Journal of COMMERCIAL BIOTECHNOLOGY

JANUARY 2014

VOLUME 20 I NUMBER 1

ISSN: 1462-8732 / eISSN 1478-565X

WWW.COMMERCIALBIOTECHNOLOGY.COM

Journal of
COMMERCIAL
BIOTECHNOLOGY
http://CommercialBiotechnology.com

Journal of
COMMERCIAL BIOTECHNOLOGY

VOLUME 20 NUMBER 1 JANUARY 2014

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Original Article

Russia-focused venture capital supports in-bound technology transfer and company building: An analysis of investment trends and outcomes

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ABSTRACT

This paper analyzes the approaches taken by the Russian government to promote innovation in the biotechnology sector within the country. Russia is economically strong, currently with a trade surplus, and the country is investing broadly in initiatives that have resulted in in-bound technology transfer, as well as an expansion of the private sector. These initiatives include government venture capital and investment funds, as well as physical technology "incubator" centers. The result has been an increase in the number of clinical-stage biotechnology companies operating in Russia, as well as an increase in the number of pharmaceutical candidates undergoing trials in the country. The biotechnology "boom" has also resulted in an increase in the number of early-stage companies.

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This paper investigates current deal and investment trends from the funds that are the principal supporters of biotechnology companies in Russia.

Journal of Commercial Biotechnology (2014) 20(1), 4–9. doi: 10.5912/jcb604
Keywords: Russia; government; venture capital; investments

INTRODUCTION

In recent years, there has been much interest in the economies and markets of the so-called "BRICS countries" (Brazil, Russia, India, China, and South Africa).[1] The evolution of the biomedical sector has followed a unique path in each country. This presents different advantages and drawbacks that are also unique to each country. For example, India has solidly developed as a manufacturer of pharmaceuticals, and the generic pharmaceuticals industry has flourished there, but nevertheless India is not commonly perceived as a country where cutting-edge research continuously spins out new technologies or therapies.[2] Likewise, Brazil has a large economy that is growing rapidly, but its pharmaceutical industry is heavily regulated, particularly in terms of price controls and compulsory licensing of technology.[3] Innovation in agricultural biotechnology is seen, but mostly in the context of alternative fuels and energy production. China has built a solid infrastructure for research and technology in the life sciences in both basic and translational research, especially in cell technology, but its history with respect to enforcement of patent rights is still a major concern for many Western companies that are otherwise enthusiastic to conduct business in China.[4]

Russia has strongly attracted the attention of foreign business interests, drawn in-part to its enormous trade surplus due largely to oil and gas revenues, as well as a stabilization of both the political landscape and Russia's currency. The biotechnology sector has likewise benefitted, and investments in technology and companies by the Russian government have increased in this sector during the period of 2011-present, after a decrease in 2009-2010. However, the current level of activity is not as pronounced as in 2008, the peak of an investment boom within the Russian biotechnology sector. Still, the sector is actively growing.[5]

Russia has always been strong in terms of basic scientific research, although until the dissolution of the U.S.S.R. access to much of that knowledge was limited for Western interests. Until the 1990's, government mandates and funding directed all research efforts, and these communist-era priorities are still reflected within the current Russian research community.[6] For example, Novosibirsk, Siberia, once the center of the U.S.S.R.'s biological weapons research, is now a major center for life sciences research for biotechnology and pharmaceuticals.[7] The presence of the nearby Tomsk University Cluster provides both scientific training and a nucleus for construction of new regional innovation centers for developing both technologies and companies. Likewise, outside of Moscow, the Skolkovo Institute of Science and Technology is a research university founded in 2011, which houses laboratories and faculty as part of a joint project between the Skolkovo Foundation and the Massachusetts Institute of Technology.[8] The Skolkovo Innovation Center located nearby is a planned technology park that is designed to cater to the various needs of science and technology companies, including but not limited to biotechnology. Corporations become residents of Skolkovo, and receive numerous incentives such as tax breaks, investment capital, grants, laboratory space and equipment. Currently, a resident is "virtual" having to promise to take up physical residence upon completion of the center.

Russia has taken numerous steps to become a more business-friendly country. In 2008, it began implementing new policies for protecting intellectual property rights, and since then has established a dedicated Patent Court, and enacted a plethora of new adaptations to the patent law, making them more predictable and giving better protection to patentees. Russia has become a signatory to the Patent Cooperation Treaty (PCT) and the process for filing and obtaining patents now more closely tracks worldwide practices. Additionally, Russia has very low patent filing fees, thereby encouraging innovation and disclosure of technology. In 2012 Russia finally won its long fought battle to become a member

1 Jim O'Neill, "The Rise of the BRICs and N-11 Consumer", Goldman Sachs, December 3, 2010.

2 Pravin Kamble et al., "Progress of the Indian pharmaceutical industry: a shifting perspective", Jnl of Intellectual Property Law & Pract, 2012, vol. 7, no. 1, pp. 48-51.

3 Shivam Vashisth et al., "A comparative study of regulatory trends of pharmaceuticals in Brazil, Russia, India and China (BRIC) countries", Journal of Generic Medicines: The Business Journal for the Generic Medicines Sector, 2012, vol. 9, no. 3, pp. 128-143.

4 XT Nguyen, "The China We Hardly Know: Revealing the New China's Intellectual Property Regime", Saint Louis University Law Journal, 2010, vol. 55, pp. 773-810.

5 National Research Council, "The Unique U.S.-Russian Relationship in Biological Science and Biotechnology: Recent Experience and Future Directions", Washington, DC: The National Academies Press, 2013.

6 Yegor Vassetzky, "Basic science in Russia under threat", Nature, 2010, vol. 467, p. 789.

7 Richard Stone, "Science in Russia Weapons Researchers Come In From the Cold", Science, 1995, vol. 270, no. 5243, p. 1754.

8 http://www.skoltech.ru/

of the World Trade Organization. Likewise in 2012, it enacted several legal changes favorable to business including a revision to the legal codes that served to simplify and expedite arbitration and dispute resolution proceedings in Russia's state court tribunal, known as the Highest Arbitrage Court, which aims to settle economic disputes between both Russian and foreign companies. Furthermore, the regulatory climate in Russia has relaxed somewhat, making Russia a potential venue for international pharmaceutical clinical trials and testing. Overall, these developments have vastly improved the climate for commercializing biotechnology in Russia. However, there is room for further improvement. As to companies and their intellectual property, punitive damages in Russia for infringement are typically hard to obtain and the amounts when awarded are often small. Likewise, the extensive discovery process that is a cornerstone of both U.S. and U.K. patent litigation doesn't exist in Russia, and so proving infringement and damages can be more challenging than in Western courts. Also, there remain issues with Customs over the import/export of biomedical materials, and companies with such needs find shipping and supply issues can still be a concern, despite the otherwise pro-business environment.[9]

With the creation of innovation centers, government support, and a legal climate that is favorable to international business interests in terms of both financial and intellectual property concerns, Russia appears to be poised as the BRICS country that could emerge as the most favorable to the development of cutting-edge technologies.[10] However, technical expertise and discovery-stage science is only the start. Governments do not commercialize technologies, and the burden of identifying discovery-stage technologies and bridging the translational research "valley-of-death" to carry these innovations forward into international markets require a robust private sector fueled with large amounts of both capital and patience. It is here that Russia (like most countries) falls short. Privatization of the Russian economy is relatively recent and still incomplete, and early efforts encouraged commercialization of lower-risk and faster time-to-market products, which in practice meant oil and gas, software, and information technologies. High-risk ventures such as biotechnology with profitability expected (if ever) only in the longer-term were naturally of lower interest to investors, who could see more immediate returns in just about every other sector. The Russian government responded with initiatives that were designed to reduce investor risk, provide limited capital, and encourage further private investments in these relatively higher-risk ventures.[11]

The most successful initiative appears to be the sovereign fund RUSNANO (formerly the Russian Corporation of Nanotechnologies). RUSNANO as well as the Fund for Infrastructure and Educational Programs are dedicated and empowered to foster the growth of the nanotechnology industry in Russia, based on the advances of Russian scientists and the transfer of cutting-edge technologies originating from other countries. RUSNANO, along with domestic and foreign private investors, co-invests in projects with substantial economic potential, such as nanotech, life sciences and medical technologies, and places investments typically in the US$20 Million to US$50 Million range. In addition, RUSNANO does provide a limited amount of mentoring, however it is not really focused on startup or early stage companies, which often have different needs from their later-stage counterparts. Contrast this with other government-created incentives, such as the Skolkovo Fund[12] and the Skolkovo Innovation Center,[13] which address more of the needs of startup and early-stage companies than RUSNANO. The Skolkovo Fund provides both seed capital later stage funding, and the Skolkovo Innovation Center providing limited capital and incubator facilities. But government initiatives do not substitute for venture capital, which ideally provides a company with business expertise as well as a funding source. However, the combination of venture capital with government incentives and supplemental government funding can

9 "IP protection key to economic development and growth in Russia, ICC BASCAP warns leaders", International Chamber of Commerce, Moscow, 22 October 2012, available at < http://www.iccwbo.org/News/Articles/2012/IP-protection-key-to-economic-development-and-growth-in-Russia,-ICC-BASCAP-warns-leaders/>

10 Robert C. Bird et al., "The Emerging BRIC Economies: Lessons from Intellectual Property Negotiation and Enforcement", 5 Nw. J. Tech. & Intell. Prop., 2006-2007, vol. 5, no. 3.

11 Mark Adomanis, "Open Government a la Russe: How the Russian Government is Trying to Modernize", Forbes, November 12, 2012, available at < http://www.forbes.com/sites/markadomanis/2012/11/12/open-government-a-la-russe-how-the-russian-government-is-trying-to-modernize/>

12 http://www.sk.ru/en/Model/AboutFund.aspx

13 http://www.sk.ru/Model/AboutFund/Clusters/BioMed/Participants.aspx

provide a strong force for moving life science companies forward.[14],[15]

Venture capital in Russia is a bit different than what is customary in Western countries. Until relatively recently, much of the startup and operational capital for emerging biotechnology companies for those lucky enough to secure funding came in the form of investments from wealthy individuals. While it is difficult to make an accurate assessment of these results, one can surmise that the differing levels of experience possessed by these investors, could create many problems for the company. A universal problem is a company's reliance on a single (or a few) wealthy investor(s), meaning that the company's priorities necessarily follow those of the capital source. However, in Russia the laws regarding venture capital were less established than in Western countries, and so there were little restraints on these individual investors in terms of corporate governance. Likewise, investments were not traditionally made through established "funds" with clear investment objectives and internal regulation of the limited partners. Even now, there are very few private venture funds in Russia, and the majority of these are focused on sectors other than biotechnology.

