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Veracity Health

Synopsis

Contents:

Developments in the Treatment of Gastrointestinal Disorders

In recent months a number of promising treatments for GI disorders have come on to our radar screen at Veracity Health, so we thought we would summarize a few of these for our readers. What follows is a selection, from one end to the other, so to speak, of diseases and the technologies (and companies) working to address these diseases. The technologies which follow are either in clinical trials, or are on the market and gaining acceptance among end users.

Barrett's oesophagus

Barrett's oesophagus (BE) is an abnormality in the cells lining the lower oesophagus, and can be a predisposing factor for oesophageal adenocarcinoma. Cancer of the oesophagus carries a high mortality rate: it is estimated to be the seventh leading cause of cancer death in the US, and is rapidly rising in annual incidence. An estimated 3.3 million people in the US have BE, although only 1 in 200 will develop cancer. BE is found in about 10-15% of patients with gastric oesophageal reflux disease (GERD).

Standard treatment for BE consists of treating the GERD and observing to see if the BE develops into oesophageal cancer. However, recent research has shown that BE can often be eliminated using endoscopic radiofrequency ablation (RFA), with most patients remaining free of BE five years after the initial procedure.

Barrx Medical developed and markets the HALO360 and the HALO90 Ablation Catheters, which employ radiofrequency energy to ablate the irregular Barrett's cells. The ablated tissue sloughs away, leaving behind a clean lesion.

C2 Therapeutics, currently in stealth mode, is developing a cryotherapy-based product to achieve the same treatment. The device consists of a catheter, a balloon, which may be placed within the oesophagus of the patient, and a refrigerant. The refrigerant is delivered into the interior of the balloon so as to place the balloon into an expanded, cooled state. The balloon then presses against the oesophageal tissue, ablating the abnormal tissue and producing a lesion.

Obesity

Sensate is developing a device to treat obesity. The removable device is delivered endoscopically to the stomach and anchored to the inner stomach wall. The device is said to be fully reversible and is designed to modestly reduce food consumption while concurrently generating a feeling of satiety. This novel mechanism of action allows gradual weight reduction. A Phase 1 study is underway at the Johannes Gutenberg University, I. Med. Klinik in Germany. The company is partnered with Shalon Ventures.

At the 2009 American College of Surgeons Clinical Congress, a start-up company called ValenTx Inc. presented the first clinical study of its endoluminal approach for the treatment of morbid obesity. According to the company, the ValenTx procedure uses an implantable, removable sleeve that mimics the mechanisms of gastric bypass surgery without the associated risks. In a collaborative study led by physicians from the University of California San Diego Medical Center and the Imperial College of London, and conducted at the Hospital San Jose de Monterrey in Monterrey, Mexico, 12 patients underwent the implantation of the ValenTx bypass sleeve during a 12-week trial. Reported results indicated that

patients completing the study achieved an average excess weight loss of 39.5%. The company, founded in 2002, is based in Carpinteria, California.

ReShape Medical continues clinical testing on the ReShape Duo. According to the company, the ReShape Duo is designed to be placed in the stomach during a 15-minute outpatient procedure for which the patient is under deep conscious sedation. The balloons are designed to serve as built-in portion control, taking up space in the stomach so that the patient feels full and satiated sooner than without the balloons, and hence eats less and loses weight. The balloons remain in place for six months and are then removed. The company says that the ReShape Duo has been used successfully over the last two years in research participants in the EU. Reportedly, results have shown weight loss as high as 40 to 60 pounds over a 6-month period. The company does not say if the weight loss is maintained once the device is removed. ReShape Medical's headquarters are located in San Clemente, CA.

BaroSense, located in Redwood City, CA, is hush-hush about its device for the treatment of obesity without invasive surgery, but investors seem to like it: the company has successfully raised $53 million, and plans to bring its device to the US market by the end of 2010. The Barosense Trans-oral Endoscopic Restrictive Implant System (TERIS) is an investigational system currently in Phase 1 clinical trials in Canada for safety. The system involves implanting a restrictive reservoir for food entering the stomach in obese and morbidly obese subjects. Backers include Delphi Ventures, Frazier Healthcare Ventures, Invesco Private Capital, RWI Ventures, Synergy Life Science Partners, Wharton Ventures and Pappas Ventures.

GI Surgery

NiTi Surgical Solutions, headquartered in Israel, has developed what it calls the first major advance in decades in tissue closure device technology for GI surgery. NiTi's BioDynamix Anastomosis uses nitinol-based elements to press together the ends of resected tissue, which according to the company, facilitates a natural reconnection of the intestine after a section has been removed - as occurs, for example subsequent to colon cancer surgery. The technology is incorporated in a family of FDA-cleared and CE marked products currently marketed by NiTi.

When the BioDynamix™Anastomosis ring device is inserted and set the nitinol springs close on the tissue to be joined. The tissue trapped within the ring or the clip is cut off from its blood supply and becomes necrotic, while the two pieces of tissue along the outside of the ring are held together to allow natural healing to take place. According to NiTi, the main difference between BioDynamix™ Anastomosis' version of healing, versus healing when stapling is utilized, is that BioDynamix™ Anastomosis healing takes place in aseptic conditions through fibrous adhesion, without suppuration and formation of granulation tissue. Thus, says NiTi, the healed area is likely to be stronger, and tissue healing is accelerated.

