

THE RISE OF COMPANION DIAGNOSTICS IN PERSONALIZED MEDICINE: CHALLENGES AND OPPORTUNITIES

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Introduction

The completion of the human genome project and the explosion of information that followed have spurred significant growth in the field of personalized medicine. Personalized medicine generally refers to “the tailoring of medical treatment to

the individual characteristics, needs, and preferences of a patient during all stages of care, including prevention, diagnosis, treatment, and follow-up.”¹ A key driver of personalized medicine is the identification and leveraging of novel biological indicators of disease or disease risk that will lead to the development of new diagnostics (and therapeutics).

In personalized medicine, the term “companion diagnostic” has been adopted by the U.S. Food and Drug Administration (FDA). The FDA defines a companion diagnostic as “an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.”² The FDA has highlighted four areas in which a companion diagnostic may be essential to the safe and effective use of a therapeutic product to:

- (1) identify patients who are most likely to benefit from the therapeutic product;
- (2) identify patients likely to be at increased risk for serious adverse

reactions as a result of treatment with the therapeutic product;

- (3) monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, or discontinuation) to achieve improved safety or effectiveness; and
- (4) identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective (i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population).³

Companion Diagnostics Are Central to Personalized Medicine

Because companion diagnostics provide individual, treatment-essential information, patients and healthcare payers (both public and private) stand to benefit significantly from the growth of the companion diagnostic device industry. These benefits include early

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¹ Personalized Medicine: FDA's Unique Role and Responsibilities in Personalized Medicine. Available electronically at: <http://www.fda.gov/scienceresearch/specialtopics/personalizedmedicine/default.htm>, last accessed May 20, 2015.

² U.S. Food and Drug Administration, “Guidance for Industry and Food and Drug Administration Staff – In Vitro Companion Diagnostic Devices,” at page 7 (2014). Available electronically at: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>, last accessed May 20, 2015.

³ *Id.*

Continued from page 1...

disease detection and risk characterization/classification/assessment, earlier therapeutic intervention, the ability to implement beneficial enhanced disease monitoring, and enhanced monitoring of therapies intended for chronic use. Companion diagnostics may also identify patients for whom a therapy may be ineffective, and in turn produce serious adverse events—thereby saving payers the burden of (i) paying for a drug that does not work, and (ii) paying the costs associated with treating potentially serious side effects.⁴

FDA Regulation of Companion Diagnostics

Companion diagnostics can be: (1) laboratory developed tests (LDTs) or (2) tests that have FDA premarket approval or clearance. LDTs are *in vitro* diagnostic tests that are intended for clinical use and designed, manufactured, and used within a single laboratory.⁵ Although the FDA asserts it has had the legal authority to regulate LDTs as medical devices since 1976, the agency initially exercised its discretion to generally not regulate LDTs.⁶ This is changing, however, and the FDA has recently taken affirmative steps toward regulating LDTs.⁷ LDTs, although important and relatively widespread (there are an

Companion diagnostics that have been subject to FDA premarket approval or clearance will continue to increase in importance in conjunction with the growth of personalized medicine and intensified FDA regulation of LDTs

estimated 11,000 LDTs offered by 2,000 laboratories in the U.S.),⁸ are not the focus of this article. Rather, we focus on companion diagnostics that have been subject to FDA premarket approval or clearance, because these companion diagnostics will continue to increase in importance in conjunction with the growth of personalized medicine and intensified FDA regulation of LDTs.⁹

For these companion diagnostics, the FDA applies a risk-based approach to determine the appropriate regulatory pathway.¹⁰ The

level of risk, together with available risk-mitigation controls, establishes whether a companion diagnostic requires a premarket approval application (PMA) or a premarket notification submission (510(k)).^{11,12,13}

For medical devices in general, including companion diagnostics, three risk classifications (Class I, Class II, and Class III) determine the level of FDA scrutiny (premarket clearance/approval) required prior to marketing.^{14,15} “Device classification depends on the [claimed] intended use [and indications] of the device.”¹⁶ Class I devices are generally considered low risk, and most Class I devices are exempt from premarket clearance requirements (e.g., submission and clearance of a 510(k) premarket notification). “Class II devices are considered to carry moderate risk and are reviewed for substantial equivalence to legally marketed products (e.g., predicate) that have clearance for the same intended use by the premarket notification or 510(k) process . . .”¹⁷ A 510(k) submission is required for non-exempt Class I or II devices.¹⁸ Class III devices are considered high-risk devices that are life-saving or life-sustaining, and the majority of these devices require submission of a PMA.¹⁹

⁴ See, e.g., Davis, et al., “The Microeconomics of Personalized Medicine: Today’s Challenge and Tomorrow’s Promise,” *Nature Reviews Drug Discovery*, 8: 279-286, April 2009, page 279.

⁵ Framework for Regulatory Oversight of Laboratory Developed Tests, FDA, at page 5 (2014).

