BIOTECH BULLETIN
FALL 2015

TRACKING THE PULSE OF THE PHILADELPHIA LIFE SCIENCES INDUSTRY

Life Sciences Executive Network at THE SARIAN GROUP

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Stay up to date on the pulse of the Philadelphia Life Sciences industry with our **Biotech Bulletin**. This is a quarterly newsletter, with data and perspectives from local leaders within the industry. Greg Sarian of The Sarian Group at HighTower and Regina Maxwell of Maxwell Research Services, LLC are the co-authors of the Biotech Bulletin. Each issue will include insight on the latest industry trends, performance metrics on local biotech companies as well as current acquisitions and IPO news in this area.

505(B)(2): A SPEEDY, LOW-COST, REWARDING APPROVAL PATHWAY

by Regina Maxwell, MLIS, Principal, Maxell Research Services

Of the three regulatory pathways to gain new drug approval, that is:

1. 505(b)(1) – Traditional NDA for pioneer products
2. 505(b)(2) – Streamlined approval process for new products with same active moiety as previously approved drug (i.e. a reference listed drug – RLD)
3. 505(j) – Abbreviated new drug application (ANDA) (i.e. generic form of an RLD)

The 505(b)(2) pathway has proven to be an increasingly attractive option since it was passed into existence with the Hatch-Waxman Amendment in 1984. And over the past five years 505(b)(2) approvals have steadily and significantly outpaced those for traditional NDAs.[1]

There are a number of features that make the 505(b)(2) application process alluring to drug developers, not the least of which are lower costs for development, expedited timelines to approval, and the protection of several years of market exclusivity.

Drugs that qualify for the 505(b)(2) application process are typically innovative variations of previously approved drugs containing the same active moiety. Among the types of innovations that may qualify for this pathway are:

- Proven pediatric safety and effectiveness for formerly adult-only approval
- Alternative formulations or new dosage strengths deemed bioequivalent to the RLD
- Modified release formulations
- Different doses, regimens or dosage forms

They're not generics, and they're not completely new. This means that while the differences from the RLD need to be supported with the sponsor's clinical data for safety and effectiveness (often in as few as a single clinical trial), the fuller safety and efficacy profile of the underlying drug can be submitted from investigations not conducted by the sponsor and "with no right of reference."

[1] Jill Orens, "2014 505(b)(2) NDA Approvals," The 505(b)(2) Blog, January 17, 2015, http://blog.camargopharma.com/index.php/2015/01/17/2014-505b2-nda-approvals/.

505(B)(2): A SPEEDY, LOW-COST, REWARDING APPROVAL PATHWAY (CONT.D)

These data are derived from:

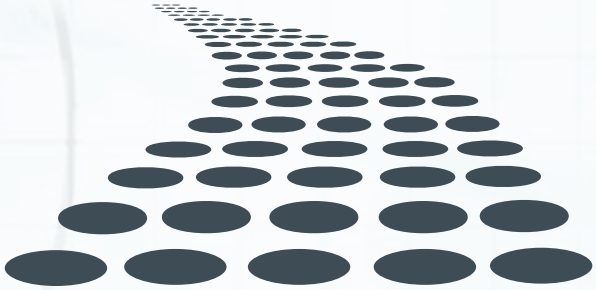
- Public scientific data from the reference-listed drug
- Previous NDA approvals
- A comprehensive review of the published medical literature

The ability to rely on a well-established safety and efficacy profile as a significant part of the submission can save a drug developer untold amounts of time and cash.

In addition to these savings, Hatch-Waxman provides another extremely attractive advantage for some 505(b)(2) approvals: market exclusivity. Depending on the extent of the differences between the 505(b)(2) drug vs. the reference-listed drug, an approval can (though not always) bring along with it three, five or even seven years of market exclusivity. This can be extended, in some cases, for six months with pediatric studies. Unlike a patent, which can be challenged and found invalid, exclusivity cannot be taken away and the term only begins upon approval.

The 505(b)(2) pathway is not available for every follow-on NDA (see here for *Guidance for Industry: Applications Covered by Section 505(b)(2)*). For this reason it is critically important to establish a dialogue early on with the FDA to determine if 505(b)(2) is a suitable path. But for smaller companies with limited resources and promising innovations on existing drugs, the rewards can be rapid, reasonably-won, and lasting.

Regina Maxwell is Principal of Maxwell Research Services, a full-service information research firm specializing in research for start-ups, and small to mid-size biotech firms. You can reach her at regina@maxwellresearchservices.com or through the company website at http://www.maxwellresearchservices.com.