Short bowel syndrome

Short bowel syndrome (SBS), also known as short gut syndrome and small bowel syndrome, is a serious condition in which the small intestine is too short to absorb enough nutrients for the body. SBS can be fatal; the condition has a mortality rate of 30%, and current treatments are not very efficacious. However, researchers at the University of Michigan Medical School and the College of

Engineering are working in unison to develop a new treatment which utilizes mechanotransduction. In many biological tissues, such as bone, skin, and bowel, an applied physical stress, such as a load, will stimulate the tissue to grow. This response is called mechanotransduction.

The goal of the researchers is to design and manufacture a fully implantable bowel extending device that can be extended by four times its initial length. Engineering requirements include:

- integrating a battery, circuit board, and load cell;
- fitting inside a pediatric abdominal cavity;
- ability to conform to the curvature of the abdominal cavity and allow passage of fluid through the bowel.

This is a tall order, but the researchers have already developed two devices: a hydraulic actuated design and a shape memory alloy (SMA) ratchet design. According to the file submitted by the University of Michigan, the hydraulic device has been tested in pig bowel and proven effective in causing the tissue to grow with the extension of the device. The SMA device has been tested in ex-vivo pig bowel to test its functionality.

A prototype of the Crawling Bowel Extender, as it is called, was manufactured and tested and is capable of meeting all of the customer requirements and engineering specifications. It is also capable of extending the bowel to more than three times its original length. Much work remains to be done, including making the device implantable, but as of January 2010, the research team is continuing to work towards its goal of producing an effective treatment for SBS.

Fecal incontinence

Fecal incontinence is the inability to control bowel movements, causing faeces to leak unexpectedly from the rectum. Common causes of fecal incontinence include constipation, diarrhea, and muscle or nerve damage, such as a weakened anal sphincter associated with aging or injury to the nerves and muscles of the rectum and anus from giving birth. Its incidence is unknown; patients rarely talk to their physicians about fecal incontinence, despite its often severe effect on quality of life.

Depending on the cause of the incontinence, treatment may include dietary changes, medications, special exercises, or surgery, such as sphincteroplasty. There are several types of anal plugs on the market which, although not permanent cures, may give the patient greater control over bowel movements. One invasive treatment which appears to more closely emulate nature is sacral nerve stimulation, or sacral neuromodulation, normally conducted only if other treatments have failed. Medtronic's InterStim device is approved for urinary incontinence and is currently under review by the FDA for the additional indication of fecal incontinence. The sacral nerves run from the spinal cord to muscles in the pelvis, and regulate the sensation and strength of the rectal and anal sphincter muscles. Direct electrical stimulation of these nerves via an implanted device can restore continence in 40-75% of people whose fecal incontinence is caused by nerve damage and whose anal sphincter muscles are intact.

Mederi Therapeutics markets a device and procedure, called Secca, for treating fecal incontinence. Secca delivers radiofrequency energy into the muscle tissue

of the anal canal, ablating the tissue and creating lesions. Once healed, the lesions help to tighten the anal sphincter muscles and return proper function.

These are just a few of the innovations occurring in the treatment of GI diseases and disorders. As other novel medical devices come to our attention, we will report on them in future issues of *Synopsis*.

Obesity Pipeline Update

It is a subject that's rarely out of the news: two-thirds of all Americans reported to be overweight or obese; populations in more developed countries gaining weight and developing diabetes and heart disease; already-stretched healthcare resources will struggle to cope with treating the coming wave of aging, obese, diabetic patients.

Experts now believe that the obesity epidemic, for so it has been called, is not the result of a sudden breakdown in willpower, but the consequences of a mix of societal and food industry factors. These include shifts in family eating habits, greater use of cars, and more sedentary jobs which result in hours parked in front of a computer. Then there's the explosion in cheap, high fat, high sugar foods made almost irresistibly tasty and available everywhere, and billions spent on advertising these foods to children and their parents.

Although the demand for pharmaceutical treatment of obesity continues to be vast, the current antiobesity drugs on the market yield, at best, modest results. Hence, the healthcare industry is crowded with companies racing to develop a drug which might be the 'magic bullet'—or at least moderately effective—for the treatment of obesity. Their driving force is clear: if such a drug were found in clinical studies to demonstrate a safety and efficacy profile exceeding those of currently marketed drugs, then the revenues from that product might exceed $1 billion annually.

However, that race is a marathon, and no company has won the prize yet, although some have seen limited success. The field is littered with products once trumpeted as the Great Success, but which for one reason or another disappointed:

- Fen-Phen, pulled off the market in 1997 when it was reportedly linked to potentially fatal heart valve problems
- Orlistat, marketed by Roche in most countries as Xenical and over the counter in the US by GlaxoSmithKline as Alli, which blocks fat absorption but can cause explosive 'oily discharge' (Alli packaging suggests that for the first few days, the user take an extra pair of slacks to work);

- Abbott's sibutramine, marketed as Meridia, Reductil or Sibutrex, which showed mild effectiveness—10-12 pounds in one year—but how many obese people are happy with losing, on average, one pound per month?
- Other appetite suppressants with limited effectiveness include Didrex (benzphetamine), Tenuate (diethylpropion) and Bontril (phendimetrazine).