⁶ LDTs have traditionally been regulated by, e.g., the Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments (CLIA) (42 U.S.C. § 263a), various state law provisions, and laboratory accreditation entities such as the College of American Pathologists (CAP). See, e.g., http://www.cap.org/web/home?_afLoop=688668121485668#%40%3F_afLoop%3D688668121485668%26_adf.ctrl-state%3Daxuo1qbl1_4, last accessed May 20, 2015.

⁷ See, e.g., V. Norviel, D.M. Hoffmeister, and C. Andres, “FDA Regulation in Clinical Labs,” *Clinical Lab Products* 45(3), March 2015.

⁸ A. Pollack, “FDA Acts on Lab Tests Developed In-House,” *The New York Times*, July 31, 2014. Available electronically at: http://www.nytimes.com/2014/08/01/business/fda-to-regulate-lab-developed-test-kits.html?_r=0, last accessed May 20, 2015.

⁹ The authors note that the FDA’s eventual regulation of LDTs is likely to force a significant number of LDT providers to either gain FDA premarket approval or clearance, or to exit the diagnostic marketplace.

¹⁰ U.S. Food and Drug Administration, “Guidance for Industry and Food and Drug Administration Staff – In Vitro Companion Diagnostic Devices,” at page 10 (2014).

¹¹ *Id.*

¹² *Id.*

¹³ Philip, et al., “U.S. FDA Perspective on Challenges in Co-developing *In Vitro* Companion Diagnostics and Targeted Cancer Therapeutics,” *Bioanalysis* 3(4): 383-389, February 2011, page 383.

¹⁴ *Id.*

¹⁵ Classify Your Medical Device. Available electronically at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/>, last accessed May 20, 2015.

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.*

Many companion diagnostics have been, and will likely continue to be, subject to a Class III designation: (1) because they will likely be categorized by the FDA as high-risk devices (e.g., used by healthcare professionals to determine whether a patient should receive or discontinue a life-saving or life-sustaining drug); and (2) most will not have a predicate device to cite in a 510(k) submission. In fact, 18 of the 19 FDA-approved companion diagnostic devices were approved via the PMA process.²⁰ Importantly, companion diagnostics approved through the PMA process may be eligible for valuable patent term extension.²¹

Companion Diagnostic Market

Globally, the companion diagnostic device market is projected to grow from an estimated \$3.1 billion in 2014 to an estimated \$8.7 billion in 2019.²² Oncology, inflammation, and auto-immune diseases are projected to lead the way in companion diagnostic growth.²³ Other areas of projected interest are companion diagnostics for anticoagulants, antipsychotics, and antidepressants.²⁴

Worldwide, Roche Diagnostics, Abbott, Agilent Technologies, Qiagen, and Thermo Fisher Scientific together accounted for

an estimated 86 percent of the global companion diagnostics market in 2013.²⁵ That same year, the United States accounted for approximately 43.9 percent of the companion diagnostic market.²⁶ The European Union was a close second, accounting for an estimated 38 percent of the companion diagnostic market.²⁷

Select Considerations When Developing New Companion Diagnostics

Although the market for companion diagnostic devices is projected to experience rapid growth, challenges exist. For example, some therapeutic product sponsors often lack expertise in co-developing novel companion diagnostics in conjunction with novel therapeutics.²⁸ Also, independent developers may view companion diagnostics as a high-risk investment because, in some cases, the success of a companion diagnostic device may be linked to the regulatory approval of a corresponding novel therapeutic product.²⁹ On the other hand, because a companion diagnostic may allow for optimal patient selection for a given therapeutic, thereby increasing the chances that an investigational product will show substantial evidence of efficacy or increased safety, co-development of a companion diagnostic and a novel

therapeutic may make it more likely that the novel therapeutic will win FDA approval and become commercially available.

In instances where the novel therapeutic and companion diagnostic may be developed by two different entities, therapeutic product sponsors should evaluate different

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approaches to ensure alignment of interest with the companion diagnostic developer. After conducting such an evaluation, a therapeutic product sponsor may elect to

²⁰ List of Cleared or Approved Companion Diagnostic Devices (*In Vitro* and Imaging Tools). Available electronically at: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>, last accessed May 20, 2015.

²¹ See, e.g., D. Hoffmeister, T. Noh, D. Van Goor, V. Norviel, M. Skubatch, and C. Andres, "Patent Term Adjustment and Patent Term Extension: Valuable Tools to Prolong Patent Protection Through Careful Vigilance," *The Life Sciences Report*, Spring 2014. Available electronically at: <https://www.wsgr.com/publications/PDFSearch/life-sciences-report/Spring14/medical-device-biotechnology-companies.htm#5>, last accessed May 20, 2015.

²² See, e.g., "Companion Diagnostics Market by Technology (Polymerase Chain Reaction, In-situ hybridization, Immunohistochemistry), Application (Breast, Lung cancer), & by End-user (Pharmaceutical Companies, Reference Lab) - Global Trends & Forecasts to 2019," September 2014. Available electronically at: <http://www.marketsandmarkets.com/Market-Reports/companion-diagnostics-market-155571681.html>, last accessed May 20, 2015.

