North American Medical and Regulatory Affairs, and Head of US Medical Research, where he led a team of over 200 professionals and oversaw the design and execution of over 50 sponsored clinical trials in 5 different therapeutic areas. Prior to his tenure at sanofi-aventis, Dr. Garceau spent 16 years with Pharmacia Corporation in Global Development and Medical Affairs, where he successfully contributed to a number of marketing applications. Dr. Garceau is a board-certified pediatrician. He earned his BS in Biology from Fairfield University in Fairfield, CT, and his MD from the University of Massachusetts Medical School. He is a Fellow of the American Academy of Pediatrics.

Special Feature

Analytical Testing of Biologics & Biosimilars

By: Cindy H. Dubin, Contributor

U.S. demand for biologics is expected to grow 6.5% per year to $102 billion in 2015, up from $74.3 billion in 2011, according to Freedonia Group. On a global scale, the biologic drug market will reach $178.4 billion in 2017, as stated in World Biological Drugs Market 2013-2023. According to the report, in 2012, biologics represented 15% of the global pharmaceutical market, including seven of the top-10 products. Monoclonal antibodies (mAbs) made up 41% of the 2012 market, fusion proteins 8%, and cellular and regenerative medicines 1%. The remainder of biologics revenues came from a range of protein therapeutics, with insulin and other recombinant hormones the most significant agents.

Also on the horizon are biosimilars, known as follow-on biologics. A growing global market for biosimilars is gaining momentum in response to the expiration of patents for a number of key biologics and consumer demand to reduce treatment costs. Thus, according to Research and Markets, the global biosimilar market, valued at $2 billion in 2012 is projected to reach $19.4 billion by 2018.

Contract manufacturers who can bring biologics and biosimilars to market fast and less expensively will be in great demand. Over the past several years, studies conducted by BioPlan Associates have shown that an increasing number of biomanufacturers, up to 70%, are outsourcing at least some of their bioprocessing activities. BioPlan tested 24 areas of bioprocess outsourcing in its 2013 global study of biomanufacturing. Results from the study indicate that the most commonly outsourced activity is analytical testing because of the need for highly specialized staff and equipment required to perform assays as well as regulatory agencies wanting more characterization and other data about products. On average, facilities outsource 32% of their analytical testing/bioassays (up from 28%) meaning that close to one-third of analytical testing is estimated to be outsourced by the industry.

Analytical testing provides quality, actionable chemical information that ferrets out process impurities, contaminants, and degradants. Several contract providers in this market recently sat down with *Drug Development & Delivery Magazine* to discuss the importance of outsourcing analytical testing in the biologic/biosimilar space, the associated challenges, and how to ensure the products get to market safely and quickly. Participants in this discussion are: Wayland Rushing, PhD, Senior Scientific Advisor, ABC Labs; James Hurst, Head of Analytical Development at Almac; Shri Thanedar, PhD, CEO and Andrew Kolbert, PhD, Vice President of Technology, Avomeen; Tammy Thompson-Madsen, Pharmaceutical Scientist, BioConvergence; Adam Lambert PhD, Director, Preformulation and Analytical Chemistry, CoreRx, Inc.; Michael J. McDowell, Vice President, Business Development and Project Management, Eurofins Lancaster Laboratories, Inc.; Assad J. Kazeminy, PhD, President and Founder, Irvine Pharmaceutical Services, Inc.; Erik Foehr, PhD, Vice President, Analytical Services for Pacific BioLabs; and Paul Skultety, PhD, Vice President, Pharmaceutical Development Services & Project Management, Xcelience.

Q: What do you consider to be the biggest trend in the analytical testing market?

Mr. McDowell: In addition to the ongoing shift in development pipelines from synthetic small molecules to biologics, there is much more diversity in the type of biologic or modality being tested. For example, we are currently supporting monoclonal antibodies, including biosimilars, bi-specific antibodies, fusion proteins, synthetic peptides, therapeutic enzymes, vaccines, gene

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therapy, and cell therapy products. This continuing trend toward greater diversity requires a broader set of expertise and equipment to evaluate the quality attributes of the drug.

Dr. Kolbert: The biggest trend in the analytical testing market is who is requesting the testing. Development of methods for assay and release testing is no longer restricted to pharmaceutical companies. Manufacturers of nutraceuticals and supplements are getting pressure from the FDA to qualify their raw materials and provide some level of release testing for their final products. In terms of GMP compliance requirements, we are seeing a much more sophisticated nutraceutical industry that is starting to behave more like pharma.

Dr. Lambert: Implementation of Quality by Design (QbD) , and its wider acceptance in the industry is creating a need for more sophisticated means of analysis. At this point, QbD is having a major impact on the work we are performing in the CoreRx analytical laboratories. The amount of work that goes into understanding the impact of different process unit operations on the quality of the finished dosage forms is substantial. Even for a simple direct blend and compression process, understanding the process design space and impact on product quality attributes can require a significant amount of sample analysis. Additionally, application of a QbD approach is leading to the identification of new analytical tools that will ultimately allow for the development of more robust processes. For example, in a granulation process, the characterization of specific granulation/blend attributes and process-related changes may link to the product performance or stability. In the past, these relationships might not have been established due to the approaches taken during the development of the process. Ultimately the application of QbD is leading to better defined manufacturing processes, and a better overall product for the consumer.

Dr. Skultety: The most noticeable trend is that we must continually find ways to do things faster. Greater efficiency in formulation development work has compressed the timelines for the analytical work. We need to get methods developed quicker so we can initiate the stability on the finished product as soon as possible after manufacture is completed. This allows for filing the IND sooner, which in turn can get the clinical study started sooner.

Q: What are the biggest challenges associated with analytical testing of small molecules and biologics?

Dr. Kazeminy: Some of the biggest challenges associated with analytical testing are timing, customization, and managing remediation of client programs. Our procedures, while compliant, are meant to serve a broad range of customer needs. Clients prefer to have services that are an extension to their own lab and manufacturing procedures. This certainly can be accomplished, but may add time and costs to a program.

Dr. Skultety: The biggest challenge we have seen over the past couple of years is development of appropriate dissolution methods. As the majority of the compounds are only very slightly soluble, it becomes more difficult to develop a method with the appropriate dissolution media that can be discriminating. Another challenge is dealing with the changes in the active ingredient from the early lots to the GMP material. In a number of cases, changes such as new impurities will show up and have to be dealt with as the GMP material is evaluated.

Mr. McDowell: We do not see the level of familiarity and experience with the outsourced molecule from the sponsor that we did in the past. Companies are in-sourcing more development candidates and outsourcing earlier in the process. When a problem arises during the method establishment phase, the client is less often in a position to help the contract laboratory troubleshoot the method. We have seen that method development expertise is the key component to executing effectively on method transfers and keeping the overall program on schedule.

Mr. Hurst: As a CDMO, the biggest trends we have seen over the last few years are towards more pediatric development and also potent molecule development. These bring with them challenges for the analytical groups that support the product development projects in that they raise new containment challenges as well as the obvious technical challenges of reliably detecting/analyzing increasingly low doses in the associated drug products.

Ms. Thompson-Madsen: In the most general terms, every active pharmaceutical ingredient (API) and presentation is unique, and must be approached on a case-by-case basis. The challenge of testing is to provide an accurate view of a sample at a particular time without bias. Small molecules may be prone to solubility issues, moisture instability or light degradation. Biologics may aggregate, be thermally sensitive, and are generally more complex. It is important to understand each material so it can be properly characterized and not create additional issues with improper sample handling techniques.

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Dr. Lambert: Issues ranging from molecule solubility to chemical stability of samples are always possibilities when analyzing small molecule drugs. Most small molecule drugs have their own peculiarities. Even with well-established, validated analytical methods, issues in performing the analysis come up. All aspects of method validation (accuracy, precision, linearity specificity, etc.) can be problematic. The most challenging problems have centered on sensitivity of the analytical methods for detecting degradation products and separation of known impurities. Chemical similarities between the drug and degradation products can often be problematic. Similarities between two or more degradation products can also create difficulties in analysis.

For biologics, tying back the analytical results to the biology of the molecule can be one of the more challenging aspects of testing. For biologicals, potency and amount are not always the same, and physicochemical changes observed during the analysis of the molecule do not always impact the potency of the drug. Conversely, structural changes of the molecule, which affect potency, are not always detectable during analysis. What this comes down to is identifying/justifying realistic ranges of analytical results that are meaningful to the drug product being developed. For example, there was a biological product that we developed for a client where large variations in a chromatographic assay were observed, while a protein specific activity assay indicated that no changes were occurring. We were tasked to identity the root cause of the changes and determine which of the two tests was predictive of product stability. Results from this investigation led to the development of a third method for analysis.

Dr. Foehr: Small molecules and biologics have become more complex to study because they are now modified in some way or formulated/delivered in unique ways. Thus, we see a trend of analytical testing of medical devices and combination drug/delivery devices increasing. Pharmaceuticals and medical devices have become increasingly complex. Combination products, delivery devices, and reformulated or re-engineered drugs are more common. These complex products require novel techniques and instrumentation to characterize. For instance, temperature-sensitive polymers can be analyzed using size exclusion chromatography with laser light scattering. Further, special care must be taken to separate and analyze the components in combination products. Sample preparation and extraction require experience and a solid background in chemistry. Multiple assays are required to fully characterize the complex pharmaceuticals.