This scenario of mixed to mild effectiveness may be about to change. Several companies are in hot competition with obesity treatment drug candidates; two of these have filed with the FDA and are due to be reviewed for market clearance within the next six months. Other companies have devices on the market or in development which add to the options available for weight loss. Under FDA guidelines for clinical trials of obesity treatments, one of two goals must be met. A trial must show that at least 35% of the drug group lost at least 5% of body weight, but that group must be double the percentage of patients with similar weight loss on the placebo. Or, a study can show that patients had an average weight loss that was at least 5% higher than the placebo group's loss. The FDA, of course, also looks at safety, and has recently become rather more sensitive about that topic.

What follows is a brief review of the lead companies, their candidate drugs, and key marketing and pricing questions that the companies should be considering.

Arena Pharmaceuticals' Lorcaserin

- New Drug Application (NDA) submitted for lorcaserin to the FDA in December 2009.
- FDA has assigned a Prescription Drug User Fee Act, or PDUFA, tentative date of October 22, 2010, for review of the application.

Arena describes itself as a company focused on discovering, developing and commercializing oral drugs that target G protein-coupled receptors, or GPCRs, in four major therapeutic areas: cardiovascular, central nervous system, inflammatory and metabolic diseases. Arena has several drugs in its pipeline; its most advanced is lorcaserin. This drug is intended for weight management, including weight loss and maintenance of weight loss, and has completed a pivotal Phase 3 clinical trial program.

According to the company, lorcaserin is a novel single agent selective serotonin 2C receptor agonist. The serotonin 2C receptor is expressed in the brain, including the hypothalamus, an area involved in the control of appetite and metabolism. Stimulation of this receptor is strongly associated with feeding behavior and satiety. Arena states that it has patent protection essentially into 2023.

In Phase 3 results from the Behavioral modification and Lorcaserin for Overweight and Obesity Management (BLOOM) clinical study, researchers evaluated 3,182 patients with an average BMI of 36.2 and baseline weight of 220 pounds. According to Arena, results were statistically significant: 66.4% of lorcaserin patients lost at least 5% of their body weight, compared to 32.1% for placebo, and average weight lost was 26 pounds; 36.2% of lorcaserin patients lost at least 10% of their body weight, compared to 13.6% for placebo. In all, lorcaserin patients achieved an average weight loss of 8.2% of their body weight, or 17.9 pounds, compared to 3.4%, or 7.3 pounds, for placebo.

In addition, researchers examined worsening or onset of valvular insufficiency, which has been observed with other nonspecific 5HT agonists, and which contributed to the retirement of Fen-Phen from the market. The assessment of echocardiograms indicated that lorcaserin was not associated with valvular insufficiency: during two years of use, rates of change in individual valvular regurgitation scores and the development of FDA-defined valvulopathy were similar between treatment groups. Rates of new FDA-defined valvulopathy in BLOOM were as follows: lorcaserin 10 mg twice daily (2.7%) and placebo (2.3%) at Week 52 and lorcaserin 10 mg twice daily (2.6%) and placebo (2.7%) at Week 104.

The company reported that the BLOSSOM trial confirmed the BLOOM results and completed the lorcaserin pivotal Phase 3 clinical trial program of 7,190 patients evaluated for up to two years.

In BLOSSOM, lorcaserin met all primary efficacy and safety endpoints, and lorcaserin patients achieved highly statistically significant categorical and absolute weight loss. Treatment with lorcaserin also resulted in statistically significant improvements as compared to placebo in multiple secondary endpoints associated with cardiovascular risk. Again, as in BLOOM, lorcaserin was very well tolerated, did not result in increased risk of depression or suicidal ideation and was not associated with the development of cardiac valvular insufficiency.

Vivus' Qnexa

- New Drug Application (NDA) submitted for Qnexa to the FDA in December 2009.
- FDA has assigned a Prescription Drug User Fee Act, or PDUFA, tentative date of July 15, 2010, for review of the application.

Vivus is developing innovative, next-generation therapies to address unmet needs in obesity, diabetes, obstructive sleep apnea and sexual health. The company's lead product in clinical development, Qnexa®, has recently completed Phase 3 clinical trials for the treatment of obesity and has filed an NDA with the FDA. Qnexa is also in Phase 2 development for the treatment of type 2 diabetes, and in Phase 2 development for the treatment of obstructive sleep apnea (OSA).

Qnexa®, formerly VI-0521, is an investigational, once a day, proprietary, oral, controlled-release formulation of low dose phentermine and topiramate. The combination is believed to address both appetite and satiety.