²³ *Id.*

²⁴ *Id.*

²⁵ *Id.*

²⁶ See, e.g., "Global Companion Diagnostic Technologies Market (Indication and Geography) - Size, Share, Global Trends, Company Profiles, Demand, Insights, Analysis, Research, Report, Opportunities, Segmentation and Forecast, 2013 – 2020," *Allied Market Research*. Available electronically at: <http://www.alliedmarketresearch.com/companion-diagnostic-technologies-market>.

²⁷ *Id.*

²⁸ See, e.g., Y. Xu, "Companion Diagnostics for Personalized Medicine Opportunities in an Evolving Landscape," *Clinical Laboratory News*, September 2014. Available electronically at: <https://www.aacc.org/publications/cln/articles/2014/september/companion-diagnostics>, last accessed May 20, 2015.

²⁹ *Id.*

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develop its own companion diagnostic in house, partner with an established diagnostic company, or acquire a diagnostic company.³⁰

In partnerships with companion diagnostic developers, therapeutic product sponsors may in some instances be reluctant to pay high premiums (e.g., development and licensing or acquisition costs) to companion diagnostic partners. This is because additional companion diagnostic devices may enter the market. For example, in the case of Herceptin®, within a decade of launch there were six different FDA-approved companion diagnostic assays that utilized different testing technologies.³¹ To accentuate the point, the 19 FDA-approved companion diagnostic devices correspond to 13 therapeutic products.³² Therefore, therapeutic product sponsors may refuse to pay a premium. As such, some therapeutic product sponsors have preferred to structure payments to diagnostic developers as fee-for-service payments or fixed milestone payments. However, these payment structures may not be enough to ensure a sufficient return on investment for the diagnostic developers.

Potential Patent Issues with Companion Diagnostics

Patent-Eligible Subject Matter

One way to protect companion diagnostic market share is to have a strong patent portfolio containing broad, issued claims. In view of cases such as the U.S. Supreme Court's *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (U.S. 2012), which address when certain subject matter becomes patent eligible,

developers should consult with experienced patent counsel to arrive at a strategy to optimally patent protect their companion diagnostic. Patents directed to diagnostic methods must be carefully crafted such that, e.g., claims therein will obviate patent subject matter eligibility (i.e., 35 U.S.C. § 101) rejections in the U.S. Patent and Trademark Office.

Potential Patent Infringement Issues

Where diagnostic method claims are drafted to include an assay and a treatment administration, the entity that carries out the assay may be different from the entity that administers the treatment. In such cases, the diagnostic method may not be directly infringed.

Along these lines, induced infringement may also not apply to some companion diagnostic claims. In *Limelight Networks, Inc. v. Akamai Technologies, Inc.*, 572 S.Ct. ___ (U.S. 2014), the U.S. Supreme Court ruled that a defendant cannot be liable for inducing infringement unless the induced party directly infringed the patent. For these and other reasons, companion diagnostic developers should work with experienced patent counsel to obtain the best possible patent protection for their companion diagnostics.

Conclusion

Personalized medicine—and the companion diagnostic device market—will continue to grow in size and importance to patients, healthcare providers, and payers of healthcare, and the market will increase in value. Developers of companion diagnostics will invest significant developmental

resources and should therefore consult with legal counsel to:

- (1) craft an optimal regulatory pathway that will lead to FDA approval;
- (2) obtain the broadest possible patent coverage; and
- (3) maximize the benefit of any available patent term extension.

For guidance in any of the above areas, please contact any member of Wilson Sonsini Goodrich & Rosati's FDA/life sciences or patents and innovation strategies practices.



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³⁰ *Id.*

³¹ *Id.*

³² List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Available electronically at: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>, last accessed May 20, 2015.

DEPARTMENT OF JUSTICE IMPOSES MORE THAN \$110 MILLION IN FINES ON MEDICAL DEVICE MAKERS

By David Hoffmeister, Partner (Palo Alto), and Charles Andres, Associate (Washington, D.C.)

On March 19, 2015, the U.S. Department of Justice and the U.S. Department of Health and Human Services issued their joint annual report on health care fraud and abuse control.¹ The annual report states that during fiscal year 2014, the federal government won or negotiated approximately \$3.3 billion in judgments and settlements, and attained additional administrative impositions in health care fraud cases and proceedings.²

The annual report details high-profile actions taken against pharmaceutical companies, physicians, pharmacies, hospitals, medical clinics, dental clinics, entities engaged in prescription drug fraud, and medical device companies.³ This article highlights the high-profile government actions against medical device manufacturers.

