Serial medtech entrepreneur Amir Belson provides physicians with innovative tools that enhance patient outcomes in dramatic ways.

When Amir Belson began seeking legal representation for his first medical device company back in 2001, he was met with a cool reception from law firms. “As the founder of an unfunded start-up, it was difficult to get a lawyer to even take a meeting,” Amir says. “Finally, an associate at one firm did sit down with us, but he said that he was going on leave for two months and that he might consider representing us when he came back.”

Luckily, Amir’s mentor Paul Yock, a noted Stanford cardiologist and co-founder of Cardiovascular Imaging Systems, then offered a suggestion: Go talk with Casey McGlynn at Wilson Sonsini Goodrich & Rosati. “At this point, my hopes were not high,” Amir continues. “But Casey said, ‘I’ll come to you.’ We presented him with our idea and at the end, I said, ‘OK, what is your process? How much time will it take your law firm to decide if you’re going to represent us?’ We were astounded when Casey simply said, ‘I’ve decided.’ Since then, WSGR has done the corporate work for all of my companies, as well as a good share of the IP legal work.”

In fact, those other law firms very well might be rueing the day they rebuffed Amir Belson, as he has turned out to be one of the most prolific entrepreneurs in the medical device industry, launching more than a dozen companies in the last 13 years. In addition, he has more than 300 pending and issued patents to his credit. Amir’s inventions encompass a broad range of healthcare-related technologies—from computer-guided colonoscopy instruments to IV insertion devices, radiation shields to noninvasive surgical closures—but all share a common characteristic: providing physicians with innovative tools that enhance patient outcomes in a dramatic way.

Experience Is the Mother of Invention(s)

Most of Amir’s inventions stem from his experiences as a physician. “I knew I wanted to be a doctor since I was about 15 years old,” says the Israeli-born entrepreneur. “I was inspired by the major impact they can have on people’s lives.” He attended Technion-Israel Institute of Technology’s medical school in Haifa, graduating cum laude, and served as a flight surgeon in the Israeli air force for several years. Amir also did a pediatric residency in Israel and then decided to focus on pediatric nephrology, securing a three-year fellowship at Lucile Packard Children’s Hospital at Stanford in 1998.

While at Stanford, two important facts became clear to Amir: As much as he loved pediatrics, nephrology, which deals with chronic pediatric patients, was not for him—but devising better tools to help other doctors treat patients certainly was. “I always liked coming up with new solutions for existing problems, and I kept seeing things during my medical career that made me think, ‘There has to be a better way.’”

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In This Issue

“There Has to Be a Better Way” ....................................Pages 1-3
The Best of Times for Early-Stage Medtech Fundraising – Looking Offshore ................................ Pages 4-6
Life Sciences Venture Financings for WSGR Clients ................................ Pages 7-8
FDA Approval of Risk Evaluation and Mitigation Strategies (REMS): A New Hurdle for Generic Drug Development ................................ Pages 9-12
Recent Life Sciences Client Highlights ................................ Pages 13-15
Upcoming Life Sciences Events .....Page 16

Continued on page 2...
to be a better way to do this,” he recalls. When his pediatric nephrology fellowship ended, he formally began to focus on medical device design, becoming one of the first fellows at Stanford’s pioneering Biodesign Program for entrepreneurial medical and engineering students.

Over the course of the next dozen years, he founded a succession of companies to produce medical devices that would provide caregivers with that “better way.” For example, one of the most common procedures in medicine is the insertion of an intravenous (IV) line to administer medicine and fluids to patients, but despite its ubiquity, the process is difficult to master. “People often are surprised to learn that starting an IV is the procedure with the highest failure rate in medicine,” Amir says, citing studies that show first attempts to insert an IV properly fail approximately 60 percent of the time, a reality that he witnessed repeatedly both in the field as a flight surgeon and in hospitals.

“I knew there had to be a better way to insert a catheter and start an effective line into a vein,” he says. So, in 2005, Amir founded Vascular Pathways. He had come up with the idea of developing a needle containing a coiled-tip NiTi guidewire that helps ensure proper placement the first time around, even in the hands of a less-experienced medical professional. How well does it work? The device, dubbed the AccuCath, proved so successful that Popular Science declared it one of the 10 best inventions of 2009.

The same year, Amir launched ZipLine Medical to tackle another thorny medical issue: traditional wound closure, where a surgeon usually has to choose between sutures, which are difficult to do well and consume expensive time in the operating room, or staples, which can be done much more quickly but leave unattractive, railroad-track-type scars.

Once again, personal experience was his inspiration. “When I was doing my OB/GYN rotation, I often was called upon to assist a doctor during a C-section,” Amir says. “The doctor would deliver a healthy baby, close up the mother’s uterus, declare it a great success, and then leave me to sew up the mom’s skin. And guess who the mother hates five years down the line, when she’s looking at the ugly scar on her abdomen?”

His conviction that there had to be a better way led him to found ZipLine. Amir and his team of engineers developed a novel noninvasive method of closing wounds, in which a force-distribution molded structure embedded in a patch is locked into place to hold the edges of the wound together. The device reduces the tension on the tissue so it heals smoothly, without the buckling and scarring that typically result from both sutures and staples. Aside from the cosmetic benefit and reduced pain, the noninvasive nature of the procedure is designed to reduce the risk of infection, and—critical to the adoption of a medtech device—the tool is easy for a doctor to learn how to use. With all these benefits, it’s no surprise that ZipLine’s Preloc system is enjoying widespread adoption in the marketplace and is currently being sold in 22 countries.