In September 2009, Vivus announced results from two final, Phase 3 pivotal 56-week studies, EQUIP (OB-302) and CONQUER (OB-303), which evaluated the safety and efficacy of Qnexa in more than 3,750 patients across 93 sites. The EQUIP and CONQUER studies met all primary endpoints by demonstrating statistically significant weight loss with all three doses of Qnexa, as compared to placebo. According to the reported results, patients taking Qnexa also achieved significant improvements in cardiovascular and metabolic risk factors including blood pressure, lipid levels, and Type 2 diabetes.
EQUATE, the first of the three Phase 3 studies, evaluated 756 obese patients over 28 weeks at 32 sites. EQUIP evaluated 1,267 morbidly obese patients with or without co-morbidities and CONQUER evaluated 2,487 overweight and obese patients with at least two co-morbid conditions. Patients treated with Qnexa for

56 weeks in the EQUIP study achieved an average weight loss of 14.7% (37 lbs). Other results included:

- Significant improvements in cardiovascular, metabolic and inflammatory risk factors among patients treated with Qnexa;
- FDA efficacy benchmarks for weight loss agents exceeded at all three doses of Qnexa;
- Completion rates up to 69% were significantly higher than placebo at all three doses of Qnexa, indicating favorable tolerability;
- Favorable benefit/risk safety profile for Qnexa.

Orexigen Therapeutics' Contrave

- New Drug Application (NDA) submitted for Contrave to the FDA in April 2010.
- PDUFA date not yet assigned.

Orexigen Therapeutics, Inc. is a biopharmaceutical company focused on the treatment of obesity. The company has not one but two lead candidates in the pipeline for the treatment of obesity; both are combinations of well-known drugs already on the market. Contrave® (naltrexone SR/bupropion SR) has completed Phase 3 clinical trials, while Empatic (zonisamide SR/bupropion SR) has completed Phase 2 clinical development. The company's Contrave NDA has been accepted for review by the FDA, but as of this writing, no review date has been set.

Contrave's NDA is based on evidence gathered through the Contrave Obesity Research (COR) clinical program, which included over 4,500 patients.

Shortly after filing its NDA, Orexigen made corrections to what it termed a clerical error found in the weight loss data it reported from a Phase 3 clinical trial. Its corrections took a little of the shine off the numbers, but Orexigen says that the results still fall within the FDA's benchmarks for clinically significant weight loss. After 56 weeks taking Contrave, 50.5% of patients lost at least 5% of their weight (original report: 56.3 %). The proportion of people who lost at least 10% of their weight was 28.3 % (original report: 32.9%). The corrections to the filing are not expected to delay the FDA's review of the application.

Below are highlights as reported from the COR program:

- Contrave met the FDA efficacy benchmark: 48% and 50.5% of patients on Contrave32 lost at least 5% of their body weight in COR-I and COR-II on an intent-to-treat basis, as compared to 16% and 18% of placebo patients who lost at least 5%, respectively ($p<0.001$).
- Significant improvements were observed in cardiometabolic risk factors such as waist circumference, visceral fat, C-reactive protein, HDL cholesterol and triglycerides.
- According to the company, in the COR-Diabetes trial, patients with Type 2 diabetes experienced significant weight loss and demonstrated meaningful reductions in HBA1c. Specifically, 45% of patients on Contrave32 lost at least 5% of their body weight on an intent-to-treat basis, compared to 19% of patients on placebo. Contrave patients also showed a 0.6% reduction in hemoglobin A1c (HbA1c) from baseline, compared to a 0.1% reduction in placebo.

The safety profile of Contrave® was found to be consistent with the safety of the two approved active ingredients. The most common adverse reactions (greater

than or equal to 5% and at least twice the incidence of placebo patients) were nausea, constipation, vomiting, dizziness and dry mouth.

Amylin Pharmaceuticals' pramlintide/metreleptin combination

- Reported results of a 52-week blinded, placebo-controlled Phase 2 extension study showed that patients who continued treatment with pramlintide/metreleptin for a total of 52 weeks demonstrated sustained weight loss, whereas those continuing on placebo regained almost all of their weight. Consistent with results at 28 weeks, the most robust efficacy was seen in patients with a body mass index (BMI) less than 35 kg/m2.
- Based on these results, in February 2010, Amylin and Takeda announced their decision to advance pramlintide/metreleptin into Phase 3.

By combining pramlintide and metreleptin, Amylin has placed its bet on an integrated neurohormonal strategy in its search for new treatments for obesity. Pramlintide, the active ingredient in Amylin's Symlin®, is a synthetic analog of amylin, a neurohormone secreted by the pancreas that plays a key role in the regulation of appetite, food intake and blood glucose concentration following a meal. Metreleptin is an analog of human leptin, which is a neurohormone secreted by fat cells that plays a central role in regulating energy homeostasis, fat and glucose metabolism and body weight.

In November 2009, Amylin and Takeda Pharmaceutical entered into a worldwide exclusive license, development and commercialization agreement to co-develop and commercialize pharmaceutical products for the treatment of obesity and related indications. Under the terms of the agreement, Takeda made an upfront payment of $75 million and agreed additional payments upon achieving certain development, commercialization and sales-based milestones that could exceed $1 billion. Takeda will lead global product commercialization and will be responsible for 100% of commercialization costs. Amylin will have the option to co-commercialize the first two approved products in the U.S. and any follow-on products containing the identical active ingredients.