The government has stepped in to provide limited sources of venture capital and incentives to assist developing companies and encourage further investment by private and/or foreign capital sources.[16] For example, one of the first government programs encouraging company formation and growth within the Russian Federation, was developed and now is being implemented in the Republic of Tatarstan, in response to active development of biotechnology research in that region. The Investment and Venture Fund of the Republic of Tatarstan (IVF RT) closed in 2005, and invests broadly in several technology sectors, such as petrochemical and chemical industries, construction materials, agriculture, foods, energy, information technologies, pharmaceuticals and medical devices. During the existence of IVF RT, the Fund has invested in 239 innovative companies, of which 26 are biotechnology companies. This encompasses seed stage investments, from US$30 Thousand to US$100 Thousand, as well as later stage investment projects averaging from US$1 Million to US$5 Million. IVF RT's investment strategy is as broad as its investments, and includes equity participation, debt financing (issuing loans on quite favorable terms to companies) and providing funds in the form of grants (with money restricted to particular stated purposes). However, the goal of IVF RT is incubation not subsidization, and investments are made with a view toward securing private capital partners at some point. According to Roman Semenihin, Deputy CEO, as a general rule for Russian innovative startups that are considered under Russian law to be small and medium size companies, IVF RT will acquire not more than 25% equity; in other investment projects (companies that are not small and medium size) a larger percentage of equity participation can be acquired by IVF RT, and participation limits for each investment project are made on a case-by-case basis.[17]

Another government initiative had targeted the shortage of private venture capital, and in 2008 resulted in the establishment of the Russia Venture Corporation (RVC), a state owned fund of funds designed to promote investments in Russian technology. As of December 2012, RVC funds had collectively invested approximately US$400 Million overall in 139 companies, and in the past year alone, completed 36 deals worth approximately US$100 Million. This was accomplished largely through three subsidiary funds and seven closed-end mutual funds. Two of the subsidiary funds (RVC Seed Fund and RVC BioFund) and two of these mutual funds (Russia Bioprocess Capital Ventures Fund (BCVF) (closed in 2007) and Maxwell Biotech Fund (closed in 2008)) were established specifically to invest in biomedical technologies.[18]

In the case of the RVC Seed Fund a maximum investment of 25 Million Rubles (about US$830 Thousand) is provided and at least 25% of its investment demand must be covered by private investors. Subsidiary fund RVC BioFund provides up to 50% of capital demand from innovative biopharma companies capped at a maximum of 100 Million Rubles (about US$3.3 Million) per project. The BCVF, which closed in 2007, has provided from US$2 million to US$8 Million for life sciences and chemical companies, and Maxwell Biotech Fund, which closed in 2008, has provided equivalent funding levels for domestic and international investments for biotech and pharmaceutical companies to develop their innovations in Russia.

Through these funds and the planned development of new ones, RVC actively participates in efforts to improve the ecosystem, legislative efforts and regulation of the industry, and to dismantle the barriers currently preventing the normal functioning of the biomedical market in Russia (*e.g.*, by educating scientists about

14 Katya Soldak, "Venture Capital, Russian Style", Forbes, December 19, 2012, available at <http://www.forbes.com/sites/katyasoldak/2012/12/19/venture-capital-russian-style/>

15 Alla Katsnelson, "Russian fund steps up investments in innovative biotechs", Nature Biotechnology, 2012, vol. 30, pp. 9-11.

16 www.rusventure.ru

17 http://ivf.tatarstan.ru/eng/

18 www.rusventure.ru/en/

innovation and company creation, and by the creation of infrastructure (company creation) to develop and produce pharmaceuticals in Russia). A good example of such support is a joint venture between the RVC BioFund and Quintiles, a worldwide clinical research operator and biomedical consultancy firm, to improve the Russian market for clinical testing.[19] In the past few years, RVC has done about 60 deals in the biotechnology/biomedical sector, investing on the average of about US$2 Million to US$15 Million in each. Investments have been made in companies developing small molecule, peptide, and antibody therapeutics, and in cancer, autoimmune disorders, and cardiovascular disease. Both therapeutics and diagnostics companies have generated interest and investments. In addition, departing from traditional life sciences investments, BCVF has invested in biomedical and fine chemical companies, and RVC's newest planned fund, RVC-Partners (projected to close in 2013), will be entertaining making investments not only in therapeutics, diagnostics and medical devices, but also in software having application in healthcare and research. RVC Partners will be targeting cross-boarder companies — either Russian startups that are entering the U.S. market that will need U.S. sales and marketing expertise and distribution chains, or U.S. startups that want to outsource (in-whole or in-part) their research and development efforts to Russia.

While there are no specific restrictions on RVC investments, nor trends in terms of industry sub-sector, in most cases, innovations close to commercialization have been (and likely will be) the cash winners. Companies that can bring or develop needed pharmaceuticals into Russia or have unique technology platforms, are also preferred. The technology around which the companies are formed can originate in Russia or be licensed from international pharma partners. The particulars of RVC fund investments in companies typically follow Western models in terms of preferred stock and subscription rights.

Like the IVF RT, RVC has openly acknowledged that excessive ownership percentages by one of its funds will discourage future entrepreneur involvement in the portfolio company. Accordingly, it prefers to limit its ownership and encourages (but does not require) a company to seek nondilutive funding sources and grants, and residency in the Skolkovo Innovation Center. However, while many Western VC's commonly syndicate their investments, the Maxwell Biotech Fund and BCVF typically do not seek such co-investors. Nevertheless, an analysis of some RVC-backed deals does reveal a bias for some level of government and/or private participation. For example, in 2009 BCVF invested US$5 million in Incuron LLC, a joint venture with U.S.-based, publically-traded Cleveland BioLabs, to develop cancer therapeutics for the Russian market around Cleveland BioLabs' solid-tumor therapeutic Curaxin.[20] The Skolkovo Foundation provided US$5 Million in additional funding for Incuron. Likewise, TheraMAB LLC was incorporated in 2009 and funded by RVC and Vnesheconombank-backed BCV and by BCV itself, with the technology originating from the German company TheraMAB GmbH. In 2011, TheraMAB Innovation Center "resident" status and now qualifies for laboratory space and additional resources.[21] Similarly, in 2011, CardioNova, Ltd. was founded to develop small molecule therapeutics for atherosclerosis and cardiovascular disease for the Russian market. The company has an exclusive license for its lead drug from AtheroNova, Inc., the joint-venture partner.[22] The Maxwell Biotech Fund provided capital, and CardioNova has been a resident of the Skolkovo Innovation Center since its founding. But not all RVC investments have Skolkovo participation or citizenship. For example, in 2012, Osteros Biomedica, Ltd. was formed to develop MBC-11, a synthetic conjugate of a cytotoxin and a bone-targeting agent for treating multiple myeloma, osteosarcoma, and other metastatic bone lesions. Rights to MBC-11 were obtained from U.S. company MBC Pharma, Inc., who is an equity holder in Osteros.[23] This point does underscore one trend we do see with RVC investments, in that many are structured as joint ventures, most commonly with Western companies that own technology, who license the technology to the new company in exchange for equity. This structure fulfills a stated objective of the Russian government, in that it stimulates in-bound technology transfer while simultaneously providing job creation and economic growth.

For Western companies seeking to capitalize on Russian markets, direct investment by Russian venture

19 "Quintiles and Russian Venture Company Biofund to Expand Clinical Development Capabilities in Russia", Business Wire, February 24, 2012, available at <http://www.businesswire.com/news/home/20120223006576/en/Quintiles-Russian-Venture-Company-Biofund-Expand-Clinical>

20 "Cleveland BioLabs Subsidiary Incuron Receives $5 Million Grant From Russian Federation Government Initiative", Marketwired, September 19, 2011, available at <http://www.marketwire.com/press-release/cleveland-biolabs-subsidiary-incuron-receives-5-million-grant-from-russian-federation-nasdaq-cbli-1562617.htm>

21 http://theramab.ru/en/news/skolkovo

22 http://www.cardionova.ru/?ln=en

23 http://maxwellbiotech.com/content/osteros-biomedica-ninth-maxwell-biotech-group-portfolio-company-listed-resident-skolkovo

capital sources is unlikely unless there is a clear connection to an existing Russia company or an opportunity to bring particular technologies into Russia. But there are indications that Russian venture capital is starting to look beyond the boarders of the country for investment opportunities. However, for many companies, the barrier to doing business in Russia is not capital, but rather local laws and customs and the lack of strategic relationships in the Russian markets. To this end, government sponsored venture capital funds may also provide access to larger initiatives such as RUSNANO and the Skolkovo Foundation. Among the BRICS countries then, due to these efforts Russia seems to be emerging as the leader in terms of advancing technical innovation and promoting a strong private biotechnology sector. With constant improvements in the laws and regulations relative to business and technology rights, government incentives and capital, strong universities and innovation centers, we expect this trend to continue.

Original Article

Funding biotech start-ups in a post-VC world

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ABSTRACT

Investment in start-up biotech companies outside the USA has essentially disappeared. VC investment in biotechnology and healthcare as a whole has nearly returned to pre-2008 levels, but almost all is in later stage opportunities. But companies continue to be founded, and continue to flourish. We examine the VC investment patterns for the past 7 years, and show that a start-up today can expect little VC support. We show from companies' financial records that companies are adopting financial models based on angel investment, grants and revenue, and moving away from business models that need substantial investment. There is a time lag, but government and research council policy is beginning to recognize and align with the new investment realities. We believe this trend will accelerate as internet-mediated angel investing, such as crowd-funding schemes seen in other sectors, become a developing force in the next decade.

Journal of Commercial Biotechnology (2014) 20(1), 10–27. doi: 10.5912/jcb628
Keywords: finance; venture capital; business angel; start-up

INTRODUCTION

Biotechnology has been perceived historically as driven by institutional investors who back private companies with substantial risk capital, commonly termed Venture Capital (VC).[1,2] After a dip in VC investment in 2008-2009,[3] VC investment was stated as being back to a 2005 level of $6bn-$7bn/quarter (www.pwcmoneytree.com), and in biotech investment was stated as being stable at $5.3bn-$5.5bn per year from 2008 to 2011 (compared to the annual figure of $6.7bn in 2007).[4] VC continues to be presented as an attractive asset class for investors compared to public stocks.[5,6] This is despite fairly robust evidence to the contrary;[7,8] and confidential surveys suggest that, privately, the industry is less optimistic.[9]

Venture Capital is "a professionally managed pool of capital that is invested in equity-linked securities of private ventures at various stages in their development".[10,11] VC usually invests in companies with high risk and correspondingly high rate of return if successful,[11] especially in early-stage companies with high capital requirements for developing new products. Biotechnology is a major category of such companies. VC mitigates the risk of such investment by substantial engagement with investee companies.[12] Conventional VC theory states that the VC management group is motivated to maximize returns

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from its investment through an interest in the profit on the funds it invests (reviewed in (13)), although it is not clear this model of VC behaviour works in the context of the biotechnology industry, where profits in funds are rare.[7] VC investee companies are claimed to be more successful than non-investee companies,[13,14] although whether this is an effect of VC intervention and investment, the effect of VC investment signalling to others the quality of the company (regardless of the VC investment or intervention itself),[15] or VC's selection of more successful firms as targets for investment[16,17] is still debated.