Business Not as Usual

Amir has had to wear many hats in the course of founding more than a dozen companies, and some fit better than others. When asked about the most challenging part of forming a company, his A Quick Tour of Amir Belson’s Companies to Date

- **Neoguide Systems.** Key product: a computer-controlled segmented endoscope that eliminates the looping that causes discomfort and scarring during colonoscopy
- **Vascular Pathways.** Key product: a guidewire-equipped catheter that ensures accurate placement of an IV line the first time around
- **Qool Therapeutics.** Key product: a method of inducing therapeutic hypothermia by employing a frozen mist inhaled by a patient to quickly cool the heart, brain, and core body
- **ZipLine Medical.** Key product: noninvasive wound closure that reduces scarring, pain, and the risk of infection
- **Radguard Medical.** Key product: shields that provide radiation protection during imaging procedures (the company was relocated to Israel in 2014 under the name Radiacton)
- **Emboline.** Key product: a proximal protection device that reduces the risk of blood clots during transcatheter aortic valve implantation (TAVI) and other cardiac procedures
- **VasoStitch.** Key product: improved large-bore vascular access closure for TAVI procedures
- **Modular Surgical.** Key product: a device that allows the introduction and operational use of surgical tools through small incisions
- **OxyVive.** Key product: a mobile hyperbaric chamber for chronic wound care
- **SuperRenal.** Key product: a technology to reduce the risk for contrast nephropathy and improve renal function in patients with chronic renal failure

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“There Has to Be a Better Way”

response is blunt, unequivocal, and immediate: “Fundraising.” He points out that he’s not unique in feeling this way and characterizes fundraising as the biggest single obstacle facing medical device companies these days. “There are great engineering teams available to help inventors develop a product,” he says. “The FDA has become more receptive to feedback and is willing to work with a company on studies and approval. It’s just the ever-present grind of fundraising that makes it all so . . .” He searches for the right word, settling on “horrible.” He concludes: “If it weren’t for the hurdle of incessant fundraising, I am confident that I would have launched many more companies by now.”

In fact, he believes that the investment climate for the entire life sciences field has become more challenging in the past few years. “The life sciences industry is going strong,” Amir says. “We’re coming up with more effective drugs, devices, and services all the time that help people live longer and better. But there are way fewer pools of investors than there used to be, and the ones that still are interested in life sciences tend to concentrate more on services, IT, and pharma—not so much medical devices.”

To counter this problem, Amir learned early on to delay looking for venture capital money until a company’s later stages, after it had a chance to demonstrate proof of concept and hit certain benchmarks that would make it seem less risky to investors. Instead, for early-stage funding, he typically turns to a consortium of individual investors, design-engineering houses, and original equipment manufacturers (OEMs) with whom he has developed a solid reputation and track record. “The key is that I bring them on as partners in the new company,” Amir says. “That gives them an incentive to be successful—the company becomes their baby as well.”

Recently, he also has been exploring opportunities in other countries where “the governments are more supportive of healthcare start-ups and are willing to help out with incentives such as reduced taxes and grants,” citing Israel, Singapore, China, and Ireland as examples.

Along with his distaste for fundraising, Amir never developed an appetite for running a business. “Being a CEO just is not a good fit for what I know and what I can do,” he says. “It takes a certain skill set to drive a business, and I don’t have those skills.” Indeed, his observations over the years have convinced him that “in most cases, founders who won’t let go usually are making a big mistake. At a certain point, they need to give it to the right people who can take the business forward and make it work.”

Just who those “right people” are depends on the stage of the business, Amir says. “At a fledgling company, you need someone who is a good salesman—and that’s not me. At the R&D stage, you need somebody who knows the right way to build and document things—and that’s not me. Now, managing IP? That is where I think I can add value, coming up with the original idea and continuing to innovate and refine it, working with the engineers and programmers who actually will build the product and the management team that will effectively run the business.”

Invention in the Genes

With so many companies and ideas on his hands, relaxation seems like an alien notion to Amir, but he clearly takes great delight in the time he is able to spend with his family. His wife, Tamar, was a civil engineer in Israel, but largely devoted herself to raising their four sons after the family moved to the United States in 1998. She also is an accomplished multimedia artist who teaches painting to young patients in children’s hospitals. With an engineer mother and a physician-inventor father, the boys haven’t fallen far from the family tree: Eyvatar, 23, earned his undergraduate and master’s degrees in mechanical engineering at Cornell and now works for Exxon Mobile in Houston. Itamar, 20, is a third-year computer science student at the Massachusetts Institute of Technology (MIT) in Boston, while Ori, 18, is a senior in high school, facing the stressful task of applying to colleges and deciding whether he wants to be a physician or an engineer. “They all are inventive,” Amir notes, but he points to his youngest son, 12-year-old Aran, as the one who showed glimmers of the inventor gene at the youngest age. “He doesn’t say, ’Dad, I have an idea,’” Amir says. “He says, ’Dad, I have a patent.’ And I must say, some of his ‘patents’ really are amazingly creative.”

Seems as if Amir might face stiff competition at some future date as one of medtech’s most prolific entrepreneurs—a prospect that he seems to relish.
The Best of Times for Early-Stage Medtech Fundraising – Looking Offshore

By Elton Satusky, Partner (Palo Alto)

Raising early-stage capital for innovative medical device ventures has been a difficult slog over the past few years. In the wake of the constrained capital environment and the ensuing headwinds facing U.S.-based medical device companies, such as the medical device tax, cost pressures, and related reductions in reimbursement, as well as the unpredictability of regulatory pathways and timelines, medtech start-ups have needed to bootstrap ideas far down the path before obtaining funds, be extremely capital efficient, be able to make big progress on small dollars, and be extraordinarily creative in their fundraising approaches. We have been very fortunate here at Wilson Sonsini Goodrich & Rosati to have been involved with many of these creative companies and have gained unique insight into where the market is going. One creative fundraising approach is looking beyond Sand Hill Road for capital—and in fact beyond California, even beyond the United States. Fundraising, especially for earlier-stage medical device companies, previously was a key differentiator for the medical device ecosystem in Silicon Valley. However, we can safely say that this is no longer the case.