On a negative note, the Phase 2 study involved four injections daily, which Amylin has apparently reduced to two injections each day of the combined compounds—which is still likely to be a wet blanket on potential sales. If Amylin cannot overcome this two-shots-per day hurdle, pramlintide/metreleptin may produce only dismal revenues, assuming it reaches the market. Amylin and Takeda were advancing another obesity candidate, davalintide, which showed promise for reducing the number of daily injections. However, in February 2010, based on results from a Phase 2 study the companies announced their decision to put further development of davalintide on hold for the time being. The study showed that davalintide's weight loss efficacy and tolerability profile was both not superior to pramlintide, and inferior to that of the pramlintide/metreleptin combination.

Filing an NDA: don't open the champagne just yet

So few drug candidates even make it out of Phase I clinical testing, much less all the way to the filing of an NDA with the FDA, so it is exciting for companies and investors alike when a drug makes it to Phase 3. However, the approval process isn't over 'til it's over: even at the eleventh hour, when a company files an NDA, the FDA may reject a drug application based on, for example, doubts about the drug's safety. One need only look at rimonabant, thought by Sanofi Aventis and

hopeful investors to be a blockbuster treatment for obesity. Rimonabant actually made it to market in the EU as Accomplia, but then was rejected by the FDA for safety reasons. The EU authorities wasted little time in pulling it from the market.

Marketing questions for companies to consider

1. **Will managed care cover the cost of obesity drugs?** Current obesity drugs are often used for cosmetic rather than for medical reasons. Managed care does not cover cosmetic drugs or procedures. Should any of these new drugs make it to market, what will convince payers to cover the cost?
2. **Should manufacturers price their obesity drugs closer to an over-the-counter level?** Would pricing at this level drive sales, or would it discredit the drug in the eyes of consumers? Orexigen's Contrave is said to be targeting a price of $5.00 per day, or about $150 per month. A low price may have to be partnered with a hefty sales campaign targeting both consumers and prescribers, and not all of these pharmaceutical companies have the resources to put on such a campaign—by themselves. Another solution is to seek a rich partner for commercialization.
3. **Will the pharmaceutical developer be further ahead by marketing the drug itself, or by selling or licensing rights to a big company?** There's a lot to be said for the latter, especially considering…
4. **The unknowns: Will these drugs be for short-term use, or chronic, as some critics suggest? What will be the results of Phase 4 testing in long-term usage? What will happen when the drug is stopped?** At this point, it's too early to say.

Table 1 - Selection of other Obesity drugs in the pipeline

Company	Drug/Combination Target	Current Status
Amylin	Byetta (Exenatide)	Approved for Type 2 diabetes; in Phase 3 to study weight-reducing effect on subjects without diabetes
Amylin	Symlin (Pramlintide)	Approved for Type 1 diabetes; has been demonstrated to cause weight loss in subjects with obesity and no diabetes.
Alizyme Therapeutics	ATL-962 (Cetilistat)	In October 2009 Cetilistat sold to Norgine BV; Alizyme Therapeutics and Alizyme plc in liquidation. Norgine expected to continue Cetilistat partnership and testing with Takeda.
Novo Nordisk	Victoza (Liraglutide)	Victoza approved in January 2010 in US for treatment of Type 2 diabetes, launched in Japan, India, US, etc. In Phase 3 for obesity.
NeuroSearch	Tesofensine	NeuroSearch preparing for Phase 3 clinical testing

Brazilian Generics Market - poised for expansion

In 2009, drugs with U.S. sales of $22bn lost patent protection opening up a global opportunity for the generic drug industry.

This trend is set to continue as products that currently generate $137 billion in sales worldwide will face generic competition from 2009 through 2013, according to IMS Health. Global generics sales rose 8.2% compared with only 5.0% for the overall drug market in 2009 registering revenues of approximately $150bn (Thomson Reuters Research).

Although there is considerable scope for market growth, pricing pressure in some markets has had a stalling or negative impact. Apart from the large Chinese market with growth within the generics market of approximately 19% in 2009, the most impressive double digit increase has been in less populous Venezuela, South Korea and South Africa.

In Latin America, and Brazil in particular, traditionally strong government backing of the indigenous industry, new legislative measures supporting research and innovation and increased prescribing habits of generics by physicians are laying the foundations for a sustained period of market expansion.

In the first issue of Synopsis we provided some background into reforms aimed at providing more comprehensive healthcare coverage to the Brazilian population and stated that follow-up issues of Synopsis would look at certain sections of the drug and medical device industries in the BRIC economies. In this issue of Synopsis we highlight the development of the Brazilian generics industry as the evolution of this sector appears to be a platform upon which a burgeoning and influential biotech sector will emerge well within the next decade.