A RECOMMENDED APPROACH TO LEASING SPACE FOR YOUR HIGH-TECH OPERATIONS

by Christopher R. DiPaolo, President and Founder of PROTECS

Locating your company operations to a new site is always an exciting time for an organization. Whether you are just starting your company, have grown out of your old space, or your lease is up and you want an upgrade in appearance and company image, you should plan ahead and strategically approach this project as you would any other. Too many times in my 25+ year career, I have seen companies wait too long to begin the site selection process. They will try to do it on their own, with internal resources and without the use of a real estate broker, thinking they will get a better deal in the market. They may also know a friend who owns or knows someone who owns a building and just start looking at properties, not really knowing the amount of space their operations require initially and to allow for growth over the term of the lease. I would like you to consider the following recommendations before you lease space:

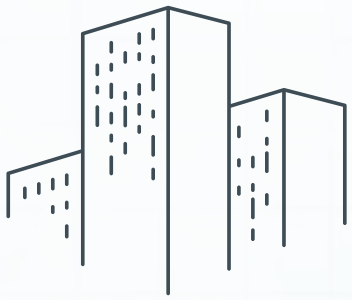
1 **IDENTIFY YOUR PROGRAM SQUARE FOOTAGE**

Hire a design/build professional to assess your current operations and perform a preliminary master plan for your future space. This will provide you with an exact program of required space (SF) and identify all required support systems with preliminary utility service capacities. The cost for these upfront services is very minimal compared to paying for more square footage than necessary over a three, five or ten year period, and all associated costs by not allowing for continuous expansion/growth and not having the required electrical and mechanical utility services to support your operations that require upgrades after the fact.

A RECOMMENDED APPROACH TO LEASING SPACE FOR YOUR HIGH-TECH OPERATIONS (CONT.D)

2 **HIRE A REAL ESTATE BROKER**

In parallel with Step 1, interview several real estate brokerage firms and identify a seasoned professional that is knowledgeable in high-tech operations and facilities. Be sure to hire a firm that is clearly representing you exclusively and not any developers/landlords of the properties you are considering, to avoid a conflict of interest. The broker's interest is more aligned with the landlord since he can do multiple deals with them and only one with you every 5-10 years. Every lease proposal considers paying a brokerage fee and is included in the basis of the market lease rate, so you are paying for it regardless. By not using a broker, you may end up paying a higher lease rate by not having their advice and negotiating experience.



3 **PERFORM AN EFFICIENT ASSESSMENT OF REAL ESTATE PROPERTIES**

Based on the information developed in Step 1, you have now armed your real estate broker with precise SF required for your occupancy along with the required electrical service, domestic water, sanitary and zoning for allowed use and parking. All of this information in conjunction with identifying a geographic radius significantly narrows down and pre-qualifies the number of potential sites, thereby making the site selection process very efficient for everyone.

4 **TEST-FITTING YOUR PROGRAM INTO PROPERTIES**

Once you have narrowed your search to three sites, the best way to get an apples to apples comparison is to take the information gathered in Step 1 and pressure test each site with your program requirements (Note: Most landlords will pay 10 to 15 cents/SF for test-fitting services). Also, by using a design/build professional you will get cost estimates for each building site under consideration that will provide you with the overall cost delta to set up your operations between each site based on leveraging existing conditions and infrastructure at each site. This all plays into making the correct financial determination for a lease agreement. You can get a great lease rate at one site, requiring demolition and rebuild, thus increasing your upfront capital costs, or you can get a higher lease rate at another that has existing office space and labs that can be repurposed for your use and reduce your capital costs but require higher long term leasing costs.