Dr. Rushing: Small molecule challenges typically revolve around analytical detection and quantitation limits. For biologics, the challenges are more centered on the types of analytical techniques. In comparison to a small molecule (which may have 4-6 analytical methods), a biologic can have easily a dozen or more high-end methods for characterization. These methods are generally specialty methods (Amino acid analysis, Glycan analysis, etc.) requiring specialty instrumentation and technical knowledge. One area that transcends between the groups is leachables resulting from the DP container closure system or from the manufacturing process. This area is garnering a greater level of regulatory scrutiny and is generally not well understand by either pharma companies or the average CRO.

Q: What advantages does an outsource provider offer to pharma with regard to analytical testing of small molecules and biologics?

Dr. Foehr: Start-ups may not have had the opportunity to learn from mistakes or successes of other innovators—contract labs share in the experience of a multitude of clients. Therefore, the experienced contract labs can be a tremendous resource to the pharmaceutical industry. As Big Pharma sheds R&D resources and virtual start-ups become the norm, in-house analytical experience and technical capabilities dry up. One of the last pools of experienced, well resourced chemists is now found in the contract lab sector.

Dr. Thanedar: For a large pharma company, CROs tend to represent additional capacity in testing. Occasionally, in very specialized areas such as metals analysis and extractable and leachable studies, CROs may offer project-specific expertise. However, in most cases the additional capacity for short-term needs is the value offered. The value added to smaller pharma, biotechs, and virtuals is quite different. These companies often do not have the internal expertise to make the correct decisions regarding drug development, and require regulatory expertise and strategy development in addition to analytical testing. Virtuals may have no capability to even store their own reference standards and distribute them where needed and this sort of logistical support is expected of their CROs

Dr. Skultety: Contract organizations have experience with a variety of active ingredients having a range of physical/chemical properties. The contract

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Karen Takahashi, Senior Policy Advisor, CDER, *FDA*

Alex Viehmann, Operations Research Analyst, CDER, *FDA*

Following the conference, there will be a post-conference workshop, ***PDA Biofilm and Bioburden Workshop*** on April 9-10. The workshop will provide the latest science and best practices around microbial control for the pharmaceutical manufacturing environment. Presentations will be provided by technical experts from academia, industry, and FDA.

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organization will develop a number of new methods each year and handle several method qualification/validations. Dealing with the larger volume of work, the contract organization becomes more efficient at getting the work initiated and completed in a timely manner. This broader exposure also allows for a better understanding of how to deal with a vast number of issues/problems that might arise when working with a new molecule.

Mr. McDowell: The main advantage is flexible capacity. Whether you are tactically outsourcing a test or strategically placing an entire development program, a contracting testing laboratory provides a flexible resource to help pharma keep fixed costs to a minimum. The robust outsource market over the past 10 years has resulted in service providers building capacity, expanding the breadth of their offerings, and gaining expertise needed to more effectively execute on complex programs. Outsourcing providers have also become more sophisticated in their delivery of services. Most offer on-site personnel at the client location and/or dedicated teams of employees in addition to the traditional fee for service model. This flexibility allows pharma to customize the service to fit each program requirement.

Mr. Hurst: An outsource partner can add real value in that their exposure to different projects and the knowledge they have gained from working with many different clients can help solve technical issues faster and speed up the development process. There are obviously strict confidentiality frameworks that an outsource partner works within, but once you have experienced a challenge you learn to approach similar challenges more efficiently the next time they occur.

Q: Looking at this past year, can you share an example of a successful small molecule or biologic analytical testing project?

Dr. Lambert: One that comes to mind (and the one I am most proud of) is actually a story with a not-so-happy ending. We were starting registration stability and we had completed the development and validation of a number of complicated chromatographic methods. The product was a drug-device combination project, so from an analytical perspective, there were a large number of complicated analyses that needed to be performed. One of the tests was evaluating the drug remaining in the device after delivery. Early on in the stability testing of the registration batches, a failure in this analysis identified a failure of one of the device components. This failure resulted in an incomplete dose being delivered from the device. We were able to quickly identify the root cause, and stop the stability studies before significant investments in analytical testing and manufacturing equipment were made. While it was disappointing to have the project end, it would have been far more disappointing (and expensive) for the client to have identified the problem after completion of the product registration and manufacturing scale-up.

Dr. Foehr: The use of cutting-edge technologies to solve analytical problems is especially rewarding. In the last year, Pacific BioLabs used Inductively Coupled Mass Spectrometry (ICP-MS) to measure low levels of specific elements. Trace metals are often used in manufacturing, combination drug-device products, and even as the active ingredient for medicinal purposes. ICP-MS is uniquely suited to detect trace elements in biological fluids and from process intermediates. We have supported clinical trials and new manufacturing processes using ICP-MS to measure trace elements.

Mr. McDowell: We were contracted to support all clinical stability and release testing on a biosimilar being developed to compete with the innovator product, Humira. The project required establishment of 15 methods, including a cell-based potency assay; ELISA binding assay; purity and impurities by SEC-HPLC, CE-SDS, and icIEF, just to name a few. All methods were fully validated in accordance with ICH guidance for both drug substance and drug product. The project was on a very tight timeline with no flexibility due to the scheduling of fill/finish activities at their CMO. All methods were fully validated and in a state of cGMP compliance within five months of project start. This timeline included the logistics of sourcing all study materials and review/approval of all protocols and reports. The methods were in place for testing of the drug substance upon release from one CMO, and the schedule was maintained for fill/finish activities on the drug product at the second CMO. We continue to support ongoing stability and release activities for this development candidate.

Ms. Thompson-Madsen: In the past year, we undertook a client project with three distinct project phases involving testing (Unfortunately, the details can only be shared in the most general way). These projects were a progression of work that included determining the most stable form of the API, identifying preferred presentation forms (lyophilized versus liquid), and discovering the best excipients for solubility, tonicity, and stability. As a result of our partnership, the client was able to tap into the expertise needed to quickly progress into GMP

manufacturing and clinical trials, for which we are now providing laboratory support.

Dr. Kazeminy: As a biologics example, a leading pharma company was in search of a company that had the range of capability and technical depth to manage multiple mAB, ADC, and peptides platform needs. Irvine adapted its facilities/systems to meet the needs of its client by providing hands-on project management and oversight of the client's programs: method development, validation, transfer, stability, release, extractable and leachable studies, and raw material testing. We also established a dedicated cell-based assay lab to support client's program needs and manage the client's procurement process.

As a small-molecule example, a start-up firm was in search of a single-solution provider to help in the development, manufacturing, and release testing of its Phase II and Phase II/III new chemical entity. Irvine guided the client through drug product formulation and process development projects from initial strategic planning to detailed technical execution. Within five months of project kick-off, Irvine helped transfer and qualify unique pieces of equipment; transfer and execute process validation batches; and manufacture clinical material and placebo. Irvine guided the development, transfer, and scale-up of the client's complex small molecule NCE to full-scale manufacturing in time for, and in some cases exceeding, aggressive clinical trial timelines.

Q: Where do you see the analytical testing market in the next five years in terms of the level of sophistication outsourcing providers will bring to the testing of small molecules and biologics?

Dr. Skultety: One item will be the increased use of UPLC's. This use is still in its infancy; it is a good concept for some compounds and can decrease the testing run time significantly. As the use of QbD is expanded, this will change the way methods are developed and validated. The more this approach can be utilized, the easier it will be to get specifications approved by the FDA.

Ms. Thompson-Madsen: While instrumentation is getting easier to use, "true experts in the field" seem to be harder to find. Outsourcing may be a means to obtain the analytical expertise one may no longer have in house. Also, the products are gaining in diversity, which may require specialized methods to be developed and performed.

Dr. Foehr: The analytical testing market trend over the next five years will continue to favor experienced providers with the capabilities to leverage both analytical (or bioanalytical) testing capabilities and in-life services when supporting complex drug and device characterization. Regulatory pressures will drive more detailed chemical analysis of drugs, diagnostics, devices, cosmetics, e-cigarettes, and nutraceuticals. New innovative drugs and medical devices will require thorough toxicology, biocomparability, and chemical characterization. The convergence of the digital age with biochemical testing will present opportunities and challenges for analytical testing labs. The use of hand-held devices able to collect and transmit analytical data is on the way. Real-time analysis of clinical samples, or in-process manufacturing samples are just a couple ways the industry will be transformed. Ultimately, instrumentation will help push the limits of what is possible to measure, but experience and savvy implementation will continue to add to the sophistication of outsourcing providers.

Dr. Rushing: In the past, the typical type of work being outsourced was the routine "QC" testing. The analytical knowledge base and scientific expertise resided within the pharma companies. This has slowly evolved with the rise of "virtual" pharma companies relying more heavily on the services of the CROs to be their analytical knowledge base and scientific experts. This resulted in the CROs adding internal experts on drug development and high-end analytical capabilities. Large pharma is now starting to adapt similar outsourcing strategies as we have observed with the closing of internal laboratory capabilities by multiple large pharma in preference to oursourcing the work.

Mr. Hurst: There is definitely a trend towards large pharma looking to mimic the smaller pharma company approach by trying to fully utilize the knowledge and expertise outsource laboratories hold. They are increasingly looking for the contract laboratories to provide a value-added service of brains as well as brawn. I can only see this trend continuing as many of the larger companies continue to develop their virtual structures.