Partnering with our medtech client base in 2014, we have helped to close financings with partners and investors from all over the world, including the European Union, Japan, China, Singapore, Australia, and other jurisdictions. Though it may be obvious, what one needs to do to obtain offshore funds will differ from country to country and from investor to investor, even within a country. However, we have observed a number of repetitive themes in these transactions.

The first is that one needs a well-thought-out corporate and fundraising roadmap, which typically includes an additional business purpose beyond just raising capital in the foreign jurisdiction. Our clients have moved some or all of their business offshore, have R&D centers, have international jurisdiction sales bases (such as Singapore for the rest of Asia and Ireland for the rest of the European Union), assign and create intellectual property, hire employees, enter into distribution arrangements, contract with outsourced manufacturing, conduct clinical trials, and/or obtain government support (both financial and otherwise) in these far-flung locations. Eitan Konstantino, CEO of QT Vascular (see the below discussion on QT Vascular’s initial public offering on the Singapore Stock Exchange), said the following of his experience in Singapore: “If a company is looking to raise funds internationally, a key will be a long-term strategic plan, coupled with a long-term effort building networks of investors, corporate partners, bankers, promoters, governmental and regulatory personnel, lawyers, and other players operating in a typical medtech ecosystem. One trip by management to the foreign jurisdiction will not show commitment; it may take a couple of years with regular in-person visits before one might see the fruits of their labor.”

An additional business purpose validates a company’s commitment to the jurisdiction and helps to complete the financing transaction, as it’s often related to the larger purpose of fostering a healthy medtech ecosystem in the country.

Another interesting and related theme is governmental assistance. We are accustomed to starting, funding, and bringing companies along through their life cycles in Silicon Valley with little or no government assistance. This is not the case in places like Ireland, Japan, Singapore, and elsewhere. Partnering with government initiatives can, at minimum, bring credibility and, in most cases, actually bring funds. For example, Singapore’s Economic Development Board (EDBI) has grant programs for companies that bring operations to and spend money in Singapore. In addition, EDBI has a venture arm, Bio*One, that invests in U.S.-based companies with no conditions regarding the jurisdictions in which the money must be spent. Meanwhile, the Irish government’s Enterprise Ireland is a powerful ally when you want to take your project to Ireland and have been actively investing as a
limited partner in venture funds such as Lightstone Ventures and offering incentives to set up manufacturing in the country. Similarly, Australia has an R&D tax credit program that our clients have used to get up to a 40 percent rebate for funds spent in Australia, including for things like clinical trials.

Japan is another jurisdiction where we are seeing a lot of activity. People like Allan Johnston of Synergy Partners have been helping companies with their Japanese commercialization and financing strategies for nearly 20 years. There is also a Japanese government initiative started within the last two years with a stated goal of fostering a medtech start-up ecosystem in Japan—and there are substantial funds set aside to achieve this goal. Japan is obviously a significant market for medical devices, but a large percentage of medical devices sold in Japan are not produced domestically. The government initiative, which is designed to address this issue, has resulted in investments and will likely lead to more acquisitions of U.S.-based medical device companies by larger Japanese players. Japanese distributors are eager to strike deals and will do so in connection with medtech start-up investments. Century Medical, a division of Itochu Corporation, has been active in this regard.

We are also seeing a trend of Japanese corporate partners investing in preferred stock financings to obtain a front-row seat to witness the development of new technologies and gain the inside track to acquire the companies. Further, a number of large Japanese corporates, including Terumo and Development Bank of Japan, are limited partner investors in Thomas Fogarty’s Emergent Medical Partners. Playing to the technology strength inherent in Japan has been a common theme; an example of this would be utilizing Japan’s expertise in robotics and applying it to medical devices. The takeaway is that certain medical device subsectors may be well received in one offshore jurisdiction, but not appropriate in another, and therefore the choice of technologies and indications one pursues in a particular country must be thoroughly analyzed before embarking upon a long, multi-year process.

As previously mentioned, one innovative deal that we were involved in was QT Vascular’s initial public offering on the Singapore Stock Exchange, which raised approximately US$40 million and closed in April of this year (http://infoguh.sgx.com/FileOpen/PlacementResults.ashx?App=Announcement&FileID=293386). QT Vascular was the first U.S.-based medtech company to go public on the Singapore Stock Exchange. It is also a good example of the items discussed above with respect to government partnerships, operations in the funding jurisdiction, and global commitment to Asian growth.

Recent foreign investment deals completed by WSGR medtech clients include the following:

- Spirometrix $5 million Series B investment from Japan’s NGK Spark Plug Co. Ltd. (http://spirometrix.com/pages/press.html)
- Zipline Medical $5.7 million extension to its Series C financing led by China Materialia LLC, a Shanghai, China-based venture capital company (http://venturebeat.com/2014/10/20/zipline-medical-closes-5-7-million-extension-to-its-series-c-financing-led-by-new-investor-china-materialia/)
- Serene Medical $3.2 million investment led by Australia’s MH Carnegie (http://m.theaustralian.com.au/business/m-injection-for-skin-device/story-e6fro8zx-1227073203354?nk=2bd41c2ebe46625182c50980e702167)

The choice of technologies and indications one pursues in a particular country must be thoroughly analyzed before embarking upon a long, multi-year process.

QT Vascular’s IPO on the Singapore Stock Exchange is a good example of the items discussed here with respect to government partnerships, operations in the funding jurisdiction, and global commitment to Asian growth.

- Zipline Medical $5.7 million extension to its Series C financing led by China Materialia LLC, a Shanghai, China-based venture capital company (http://venturebeat.com/2014/10/20/zipline-medical-closes-5-7-million-extension-to-its-series-c-financing-led-by-new-investor-china-materialia/)

Continued on page 6...
The Best of Times for Early-Stage Medtech Fundraising – Looking Offshore

Continued from page 5...