Generic Law propels development of indigenous industry

Brazil remains on track to be one of the powerhouses of the global economy, but despite this income distribution remains skewed and as much as 26% of its population live in poverty, on less than $2 per day. Affordability of medicines remains problematic for many Brazilians and in recognition of this senators and representatives within the Brazilian political system began debating this amongst other related issues with the culmination in February 1999 of the passing of Law Decree 9787/99 known as the Generic Law. Over the last 10 years the Brazilian people have acquired access to a wide range of affordable generic medicines because the Generic Law led to the creation of what is now a well established, confident and ambitious generic drug industry, nearly 90% of which is controlled by domestic manufacturers. The strength of the generics industry has attracted foreign interest, with the most notable recent acquisition being Sanofi Aventis' purchase in 2009 of Medley for $664m. The Medley purchase price was considered too expensive for Teva Pharmaceuticals, the world's largest generic manufacturer by sales. Teva was also put off by what it considered Brazil's lack of rules for bioequivalence testing rendering low barriers to entry to the market and increasing competition. However, signs that the Brazilian government is tightening bioequivalence testing rules and encouraging investment in manufacturing and research laboratory sites suggest that foreign companies will be increasingly interested in merger and acquisition activity to buy into the next-tier, growth-oriented Brazilian market. Investment in Brazilian

companies will also give companies interested in acquisitions access to lower cost expertise in active pharmaceutical ingredient manufacturing.

Indigenous manufacturers adept at efficient, timely product introduction

Brazilian generic drug manufacturers are in a race to introduce new generics onto the Brazilian market. Their strategy has been to consider the "development" of a new product at least 2 years before the expiration date of a particular dug's patent as bioequivalence studies and application for registration of the medicine through the Agencia Nacional de Vigilância Sanitária (ANVISA) has an approximate 2 year timeframe. Once approval for a new generic is granted the company with the registration documentation has a deadline of 6 months within which it must launch the drug. Then, the companies have a ready and willing purchaser in the form of the Brazilian government which procures reference, branded and generic drugs at the District, State and Federal Levels for use in the public hospitals and Basic Health Units making up the Sistema Unico de Saúde. It is interesting here to look at how the market for generic Viagra will fare in Brazil. Based on current practice generic Viagra production should start in early July 2010 immediately upon expiration of the patent. It is possible that the price of the generic product could be up to 50% of the Pfizer product which has been on sale in Brazil since 1998 and currently costs $77 for a box of four 50mg tablets. The Association of Brazilian Generic Medicine s Manufacturers estimates that the market for Viagra has a value of $114m and savings from a generic form of the drug could be worth $40m to the government.

The other major drugs facing generic competition in Brazil in 2010 are shown in Table 2 below

Drug	Brand Name	Brand Manufacturer	First Patent Expiry
Valsartana	Diovan	Novartis	March 2010
Irbesartan	Aprozide	Sanofi-Aventis	April 2010
Candesartan	Atacand	Astra Zeneca	May 2010
Olanzapine	Zyprexa	Eli Lilly	May 2010
Sildenafil	Viagra	Pfizer	July 2010
Ciclesonida	Alvesco	Nycomed	October 2010

Source: Company Reports and Veracity Health research

Brazilian Government's Growth Acceleration Program targets increased generic drug use

In order to increase investment in a range of development programmes the Brazilian government set in place a series of initiatives in 2007 under the Programa de Aceleração do Crecimento, PAC or the Growth Acceleration Program. Within the PAC, the programme More Health: A Right for Everyone set out a range of strategic directives, some of which targeted the sustained development of the Brazilian generic sector which encouraged companies to consider follow-

ing the path of global generic powerhouses which are researching and developing new chemical entities.
The relevant PAC directives are highlighted here:

Measure 2.4 - Reduce the population's expenditures with medicines by encouraging the use of generic ones.

In response to this, or spurred by it, generic companies in Brazil identified the main drugs coming of patent in the time period for the PAC programme , 2007 to 2011 and planned (again see Table xxx), then implemented investment of up to $310m in acquisition of new facilities , capital purchases and equipping new facilities.

Objective 2.4.1 – Increase participation of generic medicines in the market to 25% in revenue, and to 33% in pharmaceutical units until 2011, through campaigns that stimulate prescriptions and dispensation directed to nearly 50,000 drugstores and 111,000 physicians and consumers.

Today, generic medicines are widely used throughout the Brazilian population and are increasingly prescribed by physicians. If the generics market is to reach its full potential it will have to tackle the prescribing habits of a great number of doctors who continue to prescribe branded products. Prescription of generic medicines is still low, representing 15.8% of the total in 2006, compared to 15.2% in 2005 or 11.8% in 2002. In 2009 the prescription of generic medicines as a percentage of total drug Rx was 19.2%.

For some specific substances, however, generic medicines have achieved higher prescription levels, namely omeprazole (88%), cephalexin (77%) and fluconazole (65%). Using generics, consumers saved about $2.2bn in 2006. Since generic drugs were introduced in the country in 2001, Brazilians have, to date, saved $10.28bn through the consumption of all generic medicines.

Objective 2.4.2 – Foment through REQBIO – Brazilian Public Center of Bioequivalence Network, generic medicines bioequivalence tests so as to provide registration of 1,100 new medicines up to 2011.