Federal Government Actions Against Medical Device Companies

1. Boston Scientific and its Guidant subsidiaries agreed to pay \$30 million to settle civil False Claims Act (FCA)⁴ allegations that over a period of three years, Guidant knowingly sold defective defibrillators to health care facilities, which in turn implanted the devices into Medicare patients. The settlement resolved allegations that two lines of Guidant's implantable defibrillators contained an "arcing" defect that caused the defibrillators

to short circuit. The government alleged that although Guidant fixed the defect, the company continued to sell its remaining stock of the old, defective versions of the devices and took steps to hide the problem from patients, doctors, and the U. S. Food and Drug Administration (FDA). In February 2010, Guidant pleaded guilty to criminal charges of misleading the

During fiscal year 2014, the federal government won or negotiated approximately \$3.3 billion in judgments and settlements, and attained additional administrative impositions in health care fraud cases and proceedings

FDA and failing to submit a labeling change to the FDA relating to the defective devices.⁵

2. Abbott Laboratories, Inc., agreed to pay \$5.5 million to resolve civil FCA allegations regarding false

claims submitted to Medicare for surgical procedures involving carotid and peripheral vascular and biliary stents. The government alleged that Abbott knowingly paid prominent physicians unlawful kickbacks with the expectation that these physicians would arrange for the hospitals with which they were affiliated to purchase Abbott's vascular products for use in treating Medicare beneficiaries.⁶

3. Genzyme Corp. agreed to pay \$22.3 million to resolve civil FCA allegations relating to its marketing of an unapproved version of Septrafilm. The settlement resolves allegations that Genzyme sales representatives taught doctors and other staff to dissolve Septrafilm sheets in saline to create a "slurry" for use in laparoscopic surgeries by inserting a catheter filled with the mixture into the body and squirting it into the abdominal cavity. Septrafilm is FDA-approved for use in open abdominal surgery, but not for minimally invasive surgeries, such as laparoscopic surgery. As a result of this conduct, Genzyme allegedly caused hospitals and other purchasers of Septrafilm to submit false and fraudulent claims to federal health care programs for uses of Septrafilm that were not reimbursable.⁷
4. CareFusion Corp. agreed to pay \$40.1 million to settle civil FCA allegations

¹ "The Department of Health and Human Services and The Department of Justice Health Care Fraud and Abuse Control Program Annual Report for Fiscal Year 2014" (annual report), March 19, 2015, available electronically at <https://oig.hhs.gov/publications/docs/hcfac/fy2014-hcfac.pdf>, last accessed March 31, 2015.

² Annual report at page 8.

³ *Id.* at pages 22-41.

⁴ FCA, 31 U.S.C. §§ 3729 - 733.

⁵ Annual report at page 22.

⁶ *Id.*

⁷ *Id.*

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that it paid kickbacks and promoted its products for uses that the FDA had not approved. The settlement resolves allegations that CareFusion: (1) paid kickbacks to the physician co-chair of the Safe Practices Committee at the National Quality Forum, a nonprofit organization that reviews, endorses, and recommends standardized health care performance measures and practices; and (2) knowingly promoted the sale of ChloroPrep for uses that

Statutory and regulatory violations can result in injunctions, seizures, significant fines, criminal penalties, consumer and shareholder lawsuits, unwanted publicity, and the fraying of key government agency-company relationships

the FDA had not approved, some of which were not medically accepted indications, and made unsubstantiated representations about the appropriate uses of ChloroPrep.⁸

5. Medtronic, Inc. agreed to pay \$9.98 million to resolve civil FCA allegations that the company paid kickbacks to induce physicians to use certain of the company's cardiac rhythm management devices, including pacemakers and defibrillators. The government alleged that Medtronic: (1) paid implanting physicians to speak at events intended to increase the flow of referral business; (2) gave physicians tickets to sporting events; and (3) developed marketing/business development plans for physicians at no cost.⁹

6. Smith & Nephew agreed to pay \$8.3 million to settle civil FCA allegations that the company violated the Trade Agreements Act by selling medical devices to the government that had been manufactured in Malaysia, when they were required to be manufactured in the United States.¹⁰

7. Omni Surgical L.P. (also known as Spine 360) and an Indiana spinal surgeon agreed to pay a combined \$2.6 million to settle civil FCA allegations that Spine 360 paid illegal kickbacks to the physician to induce him to use the company's products. The government alleged that payments made by Spine 360 to an entity controlled by the physician pursuant to a series of intellectual property agreements were actually shams, and that the payments were

intended to compensate the physician for using Spine 360 products in his surgeries.¹¹

Conclusion

Being the target of government actions consumes time and resources. In addition, statutory and regulatory violations can result in injunctions, seizures, significant fines, criminal penalties, consumer and shareholder lawsuits, unwanted publicity, and the fraying of key government agency-company relationships. Medical device companies can minimize these unwanted events through a variety of actions, including regularly consulting legal counsel.



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⁸ *Id.* at pages 22-23.

⁹ *Id.* at page 23.