- EchoPixel $2.35 million Series Seed financing co-led by Chile’s Aurus Ventures (http://ir.hhvc.com/releasedetail.cfm?ReleaseID=804095)
- PneumRx $33 million investment co-led by European venture capital firms Forbion Capital Partners and Endeavour Vision (http://www.pneumrx.com/2011/01/04/pneumrx-inc-raises-33-million-in-capital/)
- Mirmamar Labs $10 million Series D financing that included Russian venture capital firm Rusnano MedInvest (http://miradry.com/press-releases-series-d-funding/)
- Shockwave Medical $12.5 million Series A financing led by France’s Sofinnova Partners (http://www.sofinnova.fr/?p=7182)
- Ophthalmic tools company approximately $2.5 million investment from a Japanese corporate partner
- Women’s health company approximately $7 million investment from Chinese venture investors

If you’re on the board of directors or in senior management at a medtech company, you would be failing to fulfill your duties if you did not at least explore offshore fundraising avenues

- RefleXion Medical $11.6 million Series A financing led by France’s Sofinnova Partners (http://www.sofinnova.fr/?p=7317)
- Aerin Medical $4.5 million note financing by the National Research Foundation of Singapore
- Cephea Valve Technologies Series A investment from Italian private angel investors (http://cepha.com/)

We believe the trend of raising funds from offshore will continue. Hank Plain of Lightstone Ventures had the following insight: “It’s a confluence of the disincentives in the United States, including the constrained access to capital, combined with the meaningful incentives in these offshore jurisdictions, that has led medtech entrepreneurs and companies to look offshore in increasingly growing numbers.” Is offshore fundraising for every company? Probably not. But if you’re on the board of directors or in senior management at a medtech company, you would be failing to fulfill your duties if you did not at least explore these offshore fundraising avenues.

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Life Sciences Venture Financings for WSGR Clients

By Scott Murano, Partner (Palo Alto)

The table below includes data from life sciences transactions in which Wilson Sonsini Goodrich & Rosati clients participated in the second half of 2013 and the first half of 2014. Specifically, the table compares—by industry segment—the number of closings, total amount raised, and average amount raised per closing across the second half of 2013 and the first half of 2014.

The data generally demonstrates that venture financing activity increased during the first half of 2014 compared to the second half of 2013 with respect to total amount raised and number of closings. Specifically, medical devices and equipment experienced an increase both in total amount raised and number of closings from the second half of 2013 to the first half of 2014. Specifically, medical devices and equipment increased 95.4 percent in total amount raised, from $181.42 million to $354.42 million, and increased 44.7 percent in total number of closings, from 38 closings to 55 closings. The industry segment with the second-largest number of closings—biopharmaceuticals—also experienced an increase in total amount raised and number of closings from the second half of 2013 to the first half of 2014. Specifically, biopharmaceuticals increased 96.4 percent in total amount raised, from $102.43 million to $201.20 million, and increased 77.8 percent in total number of closings, from 9 closings to 16 closings.

The data generally demonstrates that venture financing activity increased during the first half of 2014 compared to the second half of 2013 with respect to total amount raised and number of closings of 2014. Specifically, medical devices and equipment increased 95.4 percent in total amount raised, from $181.42 million to $354.42 million, and increased 44.7 percent in total number of closings, from 38 closings to 55 closings. The industry segment with the second-largest number of closings—biopharmaceuticals—also experienced an increase in total amount raised and number of closings from the second half of 2013 to the first half of 2014. Specifically, biopharmaceuticals increased 96.4 percent in total amount raised, from $102.43 million to $201.20 million, and increased 77.8 percent in total number of closings, from 9 closings to 16 closings.

Only two industry segments experienced a decline in number of closings; however, they also saw an increase in total amount raised. Specifically, genomics experienced a 25 percent decline in number of closings, from four to three, but a 176.7 percent increase in total amount raised, from $11.53 million to $31.90 million. Similarly, healthcare services experienced a 50 percent decline in number of closings, from four to two, but a 21.3 percent increase in total amount raised.
increase in total amount raised, from $107.66 million to $130.54 million.

In addition, our data suggests that Series A financing activity compared to Series B and later-stage equity financings, bridge financings, and recapitalization financings increased during the first half of 2014 compared to the second half of 2013. Specifically, the number of Series A closings as a percentage of all closings increased from 30.6 percent to 35.2 percent. Similarly, Series C and later-stage financing activity compared to Series A, Series B, bridge financings, and recapitalization financings increased during the first half of 2014; the number of Series C and later-stage closings as a percentage of all closings increased from 11.3 percent to 18.2 percent. On the other hand, our data shows that Series B and bridge financing activity decreased during the first half of 2014: the number of Series B closings as a percentage of all closings decreased from 25.8 percent to 19.3 percent, the number of Series C and later-stage financings decreased from 14.5 percent to 11.3 percent, and the number of bridge financings decreased from 29 percent to 18.2 percent.

Pre-money valuations for mid- and later-stage life sciences companies increased significantly during the first half of 2014 compared to the second half of 2013. The average pre-money valuation for Series B financings increased by 9.2 percent, from $31.64 million to $34.55 million, and the average pre-money valuation for Series C and later-stage financings increased by 25 percent, from $126.23 million to $157.84 million. Bucking the upward trend were pre-money valuations for early-stage life science companies, as the average pre-money valuation for Series A financings decreased by 17 percent, from $12.97 million to $10.76 million.

Other data taken from transactions in which all firm clients participated in the second half of 2013 and the first half of 2014 did not change with respect to life sciences.

Access to capital improved dramatically during the first half of 2014—a welcome and refreshing change to what many entrepreneurs had come to view as a difficult, even impossible, fundraising environment.