Depending on one view of what motivates VC to invest and whether VC investment affects investee company outcomes, one might expect the "credit crunch" financial crisis of 2008-2010 to affect VC investment to a greater or lesser extent. The conventional model of VC suggests that a downturn in investor sentiment should provide an opportunity for increased VC investment, both in companies with attractive pricing and in assets being divested as companies focus on core business.[18] The aggregated figures reported above suggest that, after a slight downturn, VC enthusiasm for biotechnology has returned, indicating that VCs have an active, forward-looking view of the industry even though the market for biotechnology IPOs at the time was still weak.[19,20] However, in contrast to headline announcements of a return of VC to the sector, surveys of companies in the USA,[21] and the anecdotal reports* of many entrepreneurs in the UK, suggest that VC finance has not returned to early stage biotechnology. Money is always hard to come by, but since 2007 acquiring investment of any sort for new, innovative companies has seemed a Sisyphean task. Why is this so, if funds are expanding and investor appetite for genuinely breakthrough and disruptive businesses remains as strong as ever?

In this paper we explore this conundrum by analysing the actual evidence along two dimensions: what VC investment funds are actually being used for; and how companies actually get financed. Specifically, we explore the hypothesis that VC capital has not actually returned to early stage investing, that aggregate figures on VC investment overall reflect a return to investing in late-stage companies not innovators, and we examine how biotechnology companies in one specific biotechnology cluster have responded to this change.

We examine two aspects of the commercialization of life science knowledge as a "biotechnology" company (as discussed below): a narrow definition based around healthcare biotechnology, and a broader definition based around any commercial exploitation of life science intellectual property. VC has almost exclusively supported the former, narrow type of biotechnology.[1] Overcoming selection bias is a major problem for such studies (see for example the discussion in the introduction to (22)), and so we have attempted to survey all the VC investment in biotechnology in the 2005-2011 period, and explore how companies have adapted to changes in the investment environment with a similarly comprehensive survey of the Cambridge (UK) area biotechnology cluster.

Our study finds that VC has essentially fled from supporting new companies of this type in Europe; particularly in the UK, we live in a post-VC age. But study of both the narrow and wider type of biotechnology companies in the Cambridge cluster shows that they have nevertheless found a variety of creative alternative funding sources. This, and emerging trends in internet-mediated funding, point to a bright possible future for biotech, providing neophyte biotechnology companies are prepared to embrace the new models.

METHOD

What is biotechnology?

Biotechnology is the exploitation of knowledge of the life sciences for industrial use; in a commercial context, this means exploitation to generate wealth.[23] A broad definition of a biotechnology company is therefore any company that uses knowledge of biology to provide products or services. This we term "Broad Biotechnology". However public markets and institutional investors overwhelmingly invest in biotechnology companies that develop products for human healthcare (see, for example, the explicit or implicit definitions of the industry in (2, 24, 25, 26)). This narrower form of biotechnology we term "Healthcare Biotechnology". In principle, a scientist or an entrepreneur with novel understanding of biology or a novel concept for commercializing biological knowledge could apply that to Healthcare Biotechnology, or to a non-healthcare application within the wider envelope of Broad Biotechnology, the relative attractions of the two paths depending to an extent on the nature of the biology, but also on the financial and commercial options available to Broad Biotechnology and Healthcare

* We do not have objective or statistical data for this statement. However between us we helped raise over £60M in early-stage investment for 10 UK biotech companies, invested personally in 3 (other than as a founder or executive), and provided Board level guidance to a total of 26 start-up projects, companies or investment funds over the last 15 years. We believe that our experience, and the experience of the many entrepreneurs we have worked with in this time, gives us reason for supposing the statement to be an accurate representation of the "entrepreneurial ground-swell" in private UK biotechnology finance.

Biotechnology. We have therefore analysed both Broad and Healthcare Biotechnology in this paper. However, we have focussed our conclusions about VC funding on Healthcare Biotechnology only.

VC DEALS DATABASE ANALYSIS

Data on Venture investment deals was abstracted from the MedTrack database (http://www.medtrack.com/). All of the deals coded in the database as relating to companies in the industry sectors biotechnology, pharmaceuticals, healthcare, medical devices were used. Deals coded as Venture Financing or Venture Capital, Growth Expansion Capital with deal dates 2005-2011 were extracted. Manual inspection of these showed that some were actually sales of VC-funded companies rather than VC funding deals, and these were excluded.

Company names, the country of incorporation and websites addresses were validated manually using internet resources, primarily the Internet Wayback Archive (http://archive.org/), Bloomberg Businessweek (http://investing.businessweek.com), New Statesman (http://www.newstatesman.com/company-profiles/healthcare), and VC Experts (https://vcexperts.com/). Company ages were compiled manually from the same sources, primarily Bloomberg Businessweek or companies' own website histories. When neither of these resources nor further internet searches yielded a clear date of foundation of the company, the date for first registration of the company domain name was used as a proxy for foundation date. The year of domain-name registration was found to correlate well with the self-reported year of company formation date with a correlation coefficient of 0.643 for companies founded after 1997 (when the Internet Archive started indexing company web sites).

Company location was taken from the company web site where it was announced (or inferred from company telephone contact numbers). For companies with more than one location, the location of the major activity or corporate headquarters was used. Note that this is often not the same as the location of company registration, which is a "legal fiction" and not an operating reality.

Deal sizes were extracted automatically from MedTrack text data, and converted to US dollars.

CAMBRIDGE AREA COMPANY ANALYSIS

All the companies falling into the Broad Biotechnology category were identified in the region of Cambridge, UK using methods developed from those used by,[27,28] The Cambridge region was defined following the Library House definition of "The Cambridge cluster". [29] This source defines the area as all "CB" postal districts, PE28, PE29 and SG8, with the addition of biotech companies based in the Norwich Research Park and surrounding area (postal codes NR1, NR4 and NR20), as this sub-cluster has become active after Library House performed their cluster analysis. The data set considered only biotech companies which exist as separate entities (i.e. not part of a subsidiary) in the period between 1st January, 2008 and 31st December, 2011.

Broad Biotechnology companies were identified in the target geography through a multi-layered approach. Company names were identified from

1. The membership lists of industry interest groups (UK Bio-industry Association, London Technology Network (LTN), Eastern Region Bioindustry Association (ERBI)—ERBI and LTN have since merged to form One Nucleus)
2. Past and present industry directories
3. Science and industry park directories for Cambridge Science Park, Granta Park, Great Chesterford Park, Cambridge Research Park at Waterbeach, and Norwich research park
4. Social network groups relating to UK science and technology, especially LinkedIn
5. Personal contact lists and databases compiled for previous studies of the Cambridge biotechnology cluster, especially ref. 28.

Most companies were identified multiple times through these different sources, which gives us confidence that few companies were not identified by this method.In addition, the list was spot-checked with eight Cambridge-area entrepreneur/investors, who found no companies of which they were aware were missing from the list.

Companies were identified as Broad Biotechnology companies from direct examination of their web site for their own statement of their principal business activity. Companies involved in any of Industrial Biotechnology, Medical Biotechnology, Bio-manufacturing, Contract Research, Crop Development, Medical or veterinary Diagnostics, Drug Discovery or Therapeutics development, Laboratory Technologies development or sale were included. Companies primarily providing professional support to biotechnology companies, such as patent agents, legal firms or general business consultancies, were not included. In marginal cases, the criterion for deciding whether a company fitted the Broad Biotechnology decision was whether the business product or service was primarily derived from knowledge of biology (not necessarily formalised into Intellectual Property (IP) Rights).

Thus, for example, a company such as Hypoxium providing specialist contract test services in the field of low oxygen cell culture was included, because their business relied on expertise in this specific area of biology, whereas a company such as BioLauncher providing business development support services to biotech SMEs was not included, because, although their staff had bench science experience in the life sciences, the company's own IP was in expertise and knowledge in marketing and contracts in the bioscience space, and the life science IP was brought to them by their client companies.

Financial and shareholder data for the Cambridge area companies was extracted from the FAME database, accessed through the Judge Business School (University of Cambridge).

A full list of the global VC investee companies and the Cambridge area Broad Biotechnology companies is available on request.

RESULTS

The global VC funding landscape

Reports of VC financing of biotechnology start-ups usually draw aggregate figures from generalist VC databases (i.e. covering a range of industry sectors), or rely on self-reporting from VC groups on their activity. Neither can be used reliably to find out how new biotech companies can be funded. We therefore analysed every VC deal in the healthcare/biotech industrial area in the 2005-2011 period in the MedTrack database (http://v1.medtrack.com/—access and data kindly provided by Biotosacana Farma S.A.). Additional data was gathered from internet sources on the companies (See Supplementary Material). Anecdotal data suggests that many companies have been funded "under the radar" in the last few years with minimum public announcement, but we found that websites, location and age data could be successfully gathered from 96.5% of the VC investee companies analysed, even when no press release had been given for the investment.

The aggregate number and value of VC investments in biotechnology dipped significantly in 2007-2009, and the exuberance of 2007 had only been partially recovered by 2011 (Figure 1). However investment is clearly returning to pre-credit-crunch levels. Around 63% of the investee companies, 67% of the deals and 73% of the invested sums were in the USA, with a heavy concentration in the known clusters in New England and California. Average amounts invested per deal are significantly higher in these clusters and lower in some European territories (Figure 2). Some territories, such as Germany and the BRIC countries, show a significant

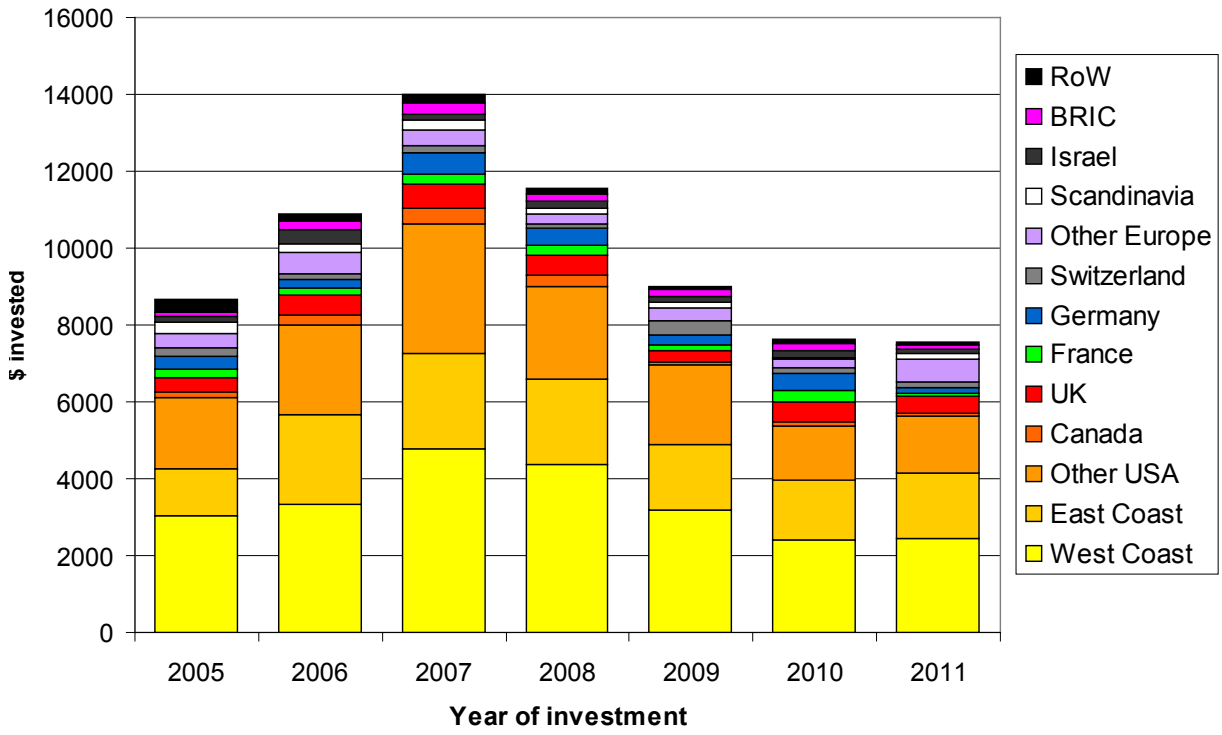


Figure 1: VC investment in biotech, 2005-2011
Aggregate value of investments in biotechnology companies, 2005-2011.