Dr. Thanedar: Testing of pharmaceuticals and the technology applied to drug development changes slowly, as the requirements are the same for everyone and the FDA is disinclined to require testing that

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uses cutting-edge instrumentation and techniques. Consequently, competitive advantage comes from providing a better client experience, some of which is affected by the application of improving technology. Increasingly, sophisticated customer relationship management programs allow CROs to keep track of client and project information and respond more quickly and effectively. Laboratory Information Systems allow clients to view data during a project through web-based portals. And client meetings and discussions are being held by Skype, Go-to-meeting, Live Meeting, and other interactive software. Finally, cloud-based storage allows the sharing of files as well as collaboration on documents. The most successful players in the CRO space will embrace these technologies. ◆

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Latin America Next-Generation Biosimilars Market: Opportunities & Future Growth

By: Lucila Rocca, Healthcare Industry Analyst, Frost & Sullivan

INTRODUCTION

Biopharmaceutical products represent one of the most important innovations in medical history. However, these breakthrough therapies, which are extremely expensive, owing to the magnitude of investment necessary in their discovery and development, drive a need for less-costly alternatives.

Latin America is a region full of opportunities when it comes to biologic drugs, especially biosimilars. There is a high expertise and development of biosimilars in Latin America, so there is a great interest of local and foreign pharmaceutical companies to penetrate the market in order to investigate, produce, and commercialize locally and on an international level.

The biologics market will grow fast in the next 5 years, mainly due to the discovery of new molecules. The advanced technology and resources needed to produce biologics create high-entry barriers for small biotechnological companies. This explains why the total biologics market in the region is dominated by big multinational companies. These companies are massively investing in R&D in order to stay ahead of the biosimilars market by constantly offering new innovative products.

Despite the efforts of big multinationals to produce breakthrough biologic drugs, the Latin American biosimilars market is constantly evolving, keeping itself competitive. In addition, the recent changes in local regulations positively affect the biosimilars market and drive the race against innovative biologics.

The main challenges faced by participants in the Latin American biosimilars market are related to the high costs of R&D and the clinical trials required proving product effectiveness and safety, along with the need to maintain low final prices. Consequently, to grow their business, regional biologics manufacturers seek to license out their products to global players. Global pharmaceutical companies and local distributors outside Latin America seek Latin American biosimilars partners from which they can purchase APIs or license finished products for their own markets.

The public market in Brazil represents the major share of the biosimilars market. This is mainly because the government provides universal access to biologics to the population, as most of the population cannot afford these expensive products. The majority of private healthcare insurers do not cover treatment costs of certain diseases related to these drugs because of their high cost.

While current regulations allow the registration of generic versions of conventional pharmaceutical products, the biosimilars drug regulation pathways are still not very clear in some Latin American countries. Regulations are being adjusted to facilitate manufacturing and registration of

biosimilars that will greatly expand this market in Latin America. Companies interested in investing in these high-cost drugs require access to international markets. Thus, companies complying with newly developed regulations in Latin America will be better positioned to comply with standards in highly regulated markets.

In Latin America, the first type of biosimilar products to enter the market was insulin: granulocyte colony-stimulating factor (G-CSF), erythropoietin, and human growth hormone. Later, interferon arrived in the region, and finally, monoclonal antibodies.

The monoclonal antibodies market is still in a nascent stage and requires further development. Many molecules are in the pipeline to be launched within the next 2 years. Prices for these products are higher than the traditional biologics market, which will drive an increase on the total biosimilars market during the penetration phase. Later, pricing will decrease as numerous monoclonal antibody biosimilars will compete in the Latin American market, reducing its growth rate.

Current biosimilars compete in a more stable and mature market. Pricing will still be affected by local inflation, new competitors that will invest in this market, and the lack of pricing controls.

In the past, it wasn't difficult to get sanitary approval for the production and commercialization of biosimilars in Latin America, as the regulation was not clearly established. Thus, there is a large number of biosimilars in the market that were approved in the past and that may not have the quality standards that the international market requires. New companies will be required to comply with more demanding registration processes, which will ensure the production of molecules with a higher quality than the ones registered in the past.

In addition, intellectual property is not protected across all Latin American countries, so companies are allowed to register biosimilars of innovative biologics drugs protected in other regions. Hence, innovative companies compete in the market with lower-priced products with similar chemical structures, in a clear disadvantage. As a response, they are putting competitive strategies in place to prevent the penetration of biosimilars in the market. For example, they educate physicians, public tenders, and medical insurance decision-makers on the differentiation between innovators and biosimilars, arguing that each single molecule may be different from the other, which makes the production process and clinical trials conducted by the manufacturing company extremely important.

LATIN AMERICA MARKET OVERVIEW

According to Frost & Sullivan's Global Next-Generation Biosimilars Market analysis, published in November 2013, the Latin America biosimilars market will continue to grow from approximately $123.1 million in 2013, to approximately $631.5 million in 2019, at a compound annual growth rate (CAGR) of 38.7 percent. The market will experience growth due to several reasons.

- While some types of biologic drugs have reduced prices, monoclonal antibodies are by far more expensive within the biologic drugs group. Monoclonal Antibodies have several indications: oncology, allergy, and rheumatoid arthritis to name a few, thus the number of patients that are candidates for their use is high. Furthermore, the entrance of products, such as rituximab, etanercep, and racotunumab in Latin America will expand the biosimilars market.

- The improvement of local regulations will encourage multinational pharmaceutical companies to enter into Latin America, to manufacture and

commercialize biosimilars to later be launched and exported to global markets, as Brazil, Mexico, and Argentina are taking measures to elevate the level of standards to register biologics.

- The Latin American public healthcare system offers universal access to medications for certain pathologies, hence, the lower costs of biosimilars will favor choosing biosimilars over innovators, thus reducing the financial burden for the acquisition of these drugs. Therefore, governments are funding initiatives to expand investments in the local production of biosimilars.

- Biosimilars of globally patented biologics is plausible in Latin America and limited to countries not recognizing intellectual property rights. Patent expiries of blockbuster biologics over the following 3 years will open large markets to existing molecules.

- Several global pharmaceutical companies have chosen the Brazilian market for their geographical expansion for its 201 million habitants and increasing economy. Because of their capabilities in the biosimilars market, they will help expand the market faster with only local companies.

- Many small- and medium-size companies are conducting research with biologic drugs. These companies are not only planning to launch biosimilars but also innovative biologics that will probably, at the same time, be launched by other biotechnological companies as biosimilars where intellectual property rights are not enforced.

- Latin American companies have been working on biologic products for 20 years. There is an important pool of knowledgeable and experienced professionals, offering significant talent to support foreign or local investments on biologics products.

The insulin biosimilars market will be impacted by the entrance in 2016 of Eli Lilly's long-acting insulin, which is a similar version of Sanofi's blockbuster Lantus. The Brazilian government's $215-million dollar investment for the production of insulin biosimilars will drive the reduction of innovator pricing, due to the increased market competitiveness. Sanofi and Novo Nordisk developed new molecules to prevent a market share loss. Sanofi's U-300 and Novo Nordisk's Tresiba are two long-acting insulins, which are expected to be launched in Latin America in 2015 and 2014, respectively.

Interferon's market will experience growth in the coming years as researchers discover new indications for the use of this type of drug, entering new therapeutic areas.

Human growth hormone and Erythropoietin are being used for recreational purposes. The first is being used for cosmetic treatment, as it reduces body fat and increases muscle; and erythropoietin improves athletes' physical performance and endurance. These two are mature markets but will continue to grow in the future, mainly due to the aforesaid uses. Most of the erythropoietin available in Latin America is in biosimilar format. Locals had a competitive advantage in time to market over innovators, due to the lack of intellectual property rights protection.

The key Latin American biotechnology companies specializing in biosimilars, such as, Sandoz, Amega Biotech, Biosidus, Sinergium Biotech, Probiomed, Orygen Biotecnologia, EMS Farma, and Blausigel, are working on developing new biosimilars to stay ahead of competition. These companies' investment on new molecules allows them to be always in the vanguard in the biosimilars market. As the region is one

of the most interesting in the world for the production of biosimilars, many local and foreign companies are trying to establish operations in Latin America. The focus on research and development today is on monoclonal antibodies due to their high potential revenues. Monoclonal antibodies' market is in a nascent stage, which offers large opportunities to biotechnological companies.

OUTLOOK

The Latin American Biosimilars market will grow at a significant rate in the next 5 years. The importance of establishing a rigorous regulation will stimulate this market growth. The investments of local and foreign biotechnological companies for the R&D of biosimilars will be increased by the improvement of Latin American regulations. Companies around the globe are intending to enter into the biosimilars market or expand their current biosimilars business, as this is a high market to be developed. Emerging markets are a viable way to introduce and develop biosimilars.

The challenge for biosimilars companies is in balancing profit versus costs of R&D. These drugs must comply with global quality standards, offering similar safety and effectiveness as the innovative medication, but maintaining reduced prices. Therefore, biopharmaceutical companies that produce biosimilars must invest in highly trained professionals, costly technologies, and manufacturing plants. In the biosimilars market, pricing is one of the key elements of companies' competitive strategy. In many Latin American countries, such as, Brazil, Mexico, and Argentina, certain insurers do not cover some treatments with biologic drugs. Consequently, patients have to either purchase the medication out-of-pocket or acquire biosimilars though the government. Thus, the lower the prices, the higher the sales would be in both the public and private sectors.

Latin America is an interesting region when it comes to the biosimilars business. Many local companies with experience in this market have excellent growth strategies, as they understand the importance of re-investing in R&D and manufacturing plants and procedures to meet and exceed quality standards. They are able to compete with innovative companies producing high-quality molecules but still offer lower final prices to patients, governments, and private insurers.