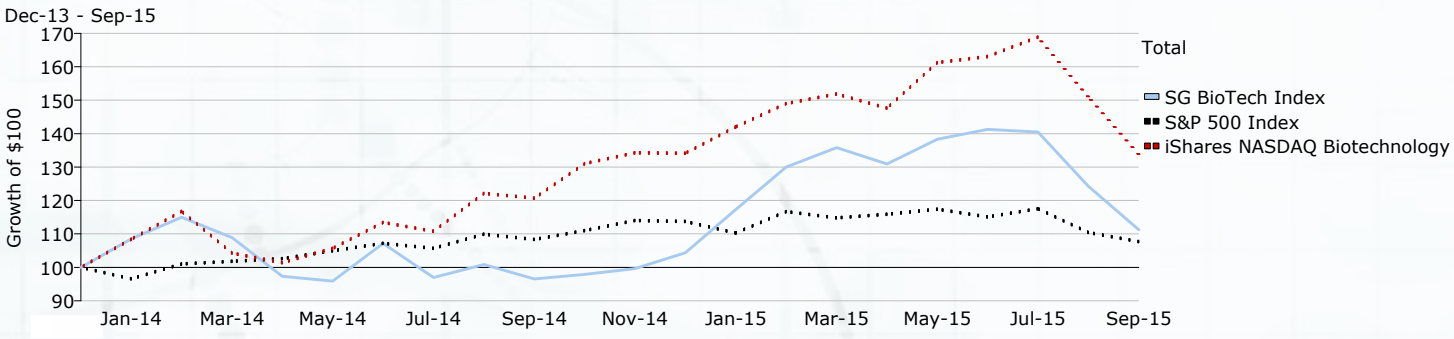
Choosing a site to locate your company is a very complicated and important decision. I highly recommend that you engage key professionals to assist you with this process to achieve an outcome that meets all of your strategic objectives.

THE PLANNING PRESCRIPTION: FRONT END LOADING A 529 ACCOUNT

For those of you who have school age children or grandchildren, you are aware of the income tax-free growth offered by a 529 Plan if the funds are used for higher education. You may not be aware that 2015 IRS rules allow for other benefits that may be useful in the year of a company transaction. The 529 allows up to five years of funding in one year without incurring a federal gift tax. So each spouse in a married couple can give $14,000 x 2= $28,000 to a 529 account up to $140,000. You can also receive a current year state income tax deduction of up to $14,000 per beneficiary. If a couple files a joint tax return, the allowable deduction is doubled to $28,000 as long as both spouses have earned income of $14,000. This can provide a current year tax benefit beyond the tax free compounding.

THE SARIAN GROUP INDEX

The Sarian Group Index started in January 2013 to track regionally located HealthCare oriented businesses whose stock is traded above $1 a share against the S&P 500 and the NASDAQ Biotechnology index. It is an equally weighted index of publicly traded life sciences companies headquartered in PA, NJ and DE and is rebalanced monthly. Below is a look at the performance pattern since December 2013 along with a list of the companies that are currently included. Also listed are the Top Ten Companies who have had the largest gains and losses YTD within the index.



PORTFOLIO HOLDINGS

Adaptimmune Therapeutics PLC	Alcobra Ltd	Advaxis Inc	Aerie Pharmaceuticals Inc
Agile Therapeutics Inc	Akers Biosciences Inc	Alliqua BioMedical Inc	Amicus Therapeutics Inc
Cancer Genetics Inc	Celator Pharmaceuticals Inc	Celgene Corp	Cyclacel Pharmaceuticals Inc
Discovery Laboratories Inc	Eagle Pharmaceuticals Inc	Echo Therapeutics Inc	Egalet Corp
Endo International PLC	Enzon Pharmaceuticals Inc	Fibrocell Science Inc	GlaxoSmithKline PLC
Globus Medical Inc	Immunomedics Inc	Incyte Corp	Inovio Pharmaceuticals Inc
Insmed Inc	Johnson & Johnson	Lannett Co Inc	Medgenics Inc
The Medicines Company	Merck & Co Inc	Mylan NV	Onconova Therapeutics Inc
Ophthotech Corp	Pacira Pharmaceuticals Inc	PhotoMedex Inc	ProPhase Labs Inc
PTC Therapeutics Inc	Tobira Therapeutics Inc	Recro Pharma Inc	Safeguard Scientifics Inc
Spark Therapeutics Inc	TetraLogic Pharmaceuticals Corporation	Vitae Pharmaceuticals Inc	Zynerba Pharmeceuticals Inc
Active Control Technology Inc	Auxilium Pharmaceuticals Inc	NPS Pharmaceuticals Inc	

TOP TEN GAINERS —YTD 9/30/2015

Eagle Pharmaceuticals Inc	377.61%
Recro Pharma Inc	320.63%
Egalet Corp	131.63%
Amicus Therapeutics Inc	68.15%
Alcobra Ltd	61.93%
Medgenics Inc	54.55%
Incyte Corp Ltd	50.91%
Fibrocell Science Inc	48.65%
The Medicines Company	37.19%
Advaxis Inc	27.72%

TOP TEN DECLINERS — YTD 9/30/2015

Discovery Laboratories Inc	-74.14%
PhotoMedex Inc	-66.01%
Immunomedics Inc	-64.17%
TetraLogic Pharmaceuticals Corporation	-61.62%
Onconova Therapeutics Inc	-58.66%
Pacira Pharmaceuticals Inc	-53.64%
PTC Therapeutics Inc	-48.43%
Alliqua Inc	-40.19%
Aerie Pharmaceuticals Inc	-39.23%
Inovio Pharmaceuticals Inc	-37.04%