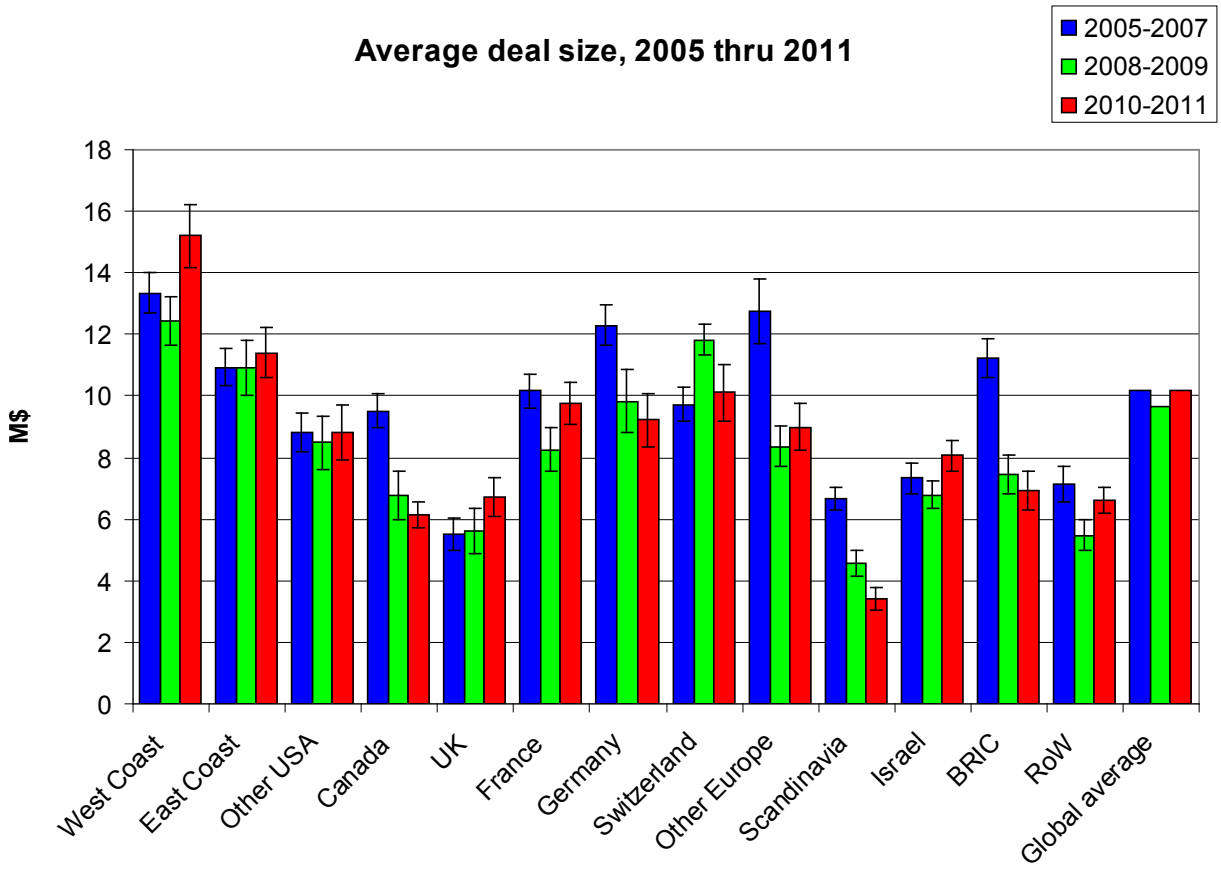


Figure 2: Investment by size
Average deal size in VC investments in biotechnology 2005-2011 . Error bars are 1.98 times standard error of the mean.

decline in average deal value between the 2005-2007 period and the 2008-2009 period.

So is the entrepreneur-reported fall-off in investment a myth? Closer examination of the data suggests otherwise. VC investments are typically described in Series—A, B, C etc—which reflect the seniority of the shares created at each round. Pre-A rounds are also common; they are referred to as "Seed" rounds in MedTrack (and this paper adopts the same terminology). The usual assumption is that Seed rounds occur around company formation; Series A rounds as soon as the company begins serious operations, Series B rounds when the funds from Series A have allowed the company to achieve a significant milestone and consequent value uplift, and so on. In other words, the share structures reflected in the A, B, C nomenclature often assumed to be a reflection of the age and maturity of the company.

However, while B rounds almost never come before A rounds, the "alphabetical terminology" does not match well with actual company age. Drug discovery company Karus Therapeutics (Southampton, UK) raised their first major VC round (labelled Series B for technical reasons) in September 2012, seven years and £3.2M of non-VC investment after the company was founded.[30] Drug discovery company Mission Therapeutics received their first major VC investment in August 2011,[31] three months after incorporation. Clearly the two are not comparable—Karus' investors, innovators and management have had to sustain the business (including substantial patent costs†) for nearly thirty times longer than

† Karus Therapeutics has 11 patent families listed in the European Patent Register, all with priority documents filed in the UK. We assume that Karus follows standard practice of filing a priority document in the UK, then proceeding through the PCT mechanism to US, EU, China and Japan. We can estimate filing and prosecution (not post-grant) costs in these territories. Filing, EU translation and prosecution costs were estimated from,[32] China and Japan translation costs from ~£5000/filing for China and Japan (from http://patentcost.co.uk/sand[32]) and professional fees of £1000 for drafting and £1000/patent/year for each of UK, EU, US and all other territories together (a low number, but not

Figure 3: Number of deals by stage, 2005-2011
A fraction of all deals done in a year, divided into "early" (seed or Series A), "mid-stage" (Series B-E) and "late" (later deals). I: deal numbers and II: deals by total declared value, are shown.

implausible—see for example the discussions in http://www.ipwatchdog.com/2011/01/28/the-cost-of-obtaining-patent/id=14668/, http://www.aboypatentlaw.com/newsite/wp-content/uploads/2011/05/Services.pdf), this suggests a minimum patent protection budget for Karus of ~£340,000 since its inception to mid 2013.

Mission Therapeutics before they were allowed significant investment. The Karus example is not unique, and companies that receive investment several years after start-up are clearly not "start-up investments" in the sense of a new business. Seven years is rather less than the average time between first VC investment and the average successful "trade sale" exit.[33]

To gain a statistical measure of the delay between foundation and investment, we estimated company age by using web resources to gather evidence of when companies had been founded. This may be some months or even years after the entrepreneur has had the "light-bulb moment" of realizing that there is an opportunity to exploit; company formation is when the corporate structure is put in place to exploit that opportunity. In the few

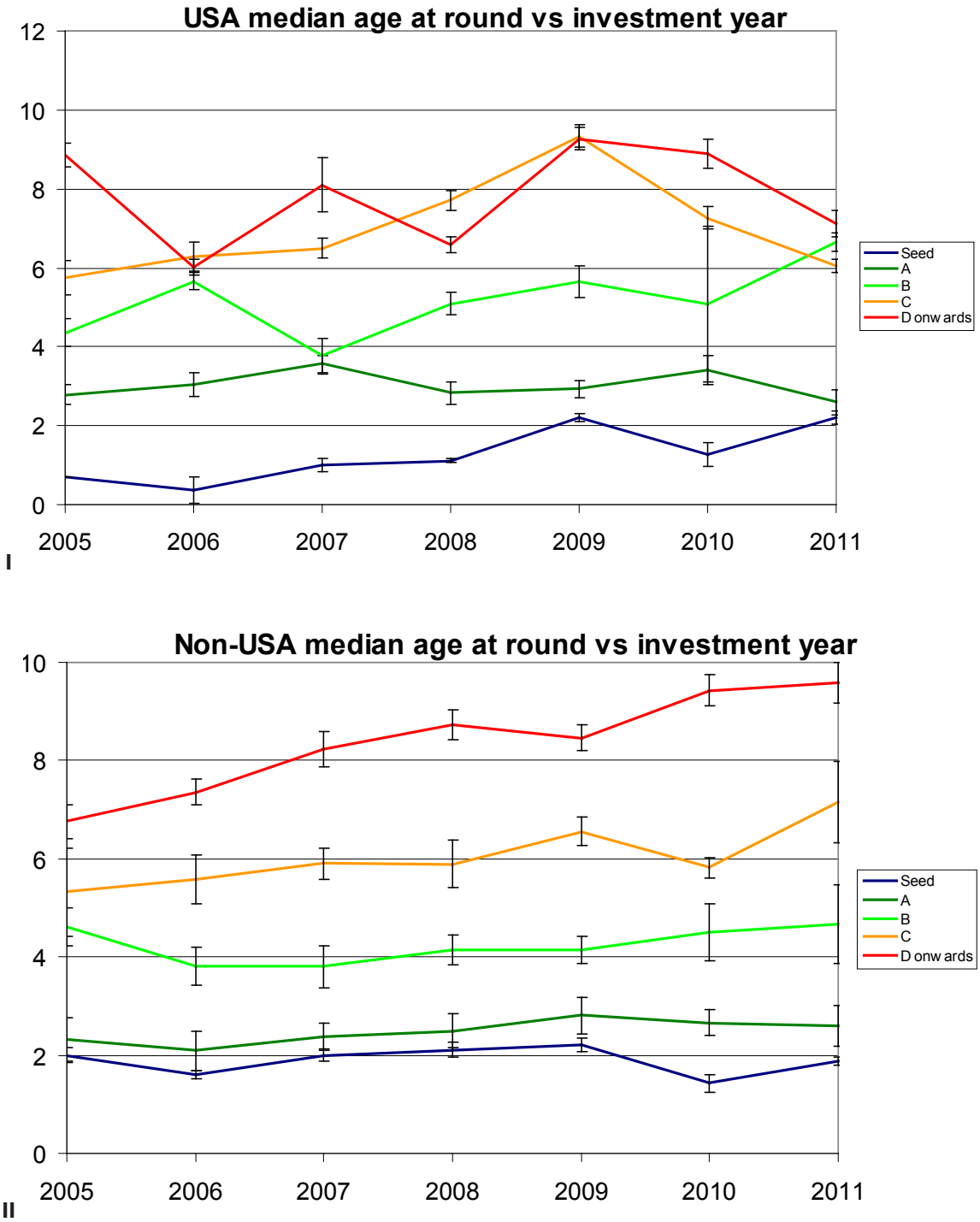


Figure 4: Age of investee companies

Median age of investee biotech companies in the VC investment dataset at the time of investment, by investment stage and year. X axis—year of investment. Y axis—age of company at time of investment. Error bars are 3 times the standard error of the mean (~99% confidence limits).

cases directories, corporate histories and the company web site itself gave no indication of when a company was founded. In these cases, the date of the company's first web site with some significant content, as determined from archived copies at www.archive.org, was used as a proxy. Comparison of the web site origination with foundation dates for companies where both are known showed that, for this set of companies, a content with significant content was created 6-12 months after company foundation.