The world should look within this region to local companies' best practices, as well as governments' biosimilars development plans to get a clear example of how to succeed and develop the biosimilars market in other emerging countries. ◆

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BIOGRAPHY

Lucila Rocca is an Industry Analyst with Frost & Sullivan's Global Healthcare Practice. Her expertise lies in pharmaceutical products, medical devices, and medical education. Ms. Rocca's knowledge base centers on conducting thorough market analysis and development of forecasts within the competitive Latin American Healthcare landscape, as well as managing and executing market intelligence consulting projects. She earned her BS in Nutrition from the University of Business and Social Sciences of Buenos Aires. For more information on Frost & Sullivan's global Healthcare practice and offerings, please email jennifer.carson@frost.com or visit www.frost.com.

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Throughout the past 2 decades, Gerresheimer has evolved into a highly specialized supplier of glass and plastic packaging products to the pharma and healthcare industry. Strategic acquisitions and the targeted further development of know-how and technologies have helped the company to position itself as one of the pharma and healthcare industry's leading global partners. The comprehensive portfolio of products includes pharmaceutical packaging products as well as convenient and safe drug delivery systems, such as insulin pens, inhalers, ready-to-fill syringes, vials, ampoules, bottles, and containers for liquid and solid pharmaceuticals with closure and safety systems, plus cosmetic packaging products. Gerresheimer realizes revenues of more than 1.2 billion euros and has around 11,000 employees at more than 40 locations in Europe, North and South America, and Asia.

Andreas Schütte joined the Gerresheimer Group's Management Board in 2009. He headed the Plastic Systems Division until the end of the 2013 fiscal year. Since the beginning of this new fiscal year, he has been responsible for the extended Plastics & Devices Division. He believes that know-how transfer between medical plastic systems and syringe systems experts is essential for the development of modern, practical, and patient-friendly drug delivery systems. Drug Development & Delivery recently spoke with Mr. Schütte to discuss his important role in Gerresheimer's divisional restructuring process, and how he is convinced the new structure better reflects customer requirements.

Andreas Schütte

Member of the Management Board Plastics & Devices Division

Gerresheimer

"Many of the device designs that customers bring to us aren't suitable for a cost-optimized production process, so time-consuming and expensive redesigns are necessary. We want to be involved in customer projects right from the initial idea onward. That's why we decided to extend our pharmaceutical and medical technology product design and development competencies. Now our portfolio extends from concept development to the ready-to-manufacture product."

Q: How is your division now structured?

A: The Plastics & Devices Division incorporates the Medical Plastic Systems, Plastic Packaging and Syringe Systems business units. Medical Plastic Systems develops complex plastic systems and system components. Gerresheimer designs and manufactures them in the framework of individual projects, mainly for customers in the pharmaceutical, diagnostics and medical technology sectors. Medical Plastic Systems provides an individual service across all supply chain processes. The medical plastic systems range extends from inhalers for the targeted treatment of respiratory diseases, lancing devices and insulin pen systems for diabetes sufferers to a wide range of test systems and disposable products for laboratory and molecular diagnostics. Plastic Packaging's portfolio includes plastic packaging systems for liquid and solid pharmaceuticals. Administration and dosing systems such as eye drop or nasal spray bottles and special containers for tablets and powder are some of the products in

our comprehensive range of high quality primary pharmaceutical packaging. Duma brand multifunctional closures with tamper evident seals, child-safe closures, senior citizen friendly features and integrated moisture absorbers are key product features in the Plastic Packaging range. Syringe Systems supplements the portfolio with ready-to-fill syringes made of glass and plastic and the relevant accessories. Gerresheimer's specialist expertise and pharma-compliant technologies enable it to offer high quality primary packaging products to its customers in the pharmaceutical and biotech sectors. Most of its syringe system revenue is generated today with the leading Gx RTF (Ready to Fill) brand syringes. These syringes are supplied to the pharma industry in a wide range of designs and in a ready-to-fill state after washing, siliconization, preassembly and sterilization.

Q: To what extent do Gerresheimer's plastics business units compete with its glass business units?

A: They only compete in terms of performance. Otherwise, glass and plastic complement each other with their specific properties and advantages. One of our priority objectives is to enhance medication efficiency through targeted and precise dosage, with a particularly strong focus on practical convenience and application safety. Our expert knowledge of the properties of glass and plastic in conjunction with our R&D activities help us to develop optimum solutions. One of the materials that is going to become firmly established in the market alongside glass is COP (cyclic olefin polymer). Multilayer vials, ready-to-fill syringes, customer-specific primary packaging, and microtiter plates made of COP play an important role supplementing their glass counterparts when highly active agents or particularly sensitive formulations have to be packaged. COP's advantages are its very high break resistance and low level of drug interaction, plus its glass-like transparency. We have developed market-ready products, some in conjunction with partners, that satisfy the very highest requirements.

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

A: There are three particularly interesting examples that demonstrate our experts' development competence. Gerresheimer has developed innovative and safe solutions for new parenteral drugs with alkaline pH ranges or toxic pharmaceuticals. Our Gx MultiShell vial, which has an outer COP layer and a middle polyamide layer, unites the advantages of glass with the break resistance of plastic. This combination improves the vial's oxygen barrier effectiveness to 40 times that of conventional COP monolayer vials. The COP contact surface also improves the stability of the highly sensitive medications and minimizes interaction between the drug and packaging. That's a progressive development with genuine benefits for healthcare.

Our well-known and proven range of Gx RTF glass syringes has been supplemented with ClearJect brand plastic syringes. COP is also used for them. Plastic ready-to-fill syringes currently have an approximately 1% share of the global market (not including Japan). They are available in low-silicone oil or silicone oil-free versions; their needle mounts do not release tungsten or adhesive residue; and they are break-resistant, customizable, and have the same break loose forces, glide forces, and other functional properties as glass syringes. This heavy metal-free material is perfect as a primary packaging for sensitive medications in oncology, ophthalmology, and other fields of medicine.

We recently showcased an excellent example of Gerresheimer's interdisciplinary collaboration, Gx® G-Fix™, at Pharmapack in Paris. Gx® G-Fix™ is a standard interface for incorporating ready-to-fill glass syringes in drug delivery devices, such as autoinjectors. It was developed due to the fact that an increasing number of glass syringes are being integrated in devices. However, integrating glass syringes in devices poses a number of challenges. The drug delivery systems have to be designed to incorporate the syringe. One problem associated with the process of inserting the actual syringe is glass breakage. We solved it by designing a standard interface for the ready-to-fill glass syringe, which simplifies its integration in the device. The advantages of this solution are simple integration, extensive prevention of in-device glass breakage, and therefore a far lower rate of product takeback. It also pays off for our customers because a standard interface minimizes the risks and costs associated with development and it can be used in combination with different devices. The technology can also be integrated in existing filling lines.

Q: In 2012, Gerresheimer acquired a product design company. Why?

A: Many of the device designs that customers bring to us aren't suitable for a cost-optimized production process, so time-consuming and expensive redesigns are necessary. We want to be involved in customer projects right from the initial idea onward. That's why we decided to extend our pharmaceutical and medical technology product design and development competencies. Now our portfolio extends from concept development to the ready-to-manufacture product. We provide advice and support in early project phases, including services such as design development and Freedom to Operate analysis, plus engineering, prototyping, and clinical study support services as well as the production of clinic samples.

Q: What are Gerresheimer's strengths, in your opinion?

A: Gerresheimer's strengths are customer orientation, quality, specialization, and global presence. Our glass and plastics experts are some of the best in their fields, and they understand our customers' needs and requirements.

Q: What do your customers expect of you, and how do you ensure these expectations are met?

A: Most of all, our customers expect quality. We implement a two-yearly customer satisfaction survey to ensure we are aware of their specific quality requirements and equipped to meet them in the long-term. We take the results of this survey very seriously and use any negative feedback as the basis for introducing improvements. Customers who tell us what they think and enter into dialog with us are interested in developing their business with us. Customers who don't talk to us are already talking to other suppliers about their business.

We have all the necessary quality certifications, plus the Gerresheimer Management System (GMS), a group-wide quality system we developed to help us to optimize our processes according to uniform global standards. After our first customer satisfaction survey in 2011, we developed and implemented binding quality regulations to raise the level of quality at all our production facilities around the world. They apply on a group-wide basis across all divisions and product categories, supported by key performance indicators, training, and feedback to our quality teams so that we can maintain our high standards.

One good example of our consistent implementation of these new quality standards is our new, fourth production line for ready-to-fill syringes at our Bünde production facility. It takes the production of ready-to-fill syringes into a new quality dimension. Key process improvements include the avoidance of glass-glass and glass-metal contact through the use of pick-and-place robots and segment transport systems; optimized washing and siliconization processes; and more effective, camera-based quality inspections. This gentle handling results in a lower syringe cosmetic defect rate. A state-of-the-art washing process guarantees compliance with both present-day and future regulatory requirements. Improved spraying technology and in-line inspections in the siliconization process ensure consistent syringe function. A modular assembly concept increases production capacity and makes it possible to respond flexibly to customer requirements. Complete dimensional control ensures the syringes' filling processability. Automated in-line inspections guarantee consistent quality. All production lines are operated under cleanroom conditions, which further improve product hygiene and safety.

Q: In which markets will Gerresheimer achieve growth?