Specifically, life sciences continues to be an attractive industry for investment among our clients, representing 20 percent of total funds raised—second only to the software industry, which represents 26 percent of total funds raised. Software and life sciences continue to dominate other industries with respect to total funds raised; the third- and fourth-most attractive industries, media and information services and services, each represented only 11 percent of total funds raised during the first half of 2014.

Overall, the data suggests that access to venture capital for life sciences companies may have turned the corner. Access to capital improved dramatically during the first half of 2014—a welcome and refreshing change to what many entrepreneurs had come to view as a difficult, even impossible, fundraising environment. It remains too early to tell whether the industry is completely out of the woods, but robust, industry-wide M&A activity, coupled with the sustained viability of the capital markets for life sciences IPOs, could be setting the stage for a continued—if not growing—appetite among investors for life sciences investment opportunities.

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Dow Jones VentureSource Ranks WSGR No. 1 for Q1-Q3 2014 Venture Financings

Dow Jones VentureSource recently ranked Wilson Sonsini Goodrich & Rosati as the top law firm for U.S. venture financings during the first three quarters of 2014. Specifically, VentureSource’s legal rankings for Q1-Q3 2014 issuer-side venture financing deals placed WSGR ahead of all other firms by the total number of rounds of equity financing raised on behalf of clients. The firm is credited as legal advisor in 204 rounds of financing, while its nearest competitor advised on 141 rounds of equity financing. Of particular interest to The Life Sciences Report, VentureSource ranked Wilson Sonsini Goodrich & Rosati first for issuer-side U.S. deals in the healthcare and medical devices and equipment industries.
FDA Approval of Risk Evaluation and Mitigation Strategies (REMS): A New Hurdle for Generic Drug Development

By David Hoffmeister, Partner (Palo Alto); Vern Norviel, Partner (San Francisco and San Diego); Doug Carsten, Partner (San Diego); Prashant Girinath, Patent Agent (Washington, D.C.); and Charles Andres, Associate (Washington, D.C.)

Generic pharmaceutical companies have always faced technical, regulatory, and legal hurdles in bringing a generic drug to market in the United States. Technical hurdles include evaluating and selecting the appropriate dosage form, formulation, and manufacturer of the generic drug. Regulatory hurdles include developing the required data to demonstrate that the generic drug is bioequivalent to the branded or “reference-listed” drug, preparing and submitting an abbreviated new drug application (ANDA) to the U.S. Food and Drug Administration (FDA), waiting out the expiration of market and data exclusivities, and gaining FDA approval. Legal hurdles can include obtaining legal and technical opinions to support submitting paragraph (IV) certification letters to brand manufacturers necessary to secure marketing exclusivity, and prevailing in a Hatch-Waxman litigation or post-grant proceeding.

In addition to the above hurdles, branded pharmaceutical manufacturers develop and employ effective life cycle management strategies to attempt to block, delay, or blunt generic drug market entry. These additional hurdles include citizen petitions filed with the FDA (e.g., raising purported regulatory, safety, or scientific issues associated with the generic drug candidate); the branded manufacturer obtaining and listing new patents in the Orange Book while the ANDA is pending, thereby requiring new certifications by the ANDA applicant; and product hopping, where the branded manufacturer attempts to switch patients to a modified form of the branded medicine (e.g., an extended release, once-a-day dosage form) for which the generic is not substitutable.

Although the challenges of bringing a generic drug to market are significant, the 2007 FDA Amendments Act to the Federal Food, Drug, and Cosmetic Act (FDAAA) created yet another significant hurdle that many generic manufacturers need to overcome in their efforts to obtain regulatory approval for their drugs. Specifically, the FDAAA authorizes the FDA to require a branded manufacturer to develop and implement a Risk Evaluation and Mitigation Strategies (REMS) program for a drug that poses known and potential safety risks.

The FDAAA authorizes the FDA to require a branded manufacturer to develop and implement a Risk Evaluation and Mitigation Strategies (REMS) program for a drug that poses known and potential safety risks. REMS can be required before or after drug approval, and the risk associated with the drug must be a serious risk that is documented in the drug’s label. REMS can be as simple as the development and distribution of a Patient Medication Guide, or as extensive as a restricted distribution and physician certification program. It is the restricted distribution and access elements of a REMS program that can create a significant hurdle for the generic manufacturer to obtain samples of the branded drug to conduct

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3 When more than $25 million is at risk, the mean estimated total cost for a Hatch-Waxman patent infringement suit is about $7,000,000. See “Report of the Economic Survey,” AIPLE, 37 (2013).
4 See, e.g., 21 C.F.R. § 10.30.
5 The Orange Book, also known as Approved Drug Products with Therapeutic Equivalence Evaluations, is maintained by the FDA and is available electronically at http://www.accessdata.fda.gov/scripts/cder/ob/.
9 Id.
10 Id.
11 Id.

Continued on page 10...
bioequivalency studies necessary to support ANDA approval.\(^\text{12}\)

Elements to assure safe use, or ETASU, are components of certain REMS programs that require affirmative action by healthcare professionals prior to being allowed to prescribe or dispense the drug to the patient.\(^\text{13}\) ETASU requirements are typically the most extensive requirements of a REMS program.