Figure 4 summarises the data for this dataset, and shows that a "seed stage" investment is usually made 2 to 3 years after the company has been founded, and Series A (the first formal or significant investment) is made in companies of 3.5-4 years old. Both these ages have risen slightly over the last 6 years, notably in the USA where "seed stage" used to mean funding at the inception of the company, and now means (on average) funding some 30 months after inception. There is a substantial spread of ages (Figure 5) with many companies receiving VC investment up to half a decade after they started. Note that this view only covers companies that *successfully* raised VC funds.

If start-up funds for actual start-ups are absent, does this imply that VCs are directing their attention to later stage opportunities? Figure 6 confirms this is the case—the large majority of the deals and the funds are directed to older companies. But the pattern of when deals are done has changed significantly globally and in the UK, and the pattern of the aggregate amount invested in companies of different ages has changed as well. Both the number and value of deals has declined in the USA (suggesting that the amount invested per deal has remained relatively constant). In Europe, however, while the number of early stage deals (investments in companies less than 4 years old) may have increased in 2011, the aggregate value has remained low. In both territories, the number of investments and their value in older companies has increased consistently over the 2005-2011 period. Notably also, again in both territories, the amount invested in companies 2-4 years old has declined dramatically. We would expect this to have a particularly severe impact on companies in the UK which, it is clear from Figure 2, receive substantially less investment per round than the USA, or than some other European countries. In the UK funding has essentially vanished for young companies since 2007.

To summarise, the feeling "on the ground"[21] that we are living in a post-VC era is justified outside North America for start-up biotech companies. While the aggregate figures are good, investment in early-stage companies has dried up. In the USA there is an early-stage VC drought, but "the species is not yet extinct" (Figure 6).

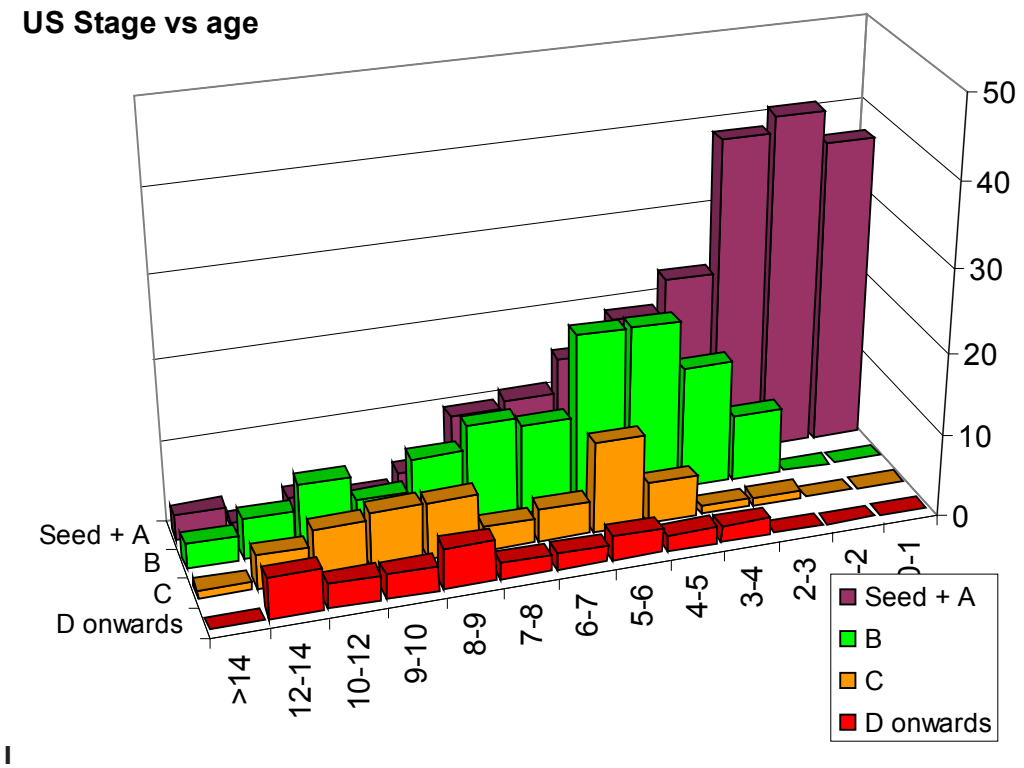
This pattern of investment is supported by analysis of the activities of individual investment houses. We examined the portfolio of three major VC groups[‡] who stated on their web sites and in promotional presentations that they invested in all stages of company, from seed to late stage growth capital. While in 2005-2006 this spread of investment was clear in their portfolio, investments from 2008 onwards were *exclusively* in: late stage, near-revenue companies; projects with Phase II clinical trials under way; or in companies that were already in their portfolio before 2007. They were not, in reality, investing in early-stage companies.

Financing sources in Cambridge (UK) Healthcare Biotechnology

The overriding view is that early-stage investment has almost dried up outside the USA. To receive VC investment, a British company has to be founded, grow, develop, make products, file IP etc, all without any external VC investment. This is clearly implausible, and the lack of VC funding consequently has led many entrepreneurs to announce that the era of biotech start-ups is over outside the USA. But a visit to a UK science park or innovation centre does not support this conclusion either: several in the Cambridge area have announced major expansion plans and near complete occupancy of new buildings (for example, see news stories in (34-37)). So if there is no money, how are these companies surviving? In an effort to find out, we examined the financial records of all the biotech companies in the Cambridge cluster in the UK. UK companies are almost uniquely well suited to such study, as the British Companies act 2006 requires extensive public disclosure of the names of shareholders, their shareholdings, and the class, attached rights and purchase price of the company shares. Private company accounts are also public documents in the UK, although Companies filing accounts under the Small Company Exemption (companies with turnover not more than £6.5m, or a balance sheet total not more than £3.26m, or no more than 5 employees—see https://www.gov.uk/audit-exemptions-for-private-limited-companies) can file much abbreviated accounts that contain little data relevant to this analysis.

Biotechnology companies were identified from trade associations, science park occupancy, a range

‡ The analyzed VC management groups were selected as being major players in biotech, one primarily operating in Continental Europe, one in the UK and one on the East Coast USA, but as we have not done a statistical survey to prove that they are representative it would be invidious to name them.



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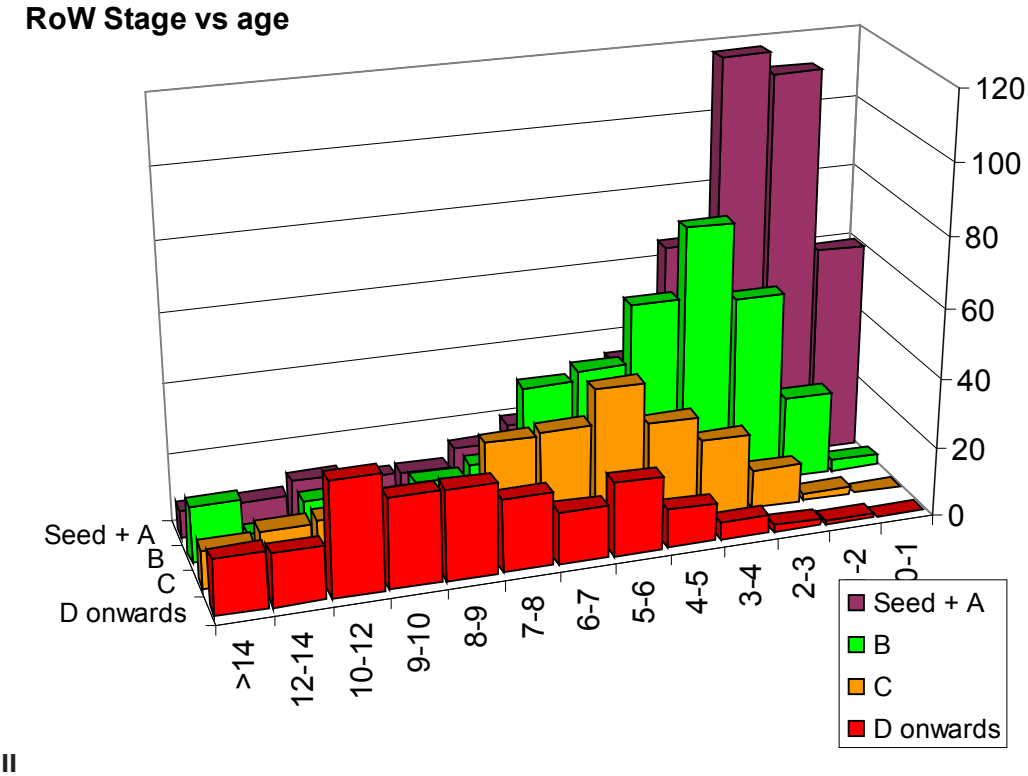
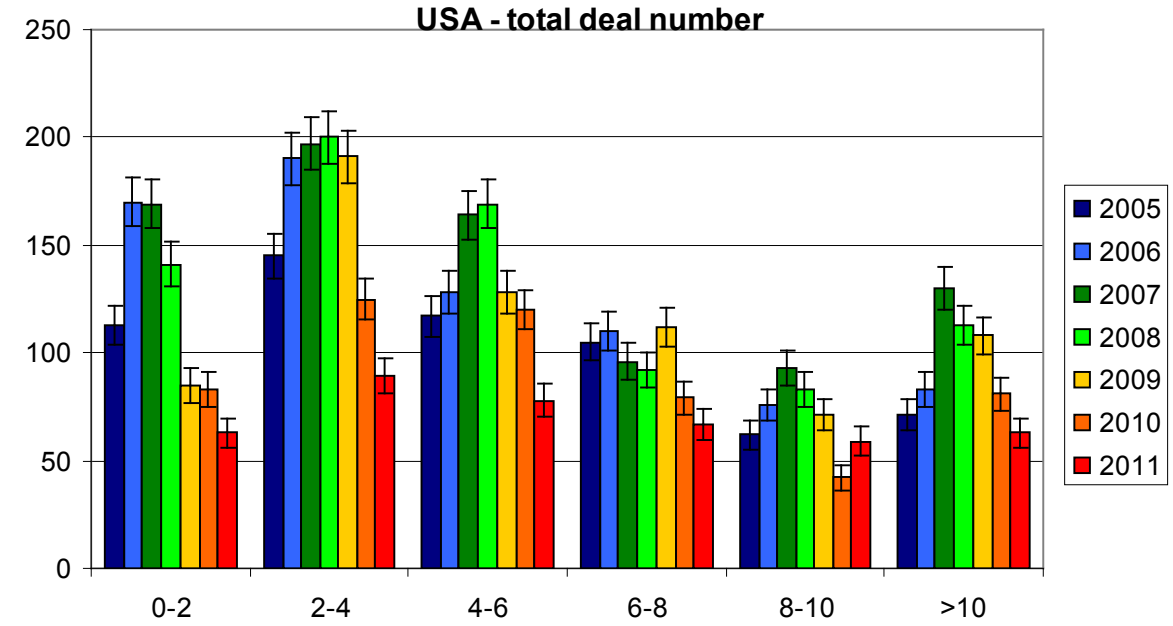


II

Figure 5: Distribution of company ages at investment 2009-2011

Number of VC investment deals, by stage and age of investee company. X axis—age of company at time of investment. Y axis—number of deals. Z axis—stage of deal. Deals 2008-2011. Panel I: USA companies, Panel II: Companies from rest of the world.