A: Last year, we invested a total of 120 million euros in specific growth projects. Although we already have extensive business operations in the developed markets of Europe and the United States, we believe there is further growth potential there. The IMS (Institute for Healthcare Informatics) estimates that the pharmerging countries, such as Brazil, China, and India, will be contributing 30% of global expenditure on healthcare in 2016. We're focusing on these growth markets. In 2012, we consolidated our position in India by taking over two companies there. In Brazil, we have been the leading supplier of pharmaceutical plastic packaging products since taking over Védat in 2011. I know that Gerresheimer is ideally equipped for future growth. To take advantage of this, all we have to do is keep listening to our customers and make sure we understand their needs. ◆

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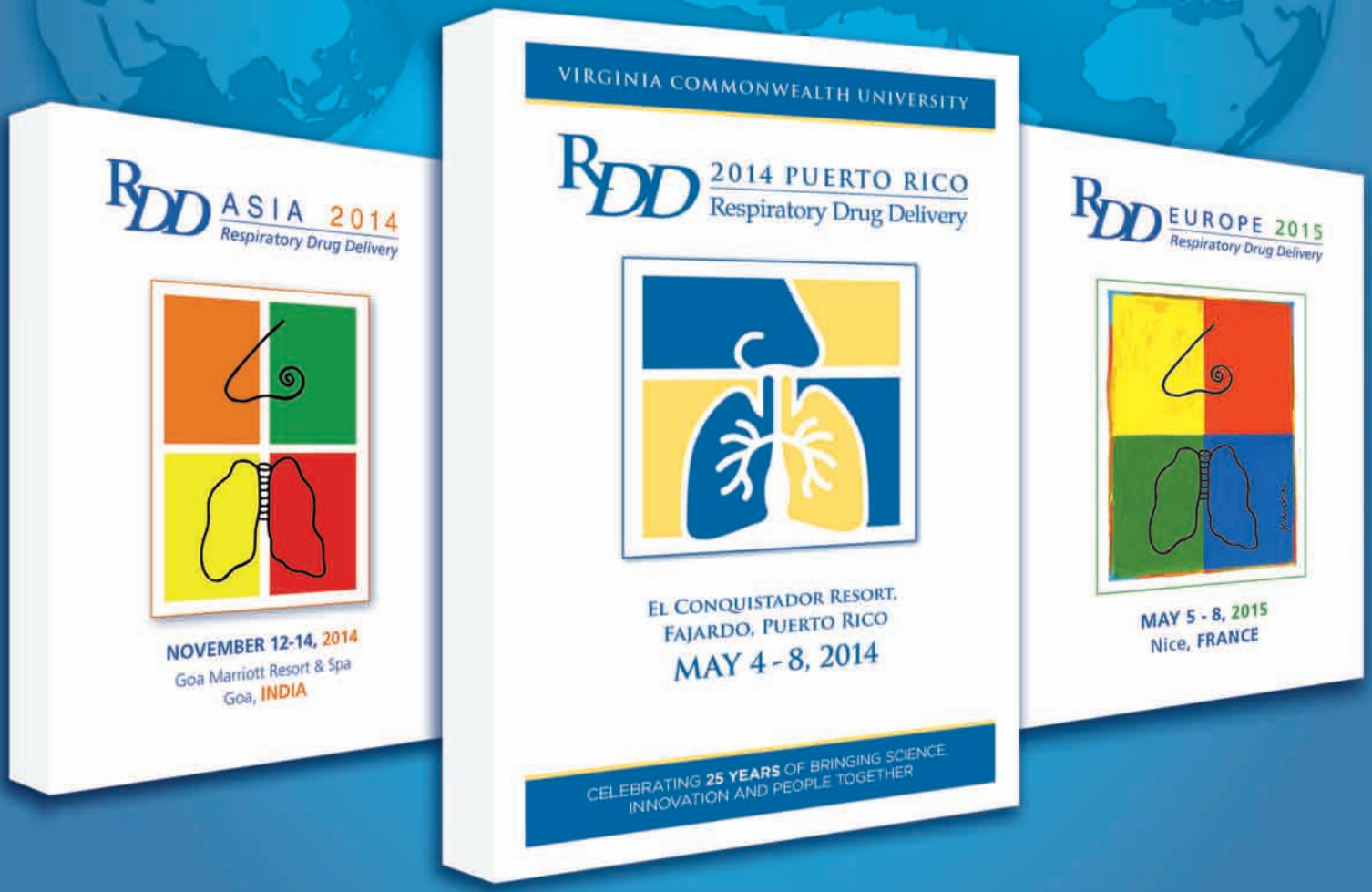

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CELL THERAPY

The Challenges & Possible Solutions for Transferring Cell Therapy From the Bench to the Industry

By: Lior Raviv, MMedSc, and Ohad Karnieli, PhD

INTRODUCTION

In the past decade, it has been proven that cell therapy works in the lab, in preclinical settings, and in small-scale clinical trials. The need for large quantities of cells with high quality becomes crucial as product candidates advance into clinical trials and early commercial products. Throughout recent years, many companies had invested efforts in developing culturing technologies that will allow large-scale culturing and manufacturing of cells. These technologies are evolving from tissue culture dishes and flasks to high-end, fully controlled bioreactor systems, which will allow production of large quantities of cells under cGMP (Current Good Manufacturing Procedures). The challenge becomes even bigger when looking at "off-the-shelf" allogeneic therapy. When mature, the industry will face an even larger challenge of downstream processing of the cell products. The following will discuss the significant emerging challenges in downstream processing of cell therapies focused mostly on allogeneic therapies.

LOT SIZE

Based on the publicly available information, the dose range for cell therapy clinical treatment can raise up to 600 million cells per treatment in repeated dosages. For this exercise, let's assume a dose range of 300 million cells per patient and 100,000 patients a year. Taking in to consideration quality control and testing, the gross amount of cells that should be manufactured to meet such a need will be 50% higher. Therefore, 150,000 x 300 million cells = 45 trillion cells annually, resulting in a minimal batch size of 1 trillion cells. Once understanding the quantities needed to become an industry, monolayer, traditional culturing systems, such as 10 or 40 layers, become irrelevant as one will need more than 1000 trays of 40 layers cultured simultaneously. Using traditional and multi-layer culturing systems has even larger drawbacks that include very high cost of goods as well as very large infrastructure and labor costs. Regardless of the cost, the most problematic issue of such technology would be the quality of the cells. This quality would be hindered by the very long processing times, high variation associated with different culturing vessels, different incubators, different processing and stalling times, and mostly by the variation due to handling of the cells and vessels. Therefore, the only true scalable technology for culturing cell therapies for allogeneic therapies would be large bioreactors.

BIOREACTORS

Bioreactors are vessels that can grow cells in a controlled and monitored manner with a high volume-to-surface ratio, allowing culturing cells in high quantities per vessel. These technologies range from automated, closed system mono-layer surfaces, throw hollow-fiber culture surfaces, and micro-carrier based systems all the way to packed bed three-dimensional surfaces. As an example, the Fibra-cell packed bed technology used to culture cells for the protein industry has

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been adapted for cell therapy culturing and modified by Pluristem Therapeutics. This technology allows for the culturing of approximately 1 trillion cells in three to four 75-litter reactors. This technology leap makes the growing of large numbers of cells feasible and very cost effective. An additional advantage of reactors lay in the fact that they are monitored and tightly controlled, allowing optimal culture conditions, resulting in high yields and low variance between vessels and batches. Once the industry matures, it is safe to assume that the bioreactor technology will become the main stream culturing technology that allows for the large-scale manufacturing of cells.

CELL HARVESTING

The first challenge facing bioengineers today is cell harvesting from the reactors and carrier systems. Adherent cells attach to the carrier surface and can only be detached by enzymatic digestion of the adhesion proteins. Detaching the cells is usually not sufficient, and additional physical force has to be added. This force has to be strong enough to detach the cells but gentle enough not to hinder cell integrity or to break the carrier, resulting in carrier residues or dead cells. Overcoming the harvest yield challenge allows using reactor technologies for cell therapy. Several technologies utilize different physical force to overcome the challenge. For example, in the hollow-fiber technology (TerumoBCT), a controlled liquid cross flow process post enzymatic digestion will result in gentle lifting and harvesting of the cells. Alternatively, in the fiber-cell reactors (Pluristem Therapeutics), a custom made proprietary technology adds controlled agitation and movement to the enzymatic reaction, allowing high harvest efficiency with high cell viability. An additional approach for harvesting could be digesting the carrier itself. Many different technologies try to address this path by using biodegradable materials as carriers.

FIGURE 1

Bioreactors are vessels that can grow cells in a controlled and monitored manner with high volume-to-surface ratio, allowing culturing cells in high quantities per vessel. These technologies range from automated, closed system mono-layer surfaces, throw hollow-fiber culture surfaces, and micro-carrier based systems all the way to packed bed three dimensional surfaces.

DOWNSTREAM PROCESSING

Downstream processing in cell therapy includes harvesting of cells out of the reactors and the carrier system, washing the cells, and eliminating all culture materials (such as media, serum, or ancillary ingredients), formulating, dosing, and cryopreserving the cells. Once the cells have been harvested, the clock begins to tick; cells are maintained outside their comforting environment without

FIGURE 2

The formulation of the cells prior to cryopreservation is conducted by determining the cell concentration and adding the final formulation additives to the suspension. This means that samples must come out of the suspension and material in it.

nutrition or suitable environmental conditions. The sensitivity of the cells to these stressful conditions differs, but the downstream processes are limited to a few hours. The downstream processes thus hold within them significant challenges with solutions that are becoming the cutting edge of cell therapy.