Encouragement for manufacture and sale of biogenerics

As part of the PAC programme government-backed research centres are being constructed. These research centres are designed to take advantage of Brazil's existing excellence in scientific research and to build upon it to drive advancements in biotechnology. As a consequence of investment in education and support of PhD programmes over the last 5 decades the country is now reaping the benefits. It is reported that 9000 PhDs graduated last year. Some of these talented individuals will find work in world class companies operating in the biotech (agricultural and human), stem cell and vaccines sectors. The generics industry will also benefit. One area where generics is expected to see expansion is in the manufacture of biogenerics (also known as biosimilars or follow-on protein products).

Brazilian generics players entering biotech

The barriers preventing biogenerics from entering the market are much higher than for small molecule generics. As a consequence, biogeneric companies need to work harder than typical generic companies. Companies face higher develop-

ment costs due to clinical testing and pharmacovigilance requirements, longer development times, higher manufacturing costs, investment in generation of substantial NDA-type dossiers and uncertainties over the approval of patent procedures. Investors and drug companies alike expect interest in the sector to be concentrated around portfolio focused deals. Indeed some signs of this and tackling of obstacles by Brazilian manufacturers are already evident.

The large Brazilian pharma company Aché (2008 sales $578m) has increased its salesforce, such that its detailing capabilities have increased. In 2009, in its quest to offer an increasingly more complete portfolio of generics, Aché prepared to launch 12 new products, planned to be released in 2010, bringing to 96 the number of molecules marketed by the company. The goal is to reach 160 molecules by 2013, through either internal development or acquisitions of companies operating in this market.

Zydus Cadila which has a Brazilian operation is targeting the biogenerics segment, considering it a global $40bn market opportunity.

In December 2009 a technology transfer agreement was signed between EMS, Brazil's largest pharmaceutical company, and the Chinese laboratory Shanghai Biomabs, for the manufacture in Brazil of six latest generation biotechnological products. The deal includes monoclonal antibodies, and medication used for serious illnesses and high cost treatment, such as cancer, rheumatoid arthritis and osteoporosis, among others.

The first target product of the EMS/Shanghai Biomabs partnership will be Etanercepte (Wyeth's Enbrel, etanercept), indicated mainly for rheumatoid arthritis, which currently generates annual expenditures of approximately $45 million to the Ministry of Health in Brazil, the main purchaser of the drug. Jose Gomes Temporao, the Minister of Health stated that "A Brazilian company entry in this market will increase competition, which must lead to the reduction in the price of the drug, since it is currently supplied to Brazil by only one multinational manufacturer. Moreover, the technology transfer strengthens the Brazilian industrial complex and contributes to reducing our dependence on external cutting edge technology in health".

Local conditions in Brazil aren't perfect, but then nothing ever is. However, a government cognizant of the need to lay the groundwork and encourage manufacturers to utilise manpower and business strengths to compete in the generics sector bodes well for development and expansion of the biogeneric and ultimately the biotech sector in Brazil. Brazilian companies are responding by adeptly using their established hybrid business model where revenues from early activities – typically generics and modification of existing technologies as well as services – are reinvested in innovative products.

News-wire

Accuray goes direct in India

In March, 2010, Accuray announced the establishment of a direct sales, marketing and service organization in India to support the systems already sold into that country. According to the company, there are currently two CyberKnife Systems installed in India, at Apollo Specialty Hospital in Chennai, which went live in March 2009, and at Health Care Global (HCG) in Bangalore, which went live in June 2009. These systems were sold through an external distribution channel; the recently established internal organization will enable local Accuray personnel to sell directly within the country and to offer customer service to its CyberKnife users.

Devicor Medical Products makes its first device play: Ethicon Endo-Surgery's Breast Care business

Ethicon Endo-Surgery (EES) had been considering selling its Breast Care business to focus on higher potential areas, and in March 2010, the company announced that it had a taker: Devicor Medical Products, a portfolio company of GTCR Golder Rauner, LLC. Financial terms of the offer were not disclosed. Upon close of the proposed transaction, Devicor will acquire the entire EES Breast Care portfolio that is sold in more than 38 countries worldwide. The portfolio includes the Mammotome® Breast Biopsy System and tissue markers (MammoMARK®, MicroMARK®, and CoreMARK®).

Thomas Daulton, Devicor's CEO, plans to build the company into a $500 million a year, thousand-plus employee power in the medical device industry. Daulton has been on the lookout for established interventional medical device businesses that manufacture and sell products to hospitals, surgery centers, or ambulatory clinics. His efforts are backed by $250 million in funding from the private equity firm GTCR, which sold Ovation Pharmaceuticals in 2009 for up to $900 million. Devicor's initial acquisitions are expected to provide infrastructure and personnel in key areas such as manufacturing, R&D, engineering, sales & marketing, finance, and human resources.