¹⁰ *Id.*

¹¹ *Id.*

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

The life sciences industry segment with the largest number of closings—medical devices and equipment—decreased both in total amount raised and number of closings during the second half of 2014 compared to the first

half of 2014. Specifically, the total amount raised for that segment decreased by 28.3 percent, from \$354.42 million to \$254.15 million, and the total number of closings decreased by 14.6 percent, from 55 closings

Life Sciences Industry Segment	1H 2014 Number of Closings	1H 2014 Total Amount Raised (\$M)	1H 2014 Average Amount Raised (\$M)	2H 2014 Number of Closings	2H 2014 Total Amount Raised (\$M)	2H 2014 Average Amount Raised (\$M)
Biopharmaceuticals	16	201.20	12.57	13	261.99*	11.66**
Genomics	3	31.90	10.63	2	5.10	2.55
Diagnostics	8	83.01	10.38	5	88.38	17.68
Medical Devices & Equipment	55	354.42	6.44	47	254.15	5.41
Digital Health	8	57.34	7.17	4	9.75	2.44
Healthcare Services	2	130.54*	65.27	7	106.15	15.16
Total	92	858.41		78	725.52	

*Includes one mega-deal (\$100 million and over).

**This is a truncated average that excludes the highest and lowest amounts raised in the calculation of the average.

in 2014. Specifically, the table compares—by industry segment—the number of closings, the total amount raised, and the average amount raised per closing across the first half of 2014 and the second half of 2014.

The data generally demonstrates that venture financing activity decreased during the second half of 2014 compared to the first half of 2014 with respect to total amount raised and number of closings. Specifically, the total amount raised across all industry segments during the second half of 2014 decreased by 15.5 percent compared to the first half of 2014, from \$858.41 million to \$725.52 million, and the total number of closings across all industry segments decreased by 15.2 percent, from 92 closings to 78 closings.

The total amount raised across all industry segments during the second half of 2014 decreased by 15.5 percent compared to the first half of 2014, from \$858.41 million to \$725.52 million, and the total number of closings decreased by 15.2 percent, from 92 to 78 closings

to 47 closings. The industry segment with the second-largest number of closings—biopharmaceuticals—also experienced an 18.8 percent decrease in number of closings during the second half of 2014, from 16 closings to 13 closings. However, the total amount raised in the biopharmaceuticals industry increased by 30.2 percent during the second half of 2014, from \$201.2 million to \$261.99 million. Similarly, the diagnostics industry experienced a modest 6.5 percent increase in total amount raised during the second half of 2014, from \$83.01 million to \$88.38 million.

With the exception of diagnostics, the average amount raised in all industry

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segments decreased during the second half of 2014 compared to the first half of 2014, most significantly in healthcare services (which decreased by 76.8 percent, from \$65.27 million to \$15.16 million), genomics (which decreased by 76 percent, from \$10.63 million to \$2.55 million), and digital health (which decreased by 66 percent, from \$7.17 million to \$2.44 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 decreased during the second half of 2014 compared to the first half of 2014. Specifically, the number of Series A closings as a percentage of all closings decreased from 35.2 percent to 26.9 percent. Similarly, both Series B financing activity and Series C and later-stage financing activity compared to all other financings decreased during the second half of 2014 compared to the first half of 2014: the number of Series B closings as a percentage of all closings decreased marginally from 19.3 percent to 19.2 percent and the number of Series C and later-stage financing closings as a percentage of all closings decreased from 18.2 percent to 16.7 percent. Filling the void was an increase in bridge and recapitalization financing activity.

Pre-money valuations for early-stage life sciences companies increased significantly during the second half of 2014 compared to the first half

Specifically, the number of bridge financing closings as a percentage of all closings increased from 18.2 percent to 26.9 percent, while the number of recapitalization financing closings as a percentage of all closings increased from 5.7 percent to 7.7 percent.

Pre-money valuations for early-stage life sciences companies increased significantly during the second half of 2014 compared to the first half of 2014. The average pre-money valuation for Series A financings increased by 35.7 percent, from \$10.76 million to \$14.6 million, and the average pre-money valuation for Series B financings increased by 136.2 percent, from \$34.55 million to \$81.62 million. Bucking the upward trend were pre-money valuations for later-stage life sciences companies: the average pre-money valuation for Series C and later-stage financings decreased by 27.3 percent, from \$157.84 million to \$114.75 million.

Other data taken from transactions in which all firm clients participated in 2014 did not change with respect to life sciences. Notably, life sciences continues to be the second-most-attractive industry for investment among our clients, representing 19 percent of total funds raised—trailing only the software industry, which represents 23.8 percent of total funds raised. Software and life sciences have historically dominated all other industries with respect to total funds raised. However, the electronics and computer hardware industry, the third-most-attractive industry for investment among our clients, represented 17 percent of total funds raised in the second half of 2014, up from a modest 3.9 percent during the first half of 2014.