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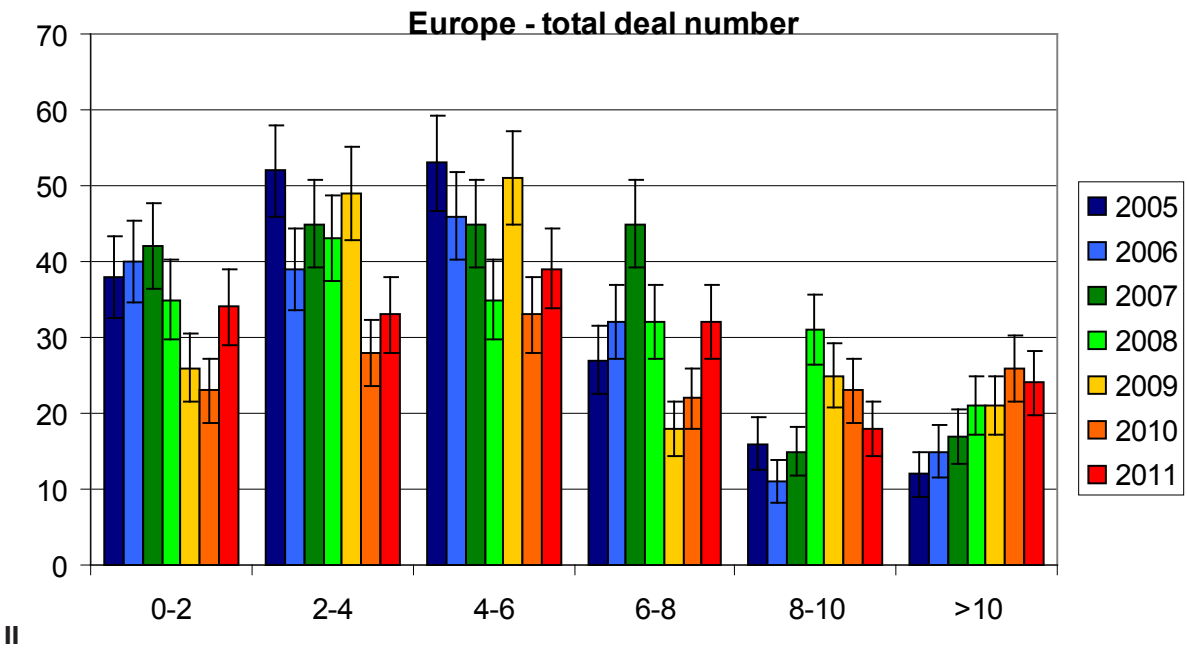
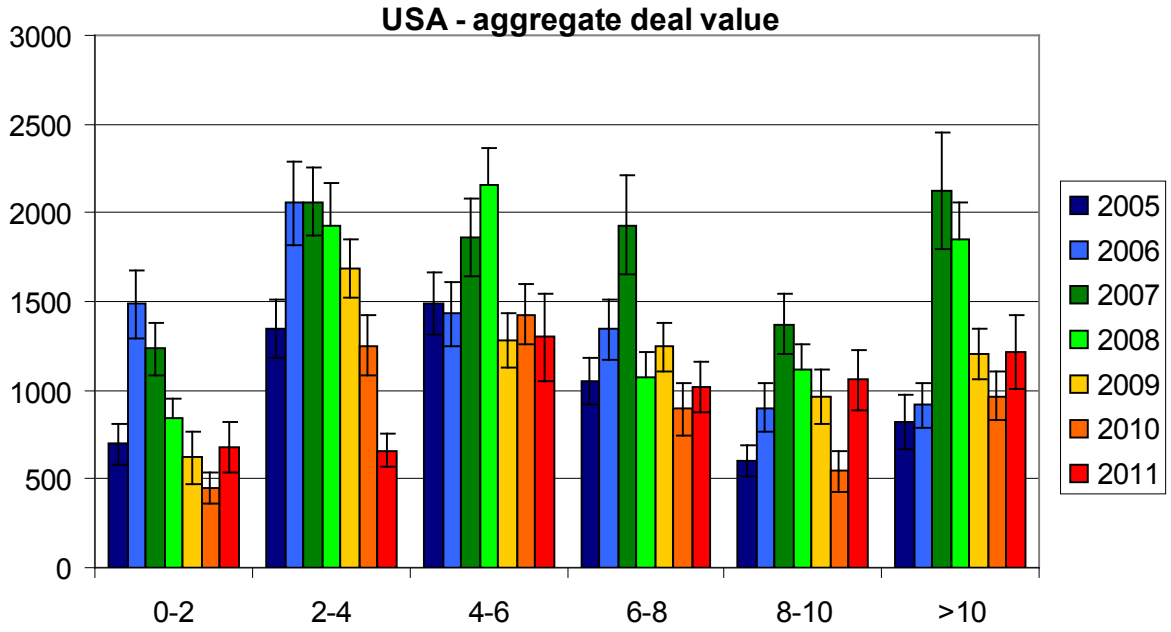


II

Figure 6: VC investment by company age, year

VC investment in biotechnology companies in the USA and Europe, by year and age of company. Data from two-year time periods (shown on X axis) was aggregate to provide a total number of investments (Panels I and II) or an aggregate declared value of the invetsments (panels III and IV) for the USA (Panels I and III) and Europe (panels II and IV). All deal values in millions of US dollars. Errors bars were computed as follows. Because the value and number of deals is not normally distributed and has very different variance year-on-year and age-on-age, an estimate of the effect of omitting deals from the data set was estimated by simulation, as follows. 4000 sets of data were generated in which 25% of the deals were randomly omitted (Excel RAND() function). The standard deviations of the total number of deals (Panels I and II) or the aggregate value of deals (panels III and IV) were calculated for each year+age combination. Error bars are plotted as 1.98 x that standard deviation. These are an *estimate* of 95% confidence limits on the numbers shown.



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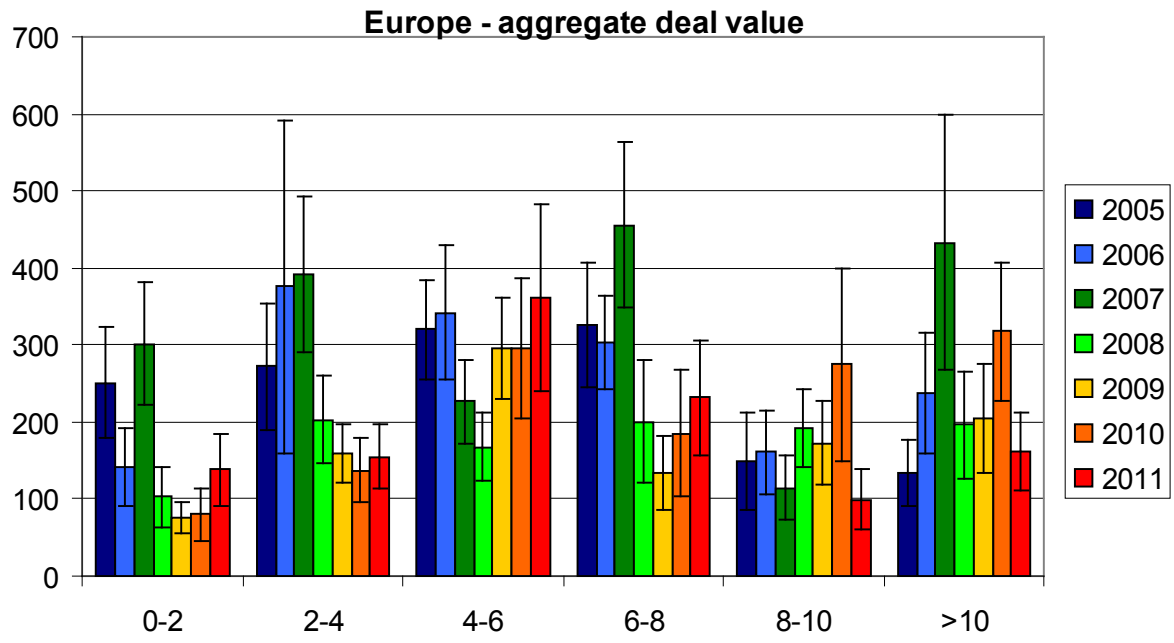


IV

Figure 6: Continued

of directories, and confirmed by personal discussions with 9 entrepreneurs and angel investors active in the Cambridge cluster biotechnology community. [38] 192 companies were identified in and around Cambridge, UK, whose business is (or was) based primarily on the exploitation of technical knowledge or IP in the life sciences, and which were active in that business in 2008 or after regardless of when they were funded.

We first examine the finances of the Healthcare Biotechnology companies in the UK. These are the companies with similar business models to those analysed in the sections above: they were founded to gain substantial investment to enable them to develop products for the human healthcare market, usually based on new scientific or technical insights into how to treat human disease, and usually with an expectation that their products would be licensed to another company before

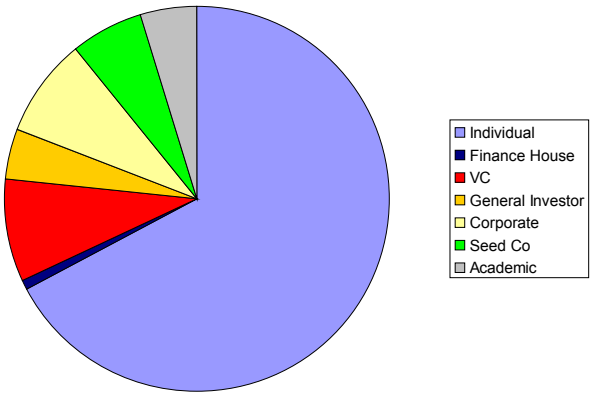


Figure 7: Average number of shareholders in Cambridge Healthcare Biotechnology companies, by shareholder category
Average number of shareholders in each category. For each company the fraction of the shareholders in each shareholder category was calculated: shown is the average of these fractions. For example, on average 67% of the shareholders listed in the Company Register were individuals.