**Elements to assure safe use (ETASU) requirements are typically the most extensive requirements of a REMS program**

For example, a REMS program may require at least one, and possibly all, of the following ETASU elements:

- Training/experience or special certifications required of prescribers
- Special certifications for dispensing pharmacies
- Restrictions on the location where the drug can be dispensed or used (e.g., infusion settings, hospitals)
- Requirements for safe-use conditions such as laboratory test results
- Requirements for patient monitoring or enrollment in a registry

For certain REMS programs, branded manufacturers have taken the position that they are prohibited from distributing drug samples to anyone, including a generic manufacturer for testing, except pursuant to the REMS distribution system.\(^\text{14}\) 21 U.S.C. § 355 recites in part: “[n]o holder of an approved application shall use any element to assure safe use required by the Secretary under this subsection to block or delay approval of an application under section 355(b)(2) or (j) of this title or to prevent application of such element under subsection (i)(1)(B) to a drug that is the subject of an abbreviated new drug application.”\(^\text{15}\) If the generic drug company cannot get actual samples of the branded drug because of the REMS program, the generic company may be unable to generate the bioequivalency data necessary to gain FDA approval and bring its drug to market.\(^\text{16}\)

The denial of branded drug samples to the generic manufacturer raises potential antitrust issues—and these REMS-associated issues continue to increase in importance. For example, a recent paper sponsored by the Generic Pharmaceutical Association asserts that 40 percent of new FDA approvals are subject to REMS, that the number of REMS programs that require distribution restrictions has increased dramatically in the last few years, that brand manufacturers have begun imposing distribution restrictions on non-REMS products, and that over $5 billion annually could be saved if 40 new generic drugs were allowed to promptly come to market.\(^\text{19}\)

In 2009, Dr. Reddy’s Laboratories, Inc., was one of the first generic companies to bring the issue to the FDA’s attention when it submitted a citizen petition to the FDA.\(^\text{20}\) The petition asserted that “REMS can be used as an excuse by New Drug Application (NDA) sponsors for not providing generic companies with drug product sample needed to conduct bioequivalence testing and for other purposes required by FDA.”\(^\text{20}\) The petition requested, among other things, that the FDA “establish procedures to facilitate the availability of generic versions of drug products subject to a

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\(^{12}\) The generic may be unable to obtain branded drug samples from the branded manufacturer, wholesalers, or distributors.


\(^{15}\) Another area of potential tension is the development of single shared REMS.


\(^{17}\) REMS can be a hurdle in a different way. The REMS, or elements thereof, may be patentable as a method of, or a tool for, delivering a drug. If the branded manufacturer obtains a patent on the REMS or one or more of its elements, this can create an additional hurdle to the generic getting its drug to market. REMS patents, depending on their claims, may be Orange Book listable. If a generic, to gain allowance, is required to develop an alternative REMS program, the generic may not have the resources to do so.


\(^{19}\) As this paper was published under Generic Pharmaceutical Association sponsorship, branded drug manufacturers may have a different viewpoint.

Risk Evaluation and Mitigation Strategy ("REMS") and enforce the FDC Act to prevent companies from using REMS to block or delay generic competition." Dr. Reddy’s also requested that the "FDA work with the Federal Trade Commission ("FTC") in an effort to prevent anti-competitive REMS abuses." In response to Dr. Reddy’s citizen petition, the FDA stated that decisions “with respect to initiating enforcement actions are generally made by the Agency on a case-by-case basis and are within the discretion of the Agency.”

The petition requested, among other things, that the FDA “establish procedures to facilitate the availability of generic versions of drug products subject to a Risk Evaluation and Mitigation Strategy (REMS) and enforce the FDC Act to prevent companies from using REMS to block or delay generic competition” initiating enforcement actions are generally made by the Agency on a case-by-case basis and are within the discretion of the Agency.”

The FDA also concluded that requests “for the Agency to initiate enforcement actions are not within the scope of the FDA’s citizen petition procedures.” The FDA agreed that “issues related to ensuring that marketplace actions are fair and do not block competition would be best addressed by the FTC, which is the Federal entity most expert in investigating and addressing anticompetitive business practices.” Since the FDA’s response, the issue of potential REMS abuse has been before the courts several times. Both district courts that have ruled on antitrust claims to date have allowed those claims to proceed beyond a motion to dismiss.

More recently, H.R. 5657, the Fair Access for Safe and Timely Generics Act of 2014 (FAST Generics Act), was introduced to the U.S. House of Representatives. The stated purpose of H.R. 5657 is to "ensure that eligible product developers have competitive access to approved drugs and licensed biological products, so as to enable eligible product developers to develop and test new products, and for other purposes." The bill’s preamble states that “[r]eference product license or approval holders are restricting competitive access to reference products by sponsors seeking to develop drugs, generic drugs, and biosimilars . . . ." The bill also notes that these “restrictions are deterring and delaying development of generic drugs and biosimilars by extending lawful patent-based monopolies beyond their lawful patent life." Finally, the bill maintains that the enforcement provisions set forth in Section 505–1(f)(8) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355–1(f)(8)) have not been sufficient to prevent anti-competitive practices that interfere with access to reference products, which is necessary for the timely development of affordable generic drugs and biosimilars.

Since the FDA’s response, the issue of potential REMS abuse has been before the courts several times. Both district courts that have ruled on antitrust claims to date have allowed those claims to proceed beyond a motion to dismiss.

H.R 5657 proposes to amend 21 U.S.C. § 355-1 by adding Section 505-2, which reads:

... the Secretary shall require that the covered product’s license holder not adopt, impose, or enforce any condition relating to the sale, resale, or distribution of the covered product, including any condition adopted, imposed, or enforced as an aspect of a risk evaluation and mitigation strategy approved by the
Secretary, that restricts or has the effect of restricting the supply of such covered product to an eligible product developer for development or testing purposes.

Regarding non-REMS restrictions, Section 505-2 recites in part that:

No license holder shall adopt, impose, or enforce any condition relating to the sale, resale, or distribution of a covered product that interferes with or restricts access to reasonable quantities of a covered product by an eligible product developer for development and testing purposes, at commercially reasonable, market-based prices, from the license holder or from any wholesaler or specialty distributor authorized by the license holder to commercially distribute or sell the covered product unless the license holder generally adopts, imposes, or enforces lawful conditions relating to the sale, resale, or distribution of a covered product, with respect to other buyers of the covered product.