WASHING & CONCENTRATION OF CELLS

When the cells are in suspension, they should be washed out of the residual culture media, serum, or ancillary materials. The classical method of washing and concentrating cells is the use of batch centrifugation, which palate the cells to the bottom of a tube using G force (normally at about 1000 g). The media will then be discarded and the cells suspended using a pipet and addition of wash buffer. This process is repeated several times until reaching the expected clearance levels. Nevertheless, this process is very stressful to the cells, time consuming, and performed in tubes that have to be opened in order to replace the buffers and re-suspend the cells. These open manipulations amplify the risk of microorganism contamination to the final product, thereby adding risk to the patient. A few technologies exist that allows a closed system with continuous flow cell washing, some of which are based on blood separation technologies but are limited in their scalability. Alternatively, tangential-flow filtration (TFF) systems that have been used in the industry for protein concentration and diafiltration have been modified by several companies, such as Lonza, for use in cell therapy. However, its scalability limits have to be overcome, and in some cases, such technologies are stressful for the cells. An evolving processing approach has been developed by KBI Biopharma called the Ksep centrifuge. This technology uses two forces, working one against the other, the flow of the cells suspension or media and the centrifugation force. Cells are pumped continuously into a chamber that rotates at high speed. Through the balance of centrifugal and fluid flow forces, the kSep® retains the cells as a concentrated fluidized bed under a continuous flow of media or buffer. This allows washing and concentrating the cells with minimal stress using a closed and automated system. One additional and critical advantage is its scalability. To date, there is a commercially available model that can handle more than 1 billion cells per run.

CELLS SEPARATION & PURIFICATION

Cell separation is usually achieved by exploiting differences in basic cell properties,

such as size, density, expression of molecular markers, or surface properties. The application of separation for large-scale production requires technologies capable of highly efficient cell purification using a completely closed environment in a short process time in order to maintain the cell's quality. To meet these requirements, Milteny Biotec developed a closed and sterile system (CliniMACS®) based on magnetic-activated cell sorting, which allows for automated cell separation to a relatively large scale (up to 1.2 × 1011 initial cells). Biosafe developed the Sepax® technology based on a different separation principle termed Ficoll density gradient separation. The Sepax® is a GMP automated mononuclear cell isolation technology for umbilical cord blood or other sources. This kind of equipment can be used directly at the point of care (for autologous treatment) or during the isolation process of cell banking (for allogeneic treatment). Another approach for in-process cell separation is the use of aptamers. Aptamers are nucleic acid molecules generated by combinatorial chemistry and have the ability to bind specifically to molecular targets. Aptamers can be easily modified by attaching magnetic beads introduced to the cells using automated processes. Due to their low cost of production when compared with monoclonal antibodies, aptamers may contribute to a wider application of high-resolution affinity-based separation techniques in cell manufacturing, which would be very difficult with the currently available antibody technology.

Different microfluidic separation devices based on filtration and sedimentation, affinity-based methods have also been developed for lab-scale production. However, in order to process large amounts of cells using these technologies, a scale-out method is needed that increases the risk of inconsistency between the devices.

FINAL FORMULATION & FILLING

The formulation of the cells prior to cryopreservation is conducted by determining the cell concentration and adding the final formulation additives to the suspension. This means that samples must come out of the suspension and material in it. Opening the container for the sampling and adding formulation additives increases the risk for contamination of the product at its final stage. As lot sizes increase, maintaining a homogenous cell's suspension and relatively short process time will be difficult. Therefore, a vast amount of development has been invested in developing closed system sampling, adding and mixing the formulated cells. Most of the final formulation technologies are custom made per product.

Final product dose and filling step duration is defined by lot size and the number of cells per dose. Currently, most of the cell therapy's final product packagings are traditional blood bags. This type of packaging is suitable for small lot sizes in the range of several hundred doses per lot. Larger lots will require a shift to pharmaceutical vials and compatible filling automation in order to decrease process duration and maintaining cell quality. The use of new plastic vials from West or Aseptic Technologies coupled with traditional pharmaceutical fill line automation can enable the processing of lot sizes in the several hundred to several thousand doses per lot using the same scalable technology.

Cells that are kept cryopreserved are maintained in liquid nitrogen, which is 196°C and thawed rapidly in a 37°C water bath. Such a significant temperature change is very stressful to most materials, thus the containers are very limited to small infusion bags, plastic tubes with a screw-on cap, or the Aseptic technology patented vials. The disadvantage of bags is that their handling is not trivial. Once frozen, they are very sensitive and break easily. Furthermore, the cells freeze in a thin layer, making them very sensitive to temperature changes that might accrue during shipment or prior to the intended thawing. The plastic screw-on cap vials are commonly used in cell culturing and preservation, but they require opening the cap for filling and extracting the cells, which can lead to contamination of the cells and result in risk to the patient. Commonly used septum vials do not survive the liquid nitrogen freeze-thaw cycle as the different material comprising the vial and septum react differently to the temperature, resulting in leaks or brakes in the glass and contamination. Aseptic technologies had developed a unique technology in which a plastic septum vial is pre-closed together and can survive the cycle without leaking. In order to fill the vial, a needle is inserted through the

septum, and the cells are pumped in. The septum is then sealed using a laser beam.

SHIPMENT HANDLING & DELIVERY

Because cells are cryopreserved, the shipment and handling is not straight forward. The cells must stay frozen, and the time they can remain outside of the nitrogen is very short. Temperature variations can significantly shorten their shelf-life. Therefore, shipment and storage must be done in a controlled manner with tight monitoring.

One of the most critical steps in the survival and viability of the cells is the thawing process. Generally, the thawing must be done rapidly in a water bath with gentle mixing to eliminate temperature gradients, resulting in water crystallization and cell damage. Water baths are an efficient way to thaw cells as water is a very good heat conductor. Nevertheless, water could be a risk factor for contamination, and there is a large variation in the way different people mix the cells during the thawing that results in variation of cell viability. Low cell viability will lead to low efficacy. Therefore, companies, such as Pluristem Therapeutics, have developed a custom made thawing device that can automatically thaw the cells in a controlled and uniform manner. Such a device promises high-quality cells delivered to the patient.

COST OF GOODS

Cell therapy is an expensive but promising therapy. The cost of the therapy is influenced by the cost of goods manufactured, overhead and infrastructure costs, and logistic costs of shipment and handling. Cells culture media, both serum-based and chemically defined, is very expensive. Efficient culturing conditions that would produce high yields of cells, have a major influence on the cost. Tightly controlled Bioreactors with a high surface-to-volume ratio, such as Pluristem's Fibra-cell-based reactors, are the key for highly efficient manufacturing and a reduced cost of goods. An efficient testing and downstream processing mechanism can significantly affect the yields and viability of the product and directly affect the cost of the final product. Therefore, the issue of cost should be considered upfront from day one. Efficient large-scale manufacturing should be implemented very early on in the development life cycle of the cell therapy. Having said that, most early stage cell therapy companies choose not to invest in process development or the optimization of manufacturing due to high initial investments. Only a handful of cell therapy companies see this issue as critical and address the manufacturing, cost, and scalability issues early on. One such company is Pluristem Therapeutics, which develops and manufactures cell therapy products that originate from the placenta. ◆

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BIOGRAPHIES

Lior Raviv is the Product Development Team Leader with the Process Development Department at Pluristem Therapeutics, where he develops new technologies for cells downstream process and final packaging. Prior to joining Pluristem, Lior was a R&D Analytical Researcher at Teva Pharmaceutical Industries Ltd. He earned his MMedSc in Pharmacology and his BSc in Biotechnology Engineering at the Ben Gurion University in Israel.

Dr. Ohad Karnieli earned his PhD in Biotechnology and Genetic Engineering from the Sackler School of Medicine at Tel Aviv University. Furthermore, Dr. Karnieli earned his MBA from the graduate school of Management at the Haifa University. In his PhD, Dr. Karnieli developed insulin-secreting cells from human mesenchymal stem cells using genetic modulations. Prior to joining Pluristem, Dr. Karnieli served as the General Manager of High Tech Lipids, an innovative IV nutrition company; the Vice President of Research and Development in an innovative nanobiotechnology start-up; and as the Vice President, Head of the Biomedical division at Goji solutions, where medical devices are developed using radiofrequency technology. Dr. Karnieli is the Founder of Karnieli Ltd., a leading molecular diagnostic and development lab.