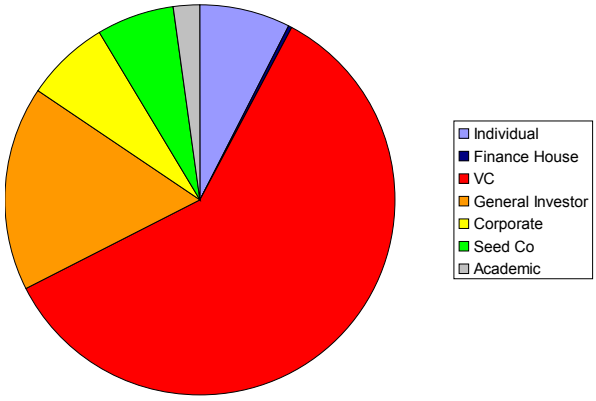


Figure 8: Average fractional shareholding in Cambridge (UK) Healthcare Biotechnology companies, by investor category
Average fraction of shareholding held by shareholders in each category. For each company, the fraction of the total shares in each company that were held by each shareholder was calculated: shown is the average of those values. For example, on average 61% of the shares in this set of companies was held by Venture Capital groups.

commercial launch. However, unlike those in the global analysis of VC investment above, they have not been selected because they are the recipient of VC investment, but only because they have a Healthcare Biotechnology business model.

We identified 42 such companies in our Cambridge (UK) dataset, most of which have received some investment, even if only from their founders. Figure 10 shows that the large majority of these companies have received investment, although a minority (8 companies) was built essentially without external investment beyond their founders and executives investment. Most however did not rely solely on investment for their financial resources, but also got funds from sales, collaborative revenues or grants.

Shareholder data was obtained from company records filed with Companies House, the UK central depository of company financial, shareholding and accounting information. The large majority of shareholders in the 42 companies analysed were individuals—only 6% of the shareholders were Venture Capital groups (Figure 7). Surprisingly, VCs held only slightly more than half the shares in this group of companies (Figure 8). This includes companies that are over a decade old, and had followed the "classic" biotech business model of reliance on VC investment, and thus have had time to accumulate a substantial VC investor base. This illustrates that VC investment is not a dominant financial mode for UK Healthcare Biotechnology companies.

Few shareholders hold shares in more than one company. Only Cambridge University and Cambridge Enterprise hold shares in more than 5 Cambridge area biotech companies (Figure 9). This implies companies are exploring a wide range of sources of funds, rather than simply approaching a small number of well-known sources of investment.

Broad Biotechnology companies in Cambridge, UK

The lack of concentration of shareholding in the Healthcare Biotechnology companies leads us to examine the wider biotechnology cluster economy in Cambridge. As noted in the Methods section, new knowledge and IP in the life sciences does not have to be applied in healthcare product development—depending on the knowledge, it can be applied in a range of commercial modes. We therefore sought to see if the Broad Biotechnology industry in Cambridge could give us further insight into how the geographic cluster was flourishing despite the observed limitations of VC investment.

The most immediately obvious result was that many of the Broad Biotechnology companies have revenue sources to support their business. Only 13% were supported exclusively by investment (Figure 10), around 42% had no investment at all, the rest having a combination of investment and revenue. Companies currently in business are more likely to be partly or entirely revenue-supported. Companies that have been acquired, liquidated or gone dormant in the last 5 years are more likely to be supported

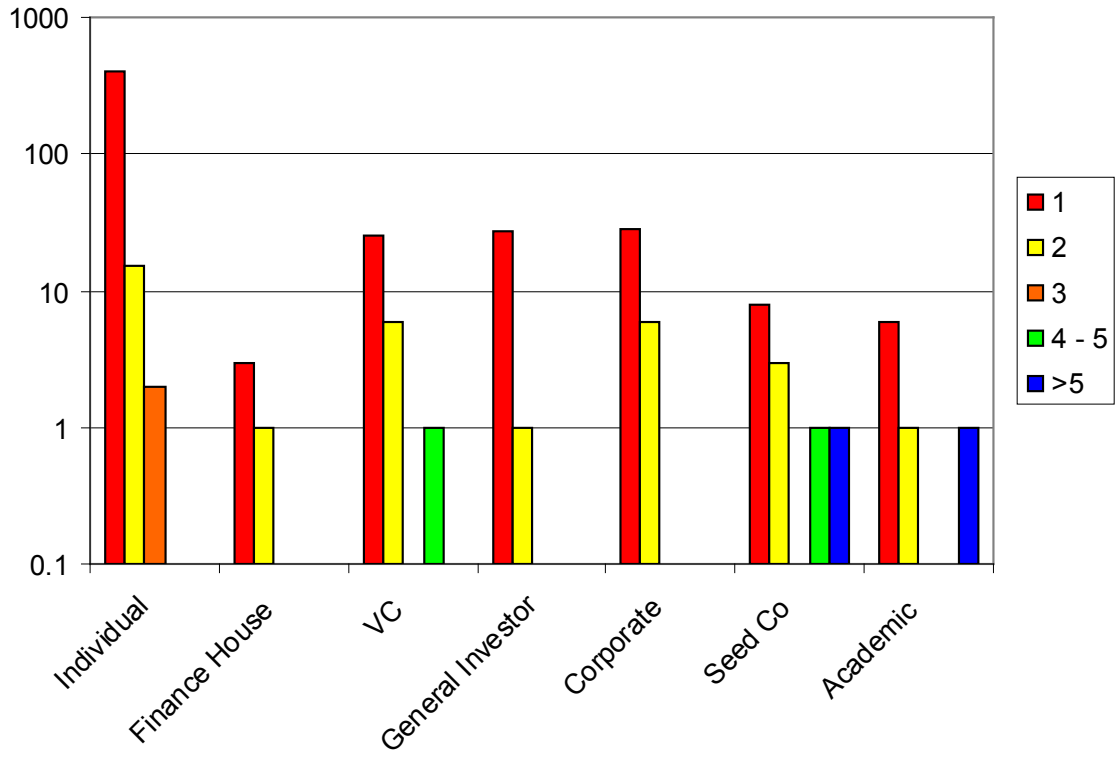


Figure 9: Shareholder dispersion in Cambridge Biotechnology companies
Number of shareholders in different classes, by number of Cambridge area companies in which they are shareholders. X axis—category of shareholder. Y axis—number of shareholders. Each bar represents the number of shareholders in that category that hold shares in 1 (red), 2 (yellow), 3 (orange), 4-5 (green) or more than 5 (blue) investee companies *in the Cambridge cluster.*

entirely by external investment. However this probably reflects the different business goals of the stakeholders in the deceased companies rather than a malign influence of investors on business survival.

Analysis of company age versus size, financing source and business model shows no clear pattern (Figure 11), companies of varying profiles can get funds from all sources. This is in part a reflection of the breadth of business models involved. Although the business model described as standard by the investment industry[39] and its government supporters (see e.g. (24, 40, 41)) is a high-growth, investment-driven therapeutics discovery company, in reality a wide range of other businesses can create value from life science IP.

Limitations

While this survey sought to be a systematic, bias-free review of a specific geography, we apply two caveats:

- It is very hard to prove any survey is complete. While we are confident that the large majority of companies operating in biotechnology in the Cambridge area were identified, based on "triangulation" of data from a number of sources, we cannot claim 100% coverage
- Similarly, we relied on Medtrack for VC deals, and this database is not universal.

CONCLUSIONS

We have analysed how start-up biotechnology companies are financing their business in the post-VC era in the UK. We have documented the decline of conventional Venture Capital, and that a diverse range of other sources of funds have been tapped to fill the gap left by the traditional VC funding of early stage start-ups exploiting the Broad Biotechnology business model. Even within Healthcare Biotechnology, companies are clearly seeking investment from a wide range of sources, are no

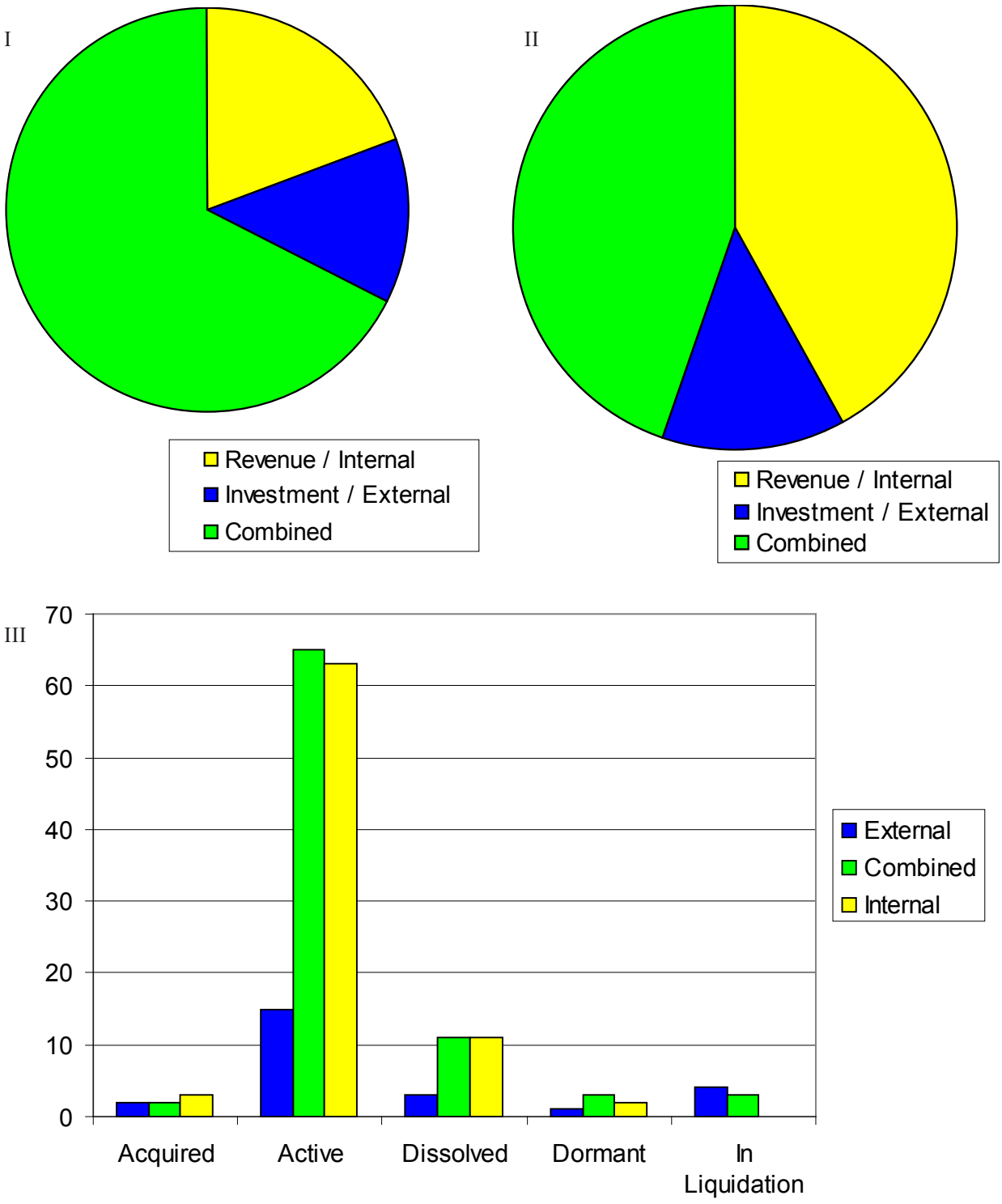
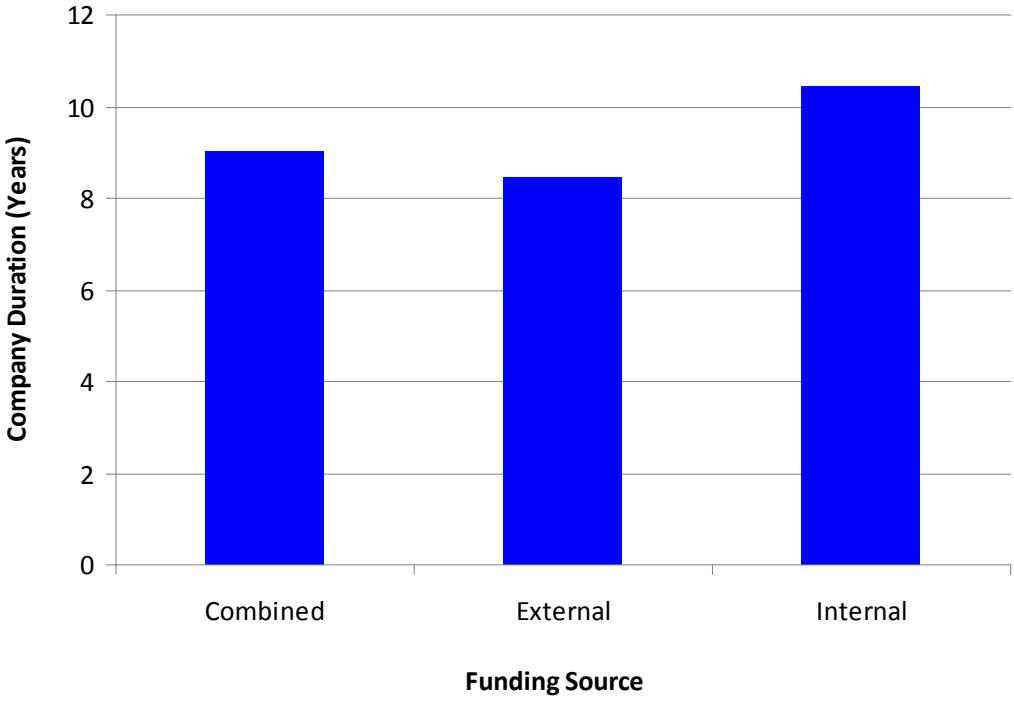