The FAST Generics Act also proposes that an eligible product developer who is injured by a violation of one of the bill’s sections through the acts of “a license holder or any wholesaler or specialty distributor authorized by the

license holder to commercially distribute or sell the covered product may sue such license holder for injunctive relief and treble damages (including costs and interest of the kind described in section 4(a) of the Clayton Act (15 U.S.C. 15(a)).”

Finally, the FAST Generics Act, inter alia:

Gives FDA the authority to prohibit, limit, or otherwise suspend a transfer of a covered product to an eligible product developer if such transfer presents an imminent public health hazard; and

Shields eligible product developers from liability claims arising out of testing and development activities conducted under Section 505-2.

In conclusion, generic and branded pharmaceutical manufacturers should continue to stay informed regarding this important and evolving area of law, as court cases may set new precedents and Congress may enact statutory amendments. Finally, generic and branded drug manufacturers should consider providing feedback to their representative or senator regarding the FAST Generics Act.

For guidance in any of the above areas, please contact David Hoffmeister, Vern Norviel, Doug Carsten, Prashant Girinath, Charles Andres, or any member of WSGR’s patents and innovation strategies, global generics, FDA, or antitrust practices.
Juno Therapeutics Files Registration Statement for Initial Public Offering
On November 17, Juno Therapeutics, a biopharmaceutical company developing cell-based cancer immunotherapies, announced that it has filed a registration statement on Form S-1 with the U.S. Securities and Exchange Commission relating to a proposed initial public offering of its common stock. The number of shares to be offered and the price range for the offering have not yet been determined. Wilson Sonsini Goodrich & Rosati is representing Juno in connection with the transaction. For more information, please see http://junotherapeutics.com/juno-therapeutics-files-registration-statement-for-initial-public-offering/.

Capnia Announces Pricing of IPO
On November 13, Capnia, a developer of diagnostics based on its proprietary Sensalyze technology for precision metering of gas flow, announced the pricing of its initial public offering of 1,650,000 units (each unit consisting of one share of common stock, one Series A warrant to purchase one share of common stock, and one Series B warrant to purchase one share of common stock) at a price to the public of $6.50 per unit. Each of the common stock and Series A warrants began trading under the symbols “CAPN” and “CAPNW,” respectively. WSGR is representing Capnia in the transaction. Additional information is available at http://investors.capnia.com/2014-11-13-Capnia-Inc-Announces-Pricing-of-Initial-Public-Offering.

Spirometrix Closes $8.6 Million Series B Financing
Spirometrix, an emerging technology healthcare company focused on the research, development and commercialization of novel breath analysis devices for applications in disease diagnosis and management, announced on November 7 the closing of an $8.6 million Series B preferred stock financing. The financing was led by biosensor manufacturing partner NGK Spark Plug Co., Ltd., which invested approximately $5 million, and also included current investor Simul Investments. WSGR advised Spirometrix in the financing. Please refer to http://spirometrix.com/pages/press.html for further information.

Xenon Pharmaceuticals Prices Initial Public Offering
Clinical-stage biopharmaceutical company Xenon Pharmaceuticals on November 4 announced the pricing of its initial public offering of 4,000,000 of its common shares at a price to the public of $9.00 per share. In addition, Xenon granted the underwriters a 30-day option to purchase up to an additional 600,000 common shares at the IPO price. The common shares began trading on the NASDAQ Global Market on November 5 under the symbol “XENE.” WSGR advised Xenon in the offering. For further details, please see http://investor.xenon-pharma.com/phoenix.zhtml?c=253202&p=irol-newsArticle&ID=1985793.

Atossa Genetics Wins Dismissal of Securities Class Action Litigation
On October 31, the U.S. District Court for the District of Washington granted the defendants’ motion to dismiss an amended complaint in a securities class action lawsuit filed on October 10, 2013, against Atossa Genetics and certain of its officers, directors, and underwriters in its initial public offering. The court has now dismissed with prejudice all claims against Atossa—a company focused on improving breast health through the development of laboratory services, medical devices, and therapeutics—and all other defendants. WSGR represented Atossa in the matter. For more information, please see http://ir.atossagenetics.com/press-releases/detail/574/atossa-genetics-inc-wins-dismissal-of-securities-class-action-litigation.

VytronUS Raises $31.6 Million in Series B Financing
VytronUS, a privately held medical device company developing novel technologies for the treatment of cardiac arrhythmias, announced on October 29 that it has secured $31.6 million in an oversubscribed Series B financing. The proceeds will be used for the development and validation of VytronUS’s proprietary Low-Intensity Collimated Ultrasound (LICU) Cardiac Imaging and Ablation System to treat atrial fibrillation and other arrhythmias in forthcoming clinical trials. WSGR advised VytronUS in the financing. Please see http://www.vytronus.com/news.html for further details.

Abbott Secures Right to Purchase Advanced Cardiac Therapeutics
On October 29, global healthcare company Abbott announced that it has secured the right to purchase private, venture-backed Advanced Cardiac Therapeutics (ACT) in the future, upon the completion of key milestones. ACT is developing a novel ablation catheter designed to improve the safety and effectiveness of ablation procedures. The financial terms of the deal were not disclosed. Wilson Sonsini Goodrich & Rosati is advising ACT in the transaction. For more information, visit http://abbott.mediaroom.com/2014-10-29-Abbott-Expands-Its-Medical-Device-Business-with-Acquisition-in-Catheter-Based-Electrophysiology-Market.

Roche Acquires Rights to Technology and Patent Applications from AbVitro
On October 9, Roche announced that it has made a technology acquisition from AbVitro, a company focused on therapeutic target discovery. Roche obtained exclusive rights to a primer extension-based target enrichment technology and associated patent applications filed by AbVitro. Under the terms of the agreement, AbVitro and Roche scientists will collaborate on the development and application of the technology. WSGR represented AbVitro in related intellectual property and licensing matters. Please see http://www.roche-sequencing.com/press-releases-2014-10-09.html for more information.