Medtronic hopes to follow Biosense Webster with next FDA-cleared ablation catheter for atrial fibrillation

On March 17, 2010, Medtronic announced that it had completed premarket approval (PMA) submission to the FDA for approval of its Arctic Front Cardiac CryoAblation Catheter System, which is designed for the treatment of atrial fibrillation. The Arctic Front Cardiac CryoAblation Catheter System uses a coolant released into the catheter's balloon to freeze and ablate the tissue; freezing helps the balloon to maintain contact with the tissue.

The Arctic Front Cardiac CryoAblation catheter is expected to be the next ablation catheter on the market which is FDA cleared for treatment of atrial fibrillation. In February 2009, Biosense Webster's NaviStar ThermoCool radiofrequency

ablation catheter became the first in the US to be FDA-cleared for the treatment of AF.

April 2010

Carestream Health books seven orders for the DRX-1 system and DRX-Evolution suite

Carestream Health, located in Rochester, NY, reported in April 2010 that it received seven orders from Canadian customers for its wireless cassette-sized Carestream DRX-1 system and Carestream DRX-Evolution suite. At March's European Congress of Radiology (ECR) convention in Vienna, Austria, the company demonstrated the new configurations of its DRX-Evolution line of DR suites.

According to Carestream, the DRX-1 system enables a system to be converted into digital. The DRX-Evolution combines the first wireless cassette-sized digital radiography (DR) detector, the Carestream DRX-1, with a flexible DR system designed to use modular components. This allows hospitals and clinics to design and install a DR suite that meets their unique workflow and budget requirements. Carestream has configured three versions of the DRX-Evolution, based on the level of automation: DRX-Evolution Standard with manual operation; DRX-Evolution Automatic with full-automated operation; or the DRX-Evolution Hybrid Solution, which is mid-priced and combines features of both the Standard and the Automatic.

Alair Bronchial Thermoplasty System receives nod from FDA

Asthmatx Inc. announced in April 2010 that the FDA had cleared the Alair Bronchial Thermoplasty System for use in adults with severe asthma. According to the company, each year asthma accounts for 2 million emergency room visits in the US, and each day, approximately 40,000 unscheduled office visits, 5,000 emergency room visits, and 1,000 hospitalizations occur due to asthma.

The Alair Bronchial Thermoplasty System consists of an expandable electrode array with four 5 mm electrodes that deliver RF energy to airways 3 mm in diameter or larger, distal to the main stem bronchi. The tip of the small diameter Alair catheter expands to contact the walls of the targeted airways, and then thermal energy is delivered to the airway walls to ablate the smooth muscle that narrows the airways in patients with asthma. Asthmatx states that in this catheter-based, minimally-invasive outpatient procedure, the Alair provides long lasting and improved asthma control for adults with severe asthma. Asthmatx is based in Sunnyvale, California.

Medtronic announces intention to acquire ATS Medical for $370 million

In April 2010, Medtronic announced that it was acquiring ATS Medical for approximately $370 million in cash and debt. ATS brings with it a variety of products in the heart valve and surgical cardiac ablation sectors. These include ATS Open Pivot Heart Valve, the 3f Biological Valve, ATS Simulus Annuloplasty Rings and Bands for mitral valve repair, and the CryoMaze Surgical Ablation System family of products. ATS says that the CryoMaze is the only surgical cardiac ablation option that can complete all lesions. This acquisition will strengthen Medtronic's CardioVascular business, which currently accounts for over 15% of Medtronic's revenues. Medtronic CardioVascular reported annual revenues of $2.86 billion for the fiscal year which ended on April 30, 2010.

Olympus and Siemens to collaborate on magnetically guided capsule endoscope (MGCE) system

In April 2010, Olympus Medical Systems Corporation and Siemens Healthcare announced collaboration on the development of an innovative technology for a magnetically guided capsule endoscope (MGCE) system. This technology is intended to allow stomach examinations to be performed easily by having the patient swallow an endoscope in the form of a capsule. According to the companies, the capsule will be about 31 mm long and 11 mm in diameter. The patient would then lie down in a magnetic guidance system, and the physician, using a joystick, would navigate the capsule within the stomach to the areas of interest. Camera systems mounted at both ends of the capsule would allow observation inside the stomach, and real-time images would display in the examination room. The companies have developed a prototype which will be used to test safety and efficacy of this latest development in endoscopy.

Companies mentioned in Synopsis, Issue 3 March/April 2010

Abbott
Accuray
Ache Pharmaceuticals
Alizyme Therapeutics
Amylin Pharmaceuticals
Arena Pharmaceuticals
Asthmatx
AstraZeneca
BaroSense
Barrx Medical
Biosense Webster
Carestream Health
C2 Therapeutics
Eli Lilly
EMS
Ethicon EndoSurgery
Glaxo SmithKline
Mederi Therapeutics
Medley
Medtronic
NeuroSearch
NiTi Surgical Solutions
Novartis
Novo Nordisk
Nycomed
Olympus Medical Systems
Orexigen Therapeutics
Pfizer
ReShape Medical
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Siemens Healthcare
Takeda Pharmaceuticals
Teva Pharmaceuticals
ValenTx Inc.
Vivus
Zydus Cadila

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UK Office:
11 Maldon Rd
Acton
London W3 6SU
UK
Tel: +44 7799-692-620