Technology & Services Showcase

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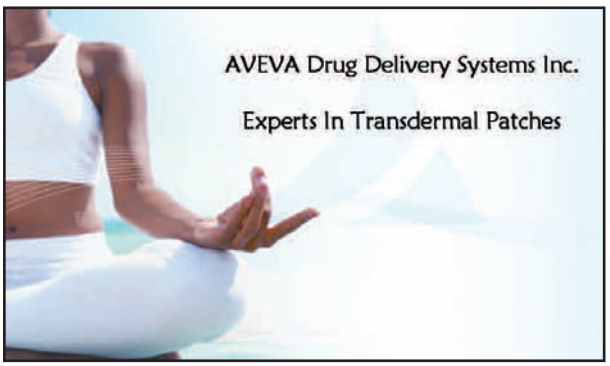
Licensing & Capabilities



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Technology & Services Showcase

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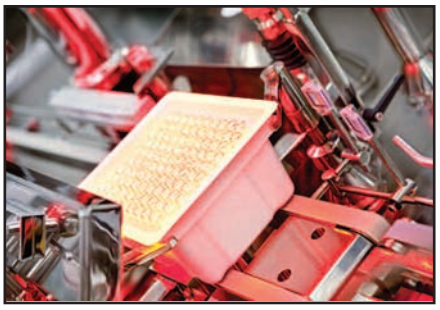

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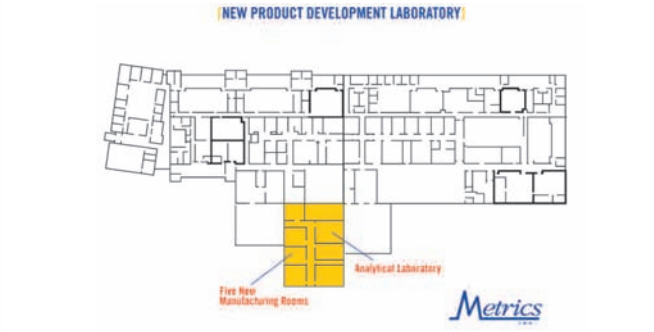
Product Development Lab



Metrics is making significant investments in facilities and equipment for the benefit of contract services clients with a new laboratory to better support fast-track development of pharmaceutical products. The $1.6-million, 4,524-sq-ft facility provides maximum flexibility for early formulation and analytical method development. The facility is designed for preclinical development of early formulation prototypes and related analytical methods. In this laboratory setting, formulators and chemists will have significant autonomy to conduct development activities more quickly. Segregated from the main Metrics operations and containing fully dedicated equipment, these new processing suites have independent HVAC systems and state-of-the-art engineering controls, such as interlocking airlock doors, room air pressure differentials, high-volume room air turnover, and 100% HEPA air filtration. For more information, visit Metrics Inc. at **www.metricsinc.com**.

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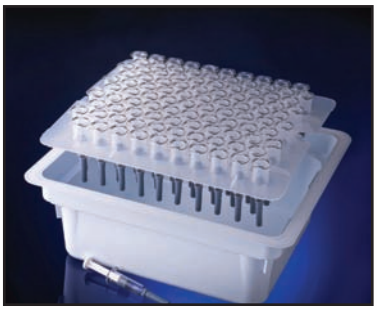

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Development & Manufacturing

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DRUG DEVELOPMENT Executive

HERMES PHARMA

Get the dose right™

HERMES PHARMA: USER-FRIENDLY DOSAGE FORMS, A WIN-WIN SITUATION FOR PATIENTS & PHARMA

Thomas Hein, PhD
Director, Sales & Business Development,
Hermes Pharma

"User-friendly oral dosage forms are particularly well-suited to patients with swallowing difficulties or those with chronic conditions requiring regular and prolonged dosing regimens. The elderly often suffer from both factors, with up to 50% of adults over 60 afflicted with dysphagia. This proportion increases up to as much as 75% for those in long-term care facilities."

Hermes Pharma is the expert in developing and manufacturing user-friendly solid oral dosage forms - including effervescent and chewable tablets, instant drinks, and orally disintegrating granules. For more than 40 years, the company has been working with pharmaceutical companies and producers of food and dietary supplements around the globe to expand their product lines and grow their brands. As a division of Hermes Arzneimittel, a leading German provider of branded high-quality medicines, Hermes Pharma offers customized solutions at every point along the pharmaceutical value chain, from new product development, to manufacturing and regulatory support. Drug Development & Delivery recently interviewed Dr. Thomas Hein, Director Sales & Business Development at Hermes Pharma, to discuss how user-friendly dosage forms help to put patients first, their advantages for patients and pharmaceutical companies, as well as the challenges associated with their development and production.

Q: What are user-friendly solid oral dosage forms, and why are they needed?

A: The easiest and simplest route of drug administration is oral ingestion. Traditionally, this has been achieved using solid tablets or capsules, which are swallowed whole and break down in the gastrointestinal tract of the patient to release their active pharmaceutical ingredients (APIs). However, swallowing large tablets is not always easy, and tablet shape, surface texture, and taste also lead many patients to dislike solid medicines. These factors combine to reduce patient compliance, subsequently impacting treatment effectiveness.

One way to circumvent these problems is to design oral dosage forms that are more user-friendly, such as effervescent and chewable tablets, orally disintegrating granules (ODGs), lozenges, and instant drinks. Consumers have embraced the

concept of user-friendliness in household electronics and consumer goods; now is the time to address the needs of the ill and those who care for them. By providing a wider range of alternative formulations, physicians, caregivers, and patients have more choice while preserving safety and efficacy. To effectively meet these needs, Hermes Pharma has been developing new ways of formulating and manufacturing dosage forms that are easy and pleasant to ingest, while offering the desired API-release characteristics, efficacy, and stability.

Q: What are the advantages of user-friendly solid oral dosage forms?

A: Advantages include ease-of-use and convenience for all patients, boosting compliance. User-friendly dosage forms can be taken with or without water to suit individual preferences and can be conveniently taken along to work, school, sports, or elsewhere. This makes it easier for patients to integrate medication into their daily lives, and reliably take medicines according to the intended and prescribed schedule. As user-friendly dosage forms are in solution when they enter the digestive tract, they do not cause esophagitis or other injuries, such as gastrointestinal lesions. As effervescent tablets and ODGs are absorbed quickly, they can also help provide rapid API release, such as is required for fast-acting drugs like analgesics. In other cases, the presence of carbon dioxide in effervescent formulations can improve bioavailability by boosting permeability through the intestinal epithelium. User-friendly solid oral dosage forms may also facilitate the incorporation of a wider range of dosage levels beyond what conventional tablets or capsule allow, enabling for example a larger amount of API to be taken in a single dose. This further simplifies administration, increasing patient compliance and making treatment more effective.

Q: Which patient groups benefit from user-friendly solid oral dosage forms?

A: User-friendly solid oral dosage forms are particularly well-suited to patients with swallowing difficulties (dysphagia), or those with chronic conditions requiring regular and prolonged dosing regimens. The elderly often suffer from both factors, with up to 50% of adults over 60 afflicted with dysphagia. This proportion increases up to as much as 75% for those in long-term care facilities. In this setting, current practice often involves crushing solid medicines for administration. However, this approach can cause API instability and unpredictable variation in dosing levels, while some medicines simply cannot be crushed and still remain effective, for example, those that have been formulated to provide slow API release. The bitter taste associated with crushed tablets also lowers patient compliance, further reducing the effectiveness of medication.

When treating chronic conditions, the impact of these factors is multiplied for every repeated dose, so it is essential that medicines are easy and convenient to administer and pleasant to take. This increases the chance that doses will not be missed and that the desired plasma concentration time profile will be achieved. For certain patients, mobility, motor, and cognitive function may also be an issue, so the simpler the treatment regimen, the more effectively it can be administered by the caregiver and followed by the patient. As those over 65 years old are already the largest users of medication in the developed world and form a growing proportion of the population, there is a great and pressing need to develop medicines that suit their requirements.

Children are another group to benefit from user-friendly dosage forms. Not only do they have smaller mouths, throats, and digestive systems than adults, thereby making swallowing adult-sized tablets difficult, their physiology is fundamentally different such that adult medicines may have unexpected effects on them. For example, gastric pH is thought to be consistently higher in younger children, impacting on the absorption of a given drug, while distribution rate is known to vary between adults and children due to relative proportions of body water, lean body mass, and fat. Currently, the predominant solution for treating children is to crush or fragment adult dosages, leading to poor palatability and bioavailability problems. This combination of factors was considered significant enough to trigger a directive from the World Health Organization (WHO) in 2007, which encouraged drug developers to "make medicines child size."

Q: Apart from boosting treatment effectiveness, what else do pharmaceutical companies gain from making medicines more user-friendly?

A: The pharmaceutical industry faces significant challenges fueled by patent protection issues, rising R&D costs, and increasing competition from generic products. User-friendly dosage forms can provide a welcome opportunity to expand existing product lines, prolong product life cycle, and revitalize brands. Such line extensions lead to increased customer awareness, greater brand value, and differentiation from competitors, factors that increase revenue and market share. For example, the Aspirin® brand owes much of its success not least to a product-line extension strategy that has resulted in the development of a multitude of dosage forms, such as effervescent products, chewable tablets, and ODGs.

As well as offering current medicines in a new form likely to boost compliance, there is the possibility to develop new drugs optimized for specialized groups of patients, such as children, the elderly, or people on long-term medication. These add extra value for patients, such as a choice of flavor and increased convenience through dosage forms that can be individually wrapped and "taken on the go." Patients and consumers who seek modern dosage forms are likely to remain more loyal to the brand and may also be prepared to accept higher prices. Often, the new dosage forms permit a more cost-effective treatment altogether, further improving the situation for patients, reimbursers, and pharmaceutical manufacturers.

Frequent regulatory changes also play an important role in the identification of appropriate patent expiration strategies. One such approach, confirmed by empirical research, is product-line extension involving the innovative modification of pharmaceutical drugs into new formulations, for example, user-friendly dosage forms. This sort of life-cycle management can also make it more difficult for rivals or developers of generics to create similar drugs, as the technical parameters are more difficult to replicate, and can often be protected by updated patents.

Q: What are the challenges associated with the development and production of user-friendly solid oral dosage forms?

A: As with all formulations, they must be physically and chemically stable enough to be manufactured, packaged, and transported without any loss of efficacy or usability, even after prolonged shelf storage. The excipients and API that will make up the final product need to be carefully selected and sourced to ensure they will work together correctly and will be reliably available from suppliers for the duration of the product life cycle. From a functional standpoint, the API itself must be released at the desired rate in the correct body location to achieve the desired therapeutic result. Successfully bringing an effective and user-friendly medicine to market also requires specific know-how across formulation and scale-up through to compounding, tableting, packaging, and marketing.