Continued on page 14...
Continued from page 13...

Sirona Genomics Enters NGS Collaboration with Immucor
On October 3, Immucor, a leader in transfusion and transplantation diagnostics, announced a collaboration with Stanford University spinout Sirona Genomics focused on human leukocyte antigen (HLA) typing using next-generation sequencing (NGS). Under the terms of the agreement, Immucor will provide development funding to support the commercialization of Sirona’s HLA typing sample preparation and bioinformatics offering that uses leading NGS instruments. WSGR represented Sirona in the matter. For further details, please refer to http://investor.immucor.com/releasedetail.cfm?ReleaseID=874522.

Immucor Announces Acquisition of Sentilus
Immucor announced on October 1 that it has acquired Sentilus, a privately held company focused on developing a novel, inkjet-printed antibody microarray-based technology, Femtoarrays. Sentilus has been developing Femtoarrays and the underlying technology for use in a variety of in vitro diagnostics areas. WSGR advised Sentilus in related intellectual property matters. For more information, please visit http://investor.immucor.com/releasedetail.cfm?ReleaseID=874152.

Best Doctors Acquires Rise Health

United Therapeutics Corporation Obtains Patent Win
On August 29, the U.S. District Court for the District of New Jersey issued a ruling in favor of United Therapeutics Corporation (UTC), a biotech company focused on the development and commercialization of products to address the medical needs of patients with chronic and life-threatening conditions. UTC brought the Hatch-Waxman patent infringement case against Sandoz after Sandoz filed an abbreviated new drug application seeking to market a generic version of Remodulin(R), and challenged patents covering Remodulin(R). The court enjoined Sandoz from marketing its generic product until the expiration of U.S. Patent No. 6,765,117, finding that both patents asserted by UTC against Sandoz were valid and that U.S. Patent No. 6,765,117 is infringed. WSGR represented UTC in the matter.

Otonomy Announces Pricing of Initial Public Offering
On August 13, Otonomy, a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapeutics for diseases and disorders of the inner and middle ear, announced the pricing of its initial public offering of 6,250,000 shares of its common stock at a price to the public of $16.00 per share. WSGR represented Otonomy in the transaction. For more information, please see http://globenewswire.com/news-release/2014/08/13/658294/1009444/en/Otonomy-Announces-Pricing-of-Initial-Public-Offering.html.

Pfenex Announces Pricing of IPO
Pfenex, a San Diego-based biotechnology company, announced on July 23 the pricing of its initial public offering of 8,333,333 shares of common stock at a price of $6.00 per share. In addition, Pfenex granted underwriters a 30-day option to purchase up to 1,250,000 additional shares of common stock at the IPO price. Wilson Sonsini Goodrich & Rosati advised Pfenex in the offering. For more information, please visit http://pfenexinvestorroom.com/2014-07-24-Pfenex-Inc-Announces-Pricing-Of-Initial-Public-Offering.

CareDx Announces Pricing of Initial Public Offering
On July 17, molecular diagnostics company CareDx announced the pricing of its initial public offering of 4,000,000 shares of its common stock at a price to the public of $10 per share, before underwriter discounts. In addition, the company granted the underwriters a 30-day option to purchase up to 600,000 additional shares of common stock at the IPO price to cover over-allotments, if any. WSGR advised CareDx in connection with the offering. More information is available at http://www.caredxinc.com/wp-content/uploads/2014/07/CareDx-IPO-Press-Release-18jul14final.pdf.
Seragon Pharmaceuticals to Be Acquired by Genentech
On July 1, Seragon Pharmaceuticals, a developer of drugs for hormone dependent cancers, announced a definitive agreement with Genentech, a member of the Roche Group, in which Seragon will be acquired for $725 million in cash up front, along with $1 billion in contingent development milestone payments that could bring the total transaction value to $1.725 billion. WSGR is advising Seragon Pharmaceuticals in the transaction. Please see http://www.seragonpharm.com/news/press-release-070214.htm for further details.

China Biologic Announces Pricing of Public Offering of Common Stock
China Biologic Products, a plasma-based biopharmaceutical company, on June 27 announced the pricing of a follow-on offering of 1,550,000 shares of common stock at a public offering price of $38 per share. The company will be offering 800,000 shares and a selling stockholder will be offering 750,000 shares of common stock. WSGR represented China Biologic Products in the transaction. More details can be found at http://chinabiologic.investorroom.com/2014-06-27-China-Biologic-Announces-Pricing-of-Public-Offering-of-Common-Stock.

Mylan Settles Patent Litigation Related to Celebrex Capsules
On June 2, global pharmaceutical company Mylan announced that it has entered into a settlement and license agreement with Pfizer relating to Mylan’s abbreviated new drug application filed with the U.S. Food and Drug Administration for Celecoxib Capsules, 50mg, 100mg, 200mg, and 400mg. This product is the generic version of Celebrex, which is indicated for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and for the management of acute pain in adults. WSGR represented Mylan in the settlement. For more information, please see http://www.mylan.com/news/press-releases/item?id=123231.

Presentations from 22nd Annual Medical Device Conference Now Available Online
On June 12, 2014, Wilson Sonsini Goodrich & Rosati hosted its 22nd Annual Medical Device Conference, at which a variety of industry experts addressed topics of critical importance to medical device companies. More than 650 executives, entrepreneurs, investors, and in-house counsel from medical device companies attended the event, which took place in San Francisco, California.

Video or audio recordings of all of the event’s presentations are now available online via the conference agenda at http://www.wsgr.com/news/medicaldevice/agenda.htm.
Casey McGlynn, a leader of the firm’s life sciences practice, has editorial oversight of The Life Sciences Report and was assisted by Elton Satusky and Scott Murano. They would like to take this opportunity to thank all of the contributors to the report, which is published on a semi-annual basis.

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