Overall, the data suggests that access to venture capital for life sciences companies decreased during the second half of 2014

Life sciences continues to be the second-most-attractive industry for investment among our clients, representing 19 percent of total funds raised

compared to the first half of 2014. However, it is important to remember that the first half of 2014 experienced a surge of financing activity relative to the second half of 2013—to be sure, the total amount raised across all industry segments during the first half of 2014 compared to the second half of 2013 increased by approximately 76.3 percent, from \$486.77 million to \$858.47 million, and the total amount raised across all industry segments during the second half of 2014 was still a very healthy \$725.52 million. What improved during the second half of 2014 were the average pre-money valuations for early-stage companies. It could be the case that investors are taking a modest step back in deal activity to reflect following a very robust first half of 2014, but continue to have an appetite for quality, early-stage deals, and that demand is translating into improved valuations. Whatever the case may be, while the data suggests that fundraising activity during the second half of 2014 did not improve over the first half of the year, interest remains strong in life science companies as compared to all other industries.



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RECENT LIFE SCIENCES CLIENT HIGHLIGHTS

Invuity Announces Pricing of Initial Public Offering

On June 11, surgical photonics company Invuity announced the pricing of its initial public offering of 4,000,000 shares of common stock at a public offering price of \$12 per share, before underwriting discounts and commissions. The shares began trading on the Nasdaq Global Market on June 15 under the ticker symbol "IVTY." WSGR is advising Invuity in connection with the offering. For more information, please see <http://investors.invuity.com/phoenix.zhtml?c=253978&p=irol-newsArticle&ID=2059518>.

China Biologic Announces Pricing of Public Offering of Common Stock

On June 10, China Biologic Products (CBPO), a leading plasma-based biopharmaceutical company in China, announced the pricing of a follow-on offering of 3,000,000 shares of common stock at a public offering price of \$105 per share. CBPO will offer 700,000 shares and certain selling stockholders will offer 2,300,000 shares of common stock. WSGR is advising CBPO and a selling stockholder in the transaction. To read more, visit <http://chinabiologic.investorroom.com/2015-06-10-China-Biologic-Announces-Pricing-of-Public-Offering-of-Common-Stock>.

Outset Medical Secures \$91 Million Financing Round

Outset Medical, a company focused on reimagining the experience of dialysis care for patients with kidney disease, announced on June 9 that it has closed a dual-stage \$91 million equity and debt round of financing. New investor Fidelity Research and Management Company led the \$51 million equity financing, with participation from existing investors Warburg Pincus and The Vertical Group, as well as new investors Partner Fund Management LP, Perceptive Advisors, and CRG. In addition, CRG led a

\$40 million debt financing. WSGR advised Outset Medical in the financing. Please see <http://www.businesswire.com/news/home/20150609005635/en/Outset-Medical-Announces-91-Million-Funding-First-Of-Its-Kind#VXdMq2d0ymQ> for more details.

AbbVie Completes Acquisition of Pharmacyclics

Global biopharmaceutical company AbbVie announced on May 26 that it has completed its \$21 billion acquisition of Pharmacyclics and the company's flagship asset Imbruvica, a first-in-class BTK-inhibitor used to treat hematological cancers. Imbruvica is approved for use in four indications in the U.S. and is the only product to have received three Breakthrough Therapy designations by the FDA. As a result of the acquisition, Pharmacyclics will be a wholly owned subsidiary of AbbVie. WSGR advised Pharmacyclics in the transaction. For additional details, please visit <http://abbvie.mediaroom.com/2015-05-26-AbbVie-Completes-Acquisition-of-Pharmacyclics>.

Rani Therapeutics Closes Series C Financing

On May 26, Rani Therapeutics, a company developing a novel approach for the oral delivery of large drug molecules, announced the closing of a Series C round of financing. Participants included Novartis, Google Ventures, InCube Ventures, and VentureHealth, as well as a number of other investors. Financial details of the transaction were not disclosed. WSGR advised Rani Therapeutics in the financing. To read more, please see <http://www.prnewswire.com/news-releases/rani-therapeutics-secures-series-c-funding-300088164.html>.

St. Jude Medical Acquires Spinal Modulation

Global medical device company St. Jude Medical announced on May 4 that it

has completed its acquisition of Spinal Modulation, a medical device company that is developing spinal cord neurostimulator systems for the treatment of chronic intractable pain. The acquisition was completed on May 1. WSGR advised Spinal Modulation in the transaction. Please see <http://media.sjm.com/newsroom/news-releases/news-releases-details/2015/St-Jude-Medical-Completes-Acquisition-of-Spinal-Modulation-Inc/default.aspx> for more information.

CRISPR Therapeutics Raises \$89 Million in Financing

On April 29, CRISPR Therapeutics, a biopharmaceutical company focused on translating CRISPR-Cas9 gene-editing technology into transformative medicines, announced that it has raised a total of \$89 million in a Series A and Series B round of financing, with \$35 million of new funding from Series A and \$29 million from Series B. The two financings were led by SR One and Celgene Corporation, and included new investors New Enterprise Associates (NEA) and Abingworth, as well as the company's founding investor, Versant Ventures. WSGR advised SR One, NEA, and Abingworth in the financing. For more information, visit <http://crisprtx.com/crispr-therapeutics-raises-additional-64-million-to-translate-breakthrough-crispr-cas9-technology-into-next-generation-therapies-for-patients/>.