CAN RULE 506(C) RAISE THE EARLY STAGE COMPANIES OUT OF THE "VALLEY OF DEATH?"

by CEO Frank Leu, Ph.D., Novapeutics

Let me preface here that I am not an attorney, accountant, or expert who specializes in the Jumpstart Our Business Startups (JOBS) Act, Title II, Rule 506(c) Raise (506 (c)) – which is an accredited investor investment rule that went into effect on September 23, 2013, one and a half years after the JOBS Act was first signed into effect. My perspective is strictly from the early stage company's perspective and reflects my own experience. In order to determine if this is a feasible mechanism for our own fund raising, I have spoken to and am now working with different professional experts in this area exploring what 506(c) could potentially do for our company, and for companies like ours.

To put it all in perspective, a brief introduction to our company, Novapeutics. We are a preclinical biopharma company that is working on a first-in-class cure for diabetes using a small molecule to regenerate insulin producing beta cells. Much like other start-up biotech or pharma companies at this stage of our life cycle, funding is needed to move our technology forward. Although the risk is high, the reward is also tremendous, especially in the diabetes market.

In 2012, the American Diabetes Association estimated that $176 billion was spent in the U.S. for diabetes medical expenses. The Center for Disease Control estimates that one in three people born after the year 2000 will eventually develop diabetes, declaring diabetes to be an epidemic. According to the International Diabetes Federation, in just a few years, one-half of a billion people world-wide will be afflicted with this disease. Since drug development has the potential to displace many current therapeutics and will effectively address current treatments, and inadequacies such as effectively controling the blood-glucose level fluctuation that too often leads to many diabetes related complications (i.e., neuropathy, blindness, kidney failure, stoke and etc.). Every single milestone achieved during our drug development could mean hundred folds of increase in our valuation. This is especially true today with the large pharmas re-appropriating capital and externalizing their R&D by acquiring, partnering, or investing through their corporate ventures in the early stage companies. Early stage companies are becoming more valuable and investable.

If early stage companies cannot find funding they would be considered in the "Valley of Death" stage. As for the shrewd (and the lucky) investors, the reward for entering at this stage can be tremendously rewarding if one is able to pick a successful company. Because of the high risk, most investing groups are reluctant to take this plunge, and consequently missing the opportunity to participate in some of the most exciting and cutting edge technologies. A potential game changer for this problem is 506(c), which is an accredited investor crowd funding mechanism that allows general solicitation that could actually work and provide funding needed for early stage biotech or pharma, thus transforming the early investment landscape for the better. Most importantly, the size of this accredited investors market appears to be massive. In 2010, SEC estimated that at least 8.7 million U.S. households qualified as an accredited investor. Wefunder.com reports that only 3% of the 8 million accredited investors are active, while investing a combined $21 billion dollars each year. There is a real potential for the rest of the 97% of the investors standing on the sidelines to invest close to $700 billion, and if the current investment participation doubles from 3% to 6%, an additional $21 billion might enter into the investments.

The article by Dennis Ford and Barbara Nelsen, "The view beyond venture capital", published in the Bioentrepreneur in December 2013, reported that almost all types of funding sources; such as angels, venture capitals, large pharma companies and corporate ventures etc., all claimed they engage in early stage companies as investments. However, upon a closer examination, the venture capitalits seldom engage investments in the early stage companies. This is not a surprise, since it is commonly expected that traditional funding mechanisms are risk averse. Perhaps that the creation of the 506(c) can help to solve this problem by allowing accredited investors to take smaller stakes in the early stage companies, and thus spreading risk evenly and thinly, leveling the playing field for everyone. This makes 506(c) an investment mechanism that is more risk tolerable, attractive and with less friction for all types of accredited investors. Traditionally, foundation money, venture capital and/or angel investors would be the typical accredited capital investment that can potentially lift the company out of the "Valley of Death". There are more companies looking for money than investors, traditional funding sources have always been conservative and prefer to invest in later stage companies. It is highly probable that the 506(c) raise mechanism will not only provide the capital that many early stage companies need, but it will also push other funding sources to look closely and compete for early stage companies.