Perhaps the key issue surrounding formulation revolves around unpleasant taste, which is considered one of the main reasons for poor patient compliance. As user-friendly solid oral dosage forms spend more time in the mouth than traditional forms, the bitter taste associated with APIs must be effectively masked to render them palatable. Of particular relevance is the fact that effervescent forms are more sensitive to moisture, being deliberately designed to dissolve upon contact with water.

Therefore, effervescent tablets must be handled and manufactured in low humidity environments to ensure maximal stability. By keeping turnaround times as short as possible and packaging the final product in-line, degradation can be minimized. In addition to protecting the product, packaging itself requires specific expertise, as the final product may need to be both child-resistant and senior-friendly. Each of these elements must be considered early on and effectively balanced, identifying a process that will yield the desired result at an acceptable cost and within the required timeframe.

Given the potential complexities, it is not surprising that many pharmaceutical companies choose to outsource the process to dedicated providers. This avoids the need to invest time, money, and resources in developing the necessary expertise in-house, and negates the requirement to purchase any dedicated manufacturing equipment. However, when choosing a contract research and manufacture organization (CRMO), it is important to select a partner that truly understands the needs, limits, and stakeholders of the

organization, whether it be a small pharma company focused on a single product, or a large player looking to explore new options for a more extensive product portfolio. The partner should also be able to provide expert knowledge and service along the full length of the pharmaceutical value chain, integrating formulation and manufacture with the other parts of the development process to successfully bring a new product to market.

Q: How is Hermes Pharma meeting these challenges?

A: At Hermes Pharma, we optimize the development of user-friendly solid oral dosage forms from multiple perspectives, including investigating new methods of drug formulation, identifying reliable, well-characterized excipients and associated suppliers, preparing manufacturing workflows for scale-up, and experimenting with adequate product protection and packaging.

In terms of formulation, our teams have been testing new coating methods capable of producing stable, pleasant-tasting products that offer customizable dissolution profiles depending on the needs of each unique medicine. One such technique is Hot Melt Coating (HMC), which allows us to reproducibly encapsulate flavors, APIs, and other excipients without the need for potentially toxic and costly solvents, while simultaneously reducing manufacturing times and costs. As part of our ongoing research into optimizing the HMC process, we can formulate medicines with immediate- or sustained-release profiles depending on requirements. The new coatings not only have an agreeable taste, they also rank highly for other desirable traits, such as mouth feel, color, and texture, as well as offering the required physical and chemical protection for the API.

We also have experience in up-scaling the process for manufacture. This is especially valuable, as many of the excipients used for manufacturing user-friendly solid oral dosage forms bring their own unique challenges. For example, many of the lipids utilized for coating are soft and must be carefully stored and transported to maintain quality and process reproducibility. Traditional manufacturing processes requiring lubricants should also be carefully considered; for example, when producing effervescent tablets, lubricants can lead to a final product with an unpleasant soapy taste that forms a cloudy solution upon dissolution. This dosage form also requires specialized, low-humidity manufacturing conditions or sophisticated technologies - such as Topo Technology - that delivers granules that are less sensitive to humidity, but remain stable during storage while keeping a good solution profile needed for effervescent products.

Q: Why else should companies partner with Hermes Pharma?

A: Hermes Pharma has over 40 years of experience working with pharmaceutical companies and producers of food and dietary supplements around the globe to expand their product lines and grow their brands. We work with our clients in many different ways, from co-developing new products to licensing market-ready products based on our proprietary over-the-counter brands. Our integrated services cover the entire pharmaceutical value chain, including product design, formulation, analytical development, stability testing, manufacturing, QA, QC, and batch release, packaging, delivery, regulatory support, and life-cycle management. We use patented manufacturing technologies, and employ PAT and QbD principles when necessary to reliably deliver outstanding product quality and stability. With a dedicated focus on user-friendly dosage forms and unique expertise in taste-masking and flavoring, we have the experience and technology to see a project through to completion. We've proven this time and time again, building up a diverse and deep knowledge bank with which to effectively serve our customers. ◆

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Chad Mirkin

Chad is the director of the International Institute for Nanotechnology and the George B. Rathmann Professor of Chemistry, Chemical and Biological Engineering, Biomedical Engineering, Materials Science and Engineering, and Medicine. He has authored over 550 manuscripts, is an inventor on over 900 patent applications worldwide (242 issued), and is one of only 12 scientists, engineers, and medical doctors to be elected to all three U.S. national academies.

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The Compensation Paradox

By: John A. Bermingham

My strong belief is that most people do not understand their entire compensation package. Nor do they think about the impact their compensation package has on themselves and the company, as an example, when receiving a promotion and a raise.

When most people think about their compensation package, they think only about their gross salary and take-home pay. What they never think about is their Cost to Company (CTC).

The CTC is the total cost the company spends on you beyond your salary. This includes, among other things, the building you are in, your desk, chair, and file cabinet; computer, monitor, mouse, keyboard, desk phone, cell phone, and iPad, contribution to medical benefits, social security, Medicare/Medicaid, pension plans, unemployment tax, payroll taxes, paid time off, and more.

Companies look at you and your total CTC when considering your value to the company. Not just your salary. This is where the paradox comes in. The employee looks primarily at his or her gross pay, take-home pay, and benefits to determine if working at their company is worthwhile. This is much more limited than how the company determines its valuation and total CTC of the employee. And the more benefits and perks the company provides, the greater the gap between the employee's valuation of the company and the company's valuation of the employee.

This situation really comes into play when a person is being given a promotion and a raise. A person will normally look at a promotion and a raise as a reward for a job well done. They take the position that they have contributed mightily to the company, achieved positive results, and met or exceeded the goals that were established for them.

But the employee may also believe the pay raise was not enough when compared to the value they bring to the company and that, even with the raise, they are not being paid fairly for the value they bring to the company. They begin to look at or estimate the pay of others in the company, at people outside the company, and websites that show what their position pays on average, and commiserate with family and friends relative to their compensation package.

The company, on the other hand, believes their compensation package for this position is competitive and at the higher end of the pay range for this position. They consider the CTC relative to the value the employee brings to the company. Beyond the cash compensation, the company may also be providing the employee with an excellent medical plan, pension, 4 weeks paid vacation, a cell phone, an iPad, an auto allowance, liberal travel and expense policy, and more.

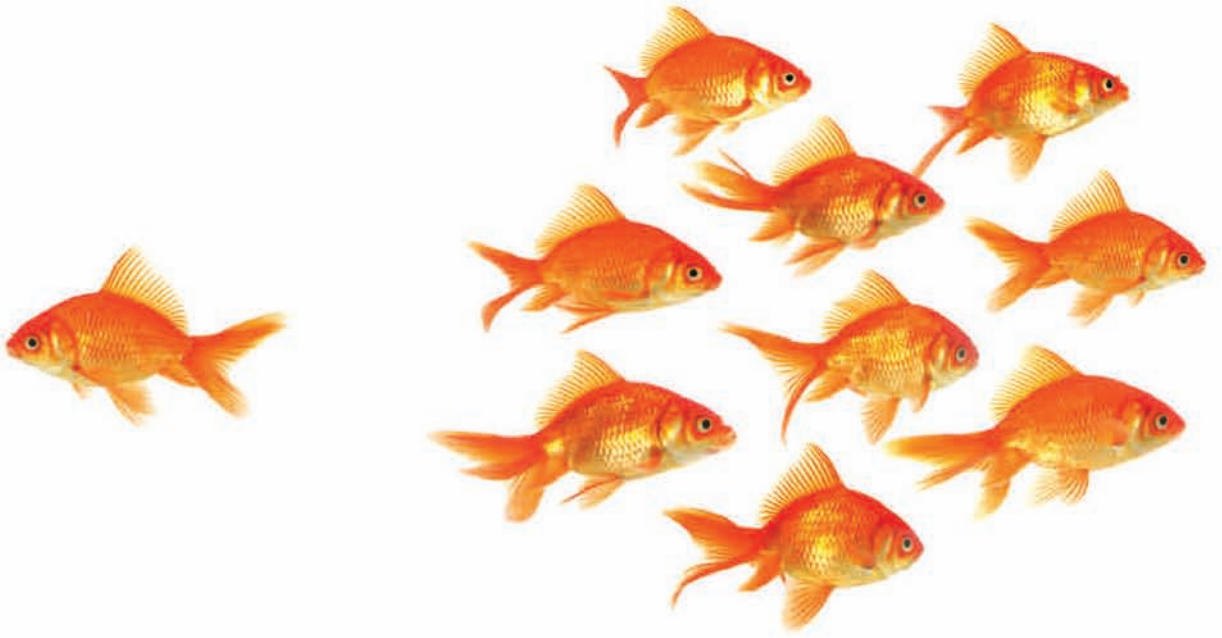
So the point of this is that a person has to consider the whole package that he or she receives from their company, not just what is in the pay envelope. You must consider the complete CTC in valuing your compensation package relative to the value that you bring to your company.

If after you have considered the CTC you still believe you are under-paid and under-valued by the company, then it is time to meet with your boss and make your case. You may not win this discussion, but at least your boss will know your concerns and understand your position. ◆

Biography

John A. Bermingham
Chief Operating Officer
1st Light Energy & Conservation Lighting

John A. Bermingham is currently the COO of 1st Light Energy & Conservation Lighting. He was previously Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc), as well as President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.



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