Pfenex Announces Pricing of Follow-On Offering

On April 24, Pfenex, a clinical-stage biotechnology company engaged in the development of biosimilar therapeutics, announced the pricing of its follow-on offering of 6,000,000 shares of its common stock at a price to the public of \$15.50 per share, raising approximately \$105 million. In addition, Pfenex granted the underwriters a 30-day option to purchase up to an additional

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750,000 shares of common stock from certain existing stockholders. WSGR advised Pfenex in the offering. Please see <http://pfenex.investorroom.com/2015-04-24-Pfenex-Inc-Announces-Pricing-Of-Follow-on-Offering> for additional details.

Mesoblast and Celgene Enter into Equity Placement and Right-of-First-Refusal Agreement

Australia-based Mesoblast Limited, a global leader in regenerative medicine, announced on April 12 that it has entered into an agreement with U.S.-based Celgene Corporation, a global biopharmaceutical company engaged in the development and commercialization of innovative therapies for the treatment of cancer and immune-inflammatory related diseases. Under the terms of the agreement, Celgene will purchase 15.3 million shares of Mesoblast's common stock for \$45 million, and has a six-month right of first refusal to certain disease fields. WSGR is counsel to Mesoblast in the transaction. More information is available at <http://globenewswire.com/news-release/2015/04/13/723565/10128531/en/Celgene-And-Mesoblast-Enter-Into-Equity-Placement-and-Right-of-First-Refusal-Agreement-To-Certain-Disease-Fields.html>.

Caribou Biosciences Raises \$11 Million in Series A Financing

Caribou Biosciences, a developer of CRISPR-Cas9 technologies for precision cell engineering, announced on April 2 that it has closed an \$11 million Series A financing round. Investors include Fidelity Biosciences, Novartis, Mission Bay Capital, 5 Prime Ventures, and an undisclosed strategic partner. In addition, Dr. Jennifer Doudna, a Howard Hughes Medical Institute investigator, UC Berkeley professor, and Caribou co-founder, joined the round as an investor. WSGR advised Caribou in the financing. To learn more, please visit <http://cariboubio.com/media/>.

Xlumena Acquired by Boston Scientific

On April 1, global medical technology leader Boston Scientific Corporation announced it has signed a definitive agreement to acquire Xlumena, a venture-backed medical device company that develops, manufactures, and sells minimally invasive devices for Endoscopic Ultrasound (EUS)-guided transluminal drainage of targeted areas within the gastrointestinal tract. The agreement calls for an upfront payment of \$62.5 million, an additional payment of \$12.5 million upon FDA clearance of Xlumena's HOT AXIOS product, and further sales-based milestones based on sales achieved through 2018. WSGR advised Xlumena in the transaction. Additional information is available at <http://news.bostonscientific.com/2015-04-01-Boston-Scientific-Agrees-to-Acquire-Xlumena>.

Pager Raises \$10 Million

Pager, a New York City start-up that has developed a mobile service that aims to better coordinate patients and medical providers between visits through a series of apps, announced on March 10 that it has closed its first round of financing at \$10.4 million. Existing investors Lux Capital and Montage Ventures led the round and were joined by Goodwater Capital and Summation Health Ventures, a strategic partnership between MemorialCare and Cedars-Sinai health systems. WSGR advised Pager in the financing. Please see <http://medcitynews.com/2015/03/today-pager/> for more information.

NuVasive Announces Successful Appeal of Medtronic Verdict

On March 3, NuVasive, a medical device company focused on developing minimally disruptive surgical products and procedures for the spine, announced that the U.S. Court of Appeals for the Federal Circuit overturned the damages award in NuVasive's ongoing patent lawsuit with Medtronic Sofamor Danek USA, Inc. and Warsaw

Orthopedic, Inc. WSGR represented NuVasive in the matter. More details can be found at <http://phx.corporate-ir.net/phoenix.zhtml?c=176872&p=irol-newsArticle&iD=2022019>.

Avinger Announces Pricing of Initial Public Offering

Avinger, a commercial-stage medical device company, announced on January 30 the pricing of its underwritten initial public offering of 5,000,000 shares of its common stock at a public offering price of \$13 per share. Also on January 30, the company's shares began trading on the Nasdaq Global Market under the ticker symbol "AVGR." Wilson Sonsini Goodrich & Rosati advised Avinger in the offering. For more information, please visit <http://investors.avinger.com/phoenix.zhtml?c=253894&p=irol-newsArticle&iD=2012040>.

Otonomy Announces Follow-On Offering

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 on January 28 the closing of its follow-on public offering of 2,932,500 shares of its common stock at a price to the public of \$29.25 per share, for total gross proceeds of approximately \$86 million before deducting underwriting discounts and commissions and other offering expenses. WSGR advised Otonomy in the offering. Please see <http://globenewswire.com/news-release/2015/01/28/700813/10117319/en/Otonomy-Announces-Closing-of-Follow-on-Public-Offering-and-Full-Exercise-of-Underwriters-Option-to-Purchase-Additional-Shares.html> to learn more.