In summary, although 506(c) has the potential to be a positive disruptive funding mechanism for early stage companies, its adaptation thus far has been gradual. Perhaps with time, and with increasing acceptance and awareness, its adaptation would eventually accelerate. After a few months of working with HealthiosXchange (HealthiosXchange.com - a broker dealer with a website interface that powers this ecosystem), Pennovation Center Ventures, and Connie Kenneally (expert in C level leaders and 506(c)) on our 506(c) raise, it appears that the traditional funding sources are also browsing for opportunities on these websites, while limited numbers of accredited individual investors are active. This is probably not a big surprise for anyone. In conclusion, to answer the question posed in the title would be that in time, I strongly believe the 506(c) will make a positive impact on many early stage companies, and help to accelerate many exciting technologies and innovative medicines to the market that would otherwise once perish in the 'Valley of Death". Provided that many exciting start-ups and early stage companies have been created in the Philadelphia area in the past few years, 506(c) will inevitably help to create more jobs and benefiting people our area as the JOBS Act originally intended to do.

PHILLY FUNDINGS

RECO PHARMA

Malvern – The specialty pharmaceutical company, which is focused on developing non-opioid pain relief medicines, raised $16 million in a private stock placement. Reco sold slightly under 1.4 million shares of common stock, at $11.60 per share, to a group of institutional investors.

ZYNERBA PHARMACEUTICALS

Devon – The developer of synthetic cannabinoid therapies closed its initial public stock offering on August 5th at an initial IPO price of $14. Zynerba said underwriters exercised their options to purchase an additional 450,000 shares of common stock to cover overallotments, resulting in gross proceeds from the stock offering of $48.3 million.

MEDGENICS INC.

Wayne - Medgenics Inc. entered into a $2 million deal on Wednesday, September 9th to acquire NueroFix Therapeutics, a company founded by the leader of Children's Hospital of Philadelphia's Center for Applied Genomics. The purchase comes nearly a year after the gene therapy company entered into a $5 million research collaboration with CHOP.

ACLARIS THERAPEUTICS INC.

Malvern - One of three Philadelphia-area life sciences seeking to go public, competed a $40 million series C venture capital financing. The financing was led by RA Capital Management, Cormorant Asset Management, Rock Springs Capital Management, Aperture Venture Partners and Mossrock Capital. Founded in 2012, Aclaris is attempting to develop new treatments for skin disorders.

TREVENA INC.

King of Prussia - Trevena Inc. took in $72.9 million from its previously announced public stock sale, an amount that topped what the Montgomery County biopharmaceutical company raised when it went public early last year. The King of Prussia, Pa., company sold just under 7.5 million shares of common stock, including 975,000 shares sold by underwriters exercise the full option to purchase additional shares to cover over-allotments, at $9.75.

REGENXBIO

UPENN/Rockville, MD - A gene therapy company spun out of the University of Pennsylvania became public in a $138.6 million IPO. Regenxbio Inc. was founded in 2009 through a collaboration of Penn, through its Center for Innovation; Penn professor Dr. James M. Wilson, director of the university's gene therapy program; and FoxKiser, a Washington, D.C.-based pharmaceutical and biotechnology consulting firm. Based in Rockville, Md., RegenxBio has its research operations based at Wilson's lab on the Penn campus in Philadelphia. The company sold 6.3 million shares of common stock at $22 per share. If underwriters exercise their option to purchase an additional 945,000 shares, the size of the IPO will swell to $159.4 million. Its shares will trade on NASDAQ under the symbol "RGNX."

NABRIVA THERAPEUTICS

King of Prussia - Nabriva Therapeutics went public, raising $92 million through its initial public stock offering. The antibiotics developer is based in Vienna, Austria, and has its U.S. headquarters in King of Prussia. The company sold nine million American depositary shares (ADSs), representing 900,000 of its common shares, at a public offering price of $10.25 per ADS before underwriting discounts. Nabriva has granted the underwriters an option, for a period of 30 days, to purchase up to 1.35 million additional ADSs at the public offering price to cover over-allotments.

SAVE THE DATE: LIFE SCIENCES EXECUTIVE NETWORK 2016 YEAR AHEAD OUTLOOK

Date & Time: Friday, January 29, 2016- Breakfast Meeting
Location: Philadelphia Marriot West, 111 Crawford Ave, West Conshohocken, PA
Topic: 2016 Year Ahead Outlook: Challenges and Opportunities in leading early to mid-stage life sciences companies
Discussion Group Facilitator: Evan Myrianthopoulos, Managing Director of GPB Capital Life Sciences Strategy & Managing Director-Life Sciences Investment Banking practice at Aegis Capital Corp.
Invite Only