Myriad and Pathway Genomics Settle BRCA Patent Infringement Case

On January 23, Pathway Genomics, a data-driven global healthcare company

and precision medicine clinical laboratory, announced a settlement agreement ending the BRCA patent litigation against the company. Under the agreement, Myriad Genetics, the University of Utah Research Foundation, HSC Research and Development Limited Partnership, Endorecherche, and the Trustees of the University of Pennsylvania (“patent owners”) and Pathway dismissed their claims and counterclaims against one another. Additionally, the patent owners granted a covenant to not sue Pathway under the patents asserted in the litigation proceedings. WSGR advised Pathway Genomics in the matter. Additional details are available at <https://www.pathway.com/myriad-and-pathway-genomics-agree-to-settle-brca-patent-infringement-case-2/>.

Alder Biopharmaceuticals Offers Additional Shares to Underwriters

Alder BioPharmaceuticals, a clinical-stage biopharmaceutical company, announced on January 22 that the underwriters—led by Credit Suisse Securities, Leerink Partners, and Wells Fargo Securities—of its previously announced public offering of common stock have exercised in full their option to purchase an additional 900,000 shares of common stock. Gross proceeds from the offering of an aggregate of 6,900,000 shares at a public offering price of \$29.50 per share were approximately \$203.6 million. WSGR advised the underwriters in the offering. For more details, please see <http://www.alderbio.com/wp-content/uploads/2015/01/Alder-Exercise-in-Full-of-Option-to-Purchase-Additional-Shares.pdf>.

10X Genomics Raises \$55.5 Million

San Francisco Bay Area start-up 10X Genomics announced on January 12 that it has raised \$55.5 million in a Series B round of financing. 10X Genomics is currently commercializing a new genomics platform that will change the definition of sequencing. WSGR advised 10X Genomics in the transaction. For further details, see <http://www.businesswire.com/news/home/20150112005163/en/10X-Genomics-Closes-55.5-Million-Series#.VV4kSWd0ymQ>.

BTG Completes Acquisition of PneumRx

On January 7, London-based BTG, an international specialist healthcare company that is active in interventional medicine and specialty pharmaceuticals, announced that it has completed its acquisition of PneumRx, a leader in the field of interventional pulmonology. On December 4, the two companies announced that PneumRx had signed an agreement to be acquired by BTG in a deal worth up to \$475 million, based on an initial consideration of \$230 million and up to \$245 million in performance-related milestone payments. WSGR represented PneumRx in the transaction. Please see <http://www.pneumrx.com/2014/12/04/pneumrx-acquired-by-btg-for-up-to-475-million/> for additional details.

Sequentia Acquired by Adaptive Technologies

Also on January 7, Adaptive Biotechnologies Corporation, a pioneer in leveraging next-generation sequencing to profile T-cell and

B-cell receptors, announced its acquisition of Sequentia, which is expected to expedite and expand the use of novel immunosequencing products for researchers and clinicians to diagnose, treat, and monitor patients with cancer, autoimmune disorders, and infectious diseases. WSGR advised Sequentia in the transaction. Please see <http://www.prnewswire.com/news-releases/adaptive-biotechnologies-announces-acquisition-of-sequentia-inc-300016959.html> for additional information.

Juno Therapeutics Announces Pricing of IPO

On December 18, Juno Therapeutics, a biopharmaceutical company developing cell-based cancer immunotherapies, announced the closing of its initial public offering of 12.7 million shares of common stock at a price to the public of \$24.00 per share. Juno raised approximately \$305 million from the offering. On a market capitalization basis, Juno’s initial public offering was the largest biotech IPO in 2014 and, based on news reports, the largest biotech IPO in the last 10 years. WSGR represented Juno in the offering. For more details, please see <http://ir.junotherapeutics.com/phoenix.zhtml?c=253828&p=irol-newsArticle&ID=2000943>.

UPCOMING LIFE SCIENCES EVENTS

Wilson Sonsini Goodrich & Rosati's Medical Device Conference

June 25-26, 2015
The Palace Hotel
San Francisco, California
<http://www.wsgr.com/news/medicaldevice/>

Wilson Sonsini Goodrich & Rosati's 23rd Annual Medical Device Conference, aimed at professionals in the medical device industry, will focus on understanding the challenges facing the medtech start-up today, as well as the strategies that are emerging to respond to these challenges.

Phoenix 2015: The Medical Device and Diagnostic Conference for CEOs

October 21-23, 2015
The Ritz-Carlton Half Moon Bay
Half Moon Bay, California
<http://www.wsgr.com/news/phoenix>

Phoenix 2015 will serve as the 22nd annual conference for chief scientific officers and the senior leadership of medical device and diagnostic companies. The event will bring together top-level executives from large healthcare companies and small, venture-backed firms to discuss critical issues of interest to the medical device industry today, as well as to network and gain valuable insights from both industry leaders and peers.

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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