Figure 10: Overview of financial resources of Cambridge area companies
Financial resources for Cambridge area biotechnology companies. Financing resources for companies are classified from their accounts and shareholder information as "External" (investment), "Internal" (revenue, including grants), or "Combined" (both investment and revenue). Panel I: breakdown of financial resources of healthcare Biotechnology companies. Panel II: financial resources for all of the Broad Biotechnology companies in the Cambridge cluster. Panel III: analysis of all of the Broad Biotechnology companies by status of companies.

I: Funding source versus company duration



II: Funding source versus company status (where inactive includes companies which were dissolved, became dormant or liquidated between 2008–2011)

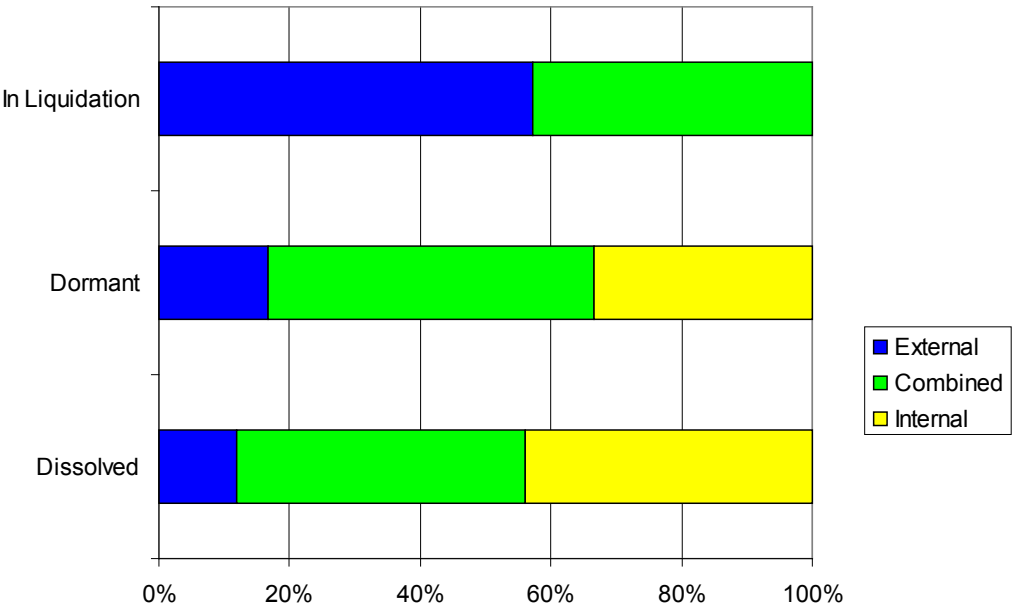


Figure 11: company business models and financing

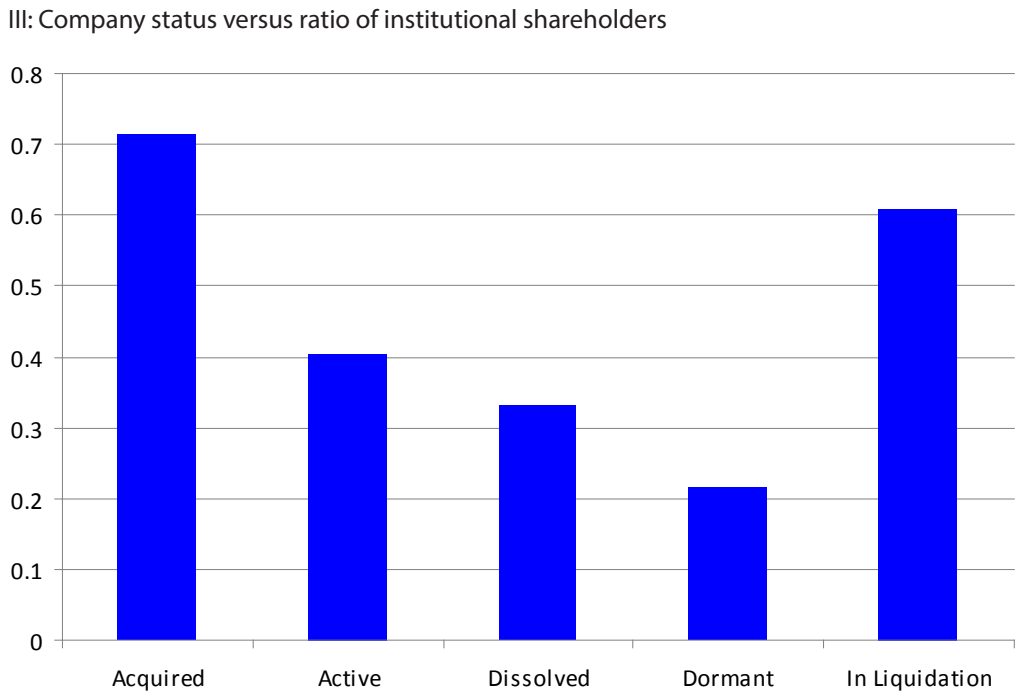


Figure 11: continued

longer relying on Venture Capital, and are seeking non-investment sources of finance.

A wide range of financial resources have been tapped into by the Companies discussed in this paper. We have not systematically surveyed the non-investment sources of income, but we note that the following have been used successfully in UK Broad Biotechnology

Business Angel investment: Loose affiliations of generally specialist investors (i.e. investors with some sector-specific knowledge or interest).

Non-VC institutional investment: Some companies have successfully acquired substantial investment from institutional investors other than Venture Capital. Oxford Nanopore Technologies[§] has raised over £130M in investment from non-VC investors.

Grants and non-dilutative support: Companies have become adept at seeking non-commercial support for their businesses, such as specific technology, new business or sector funds

Revenue: Many of the Cambridge area companies support themselves on revenue. This gives them a fundamentally different business model to that of VC-backed companies; they can then apply to VC for growth capital (as did Horizon Discovery in Cambridge in July 2010).

None of these are exclusive, and often form a continuum of financing from investment seed through non-dilutative grant and revenue funding to angel investment for growth, as illustrated by Figure 7, Figure 8 and Figure 10 above.

Other sources of finance are more speculative. One European biotech has acquired initial finance from a combination of Angel and Crowdfunding sources.[42] Crowdfunding early, applied, non-profit research projects outside conventional academia is becoming more widespread in the USA,[43] and Crowdfunding appeals for funding for treatment[44] is echoing early predictions that Crowdsourced drug development was possible in principle.[45] Although the scale of almost all Crowd fundraisings are much smaller than even Angel rounds in biotech, let alone VC investment,[46] some biotech-focussed crowdfunding platforms are being launched in the USA,[47, 48] suggesting this may be a future addition to the financing mix.

In summary, our analysis of investment trends in the biotechnology sector indicates that:

- Funding for early stage biotechnology companies has declined very substantially since 2006, and in Europe, and especially

§ https://www.nanoporetech.com/ . Note that Oxford Nanopore Technologies is not a Cambridge Company, but is included in the larger global investment dataset.

the UK, financing round numbers and investment value
- There is consequently a move away from business models that need substantial investment
- Companies are adapting by adopting financial modes based on angel investment, grants and revenue
- Internet-mediated angel investing, such as crowd-funding schemes seen in other sectors, may be the developing force in the next decade.

The future remains bright for start-ups, providing they embrace new business models, and consider VC investment as a "nice to have" source of growth capital for the future, not a mandatory part of the start-up model. Whereas once the default position for biotechnology entrepreneurs was to access VC investment, the funding picture is becoming more diverse, with scope for internet-mediated investment (crowd-funding) to become a new capital source for neophyte biotechnology companies in the next decade.

ACKNOWLEDGEMENTS

The authors are very grateful to Biotosacana Farma S.A. for access to the MedTrack database, and to the Judge Business School (The University of Cambridge) for access to business databases. Elements of the work presented in this paper were carried out as part of the Masters in Bioscience Enterprise degree at Cambridge University, and the Masters in Biotechnology, Bioprocessing and Business Management degree at the University of Warwick. The authors are grateful to both courses for their support. We are also very grateful to Ken Malone for his extensive and helpful comments on an early version of this paper.

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Original Article

Biotechnology venture investing and neurodegenerative medicine: Promise of new approaches to cure an ailing model

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ABSTRACT

Neurodegenerative diseases are one of the leading public health challenges of the next 50 years. Pharmaceutical therapies have traditionally targeted the later stages of neurodegenerative diseases; however, this strategy—as the recent failures of clinical trials for Alzheimer's drugs have highlighted - has been unsuccessful. Venture capital has underperformed as well during this time, as many new companies have been unable to maintain growth once they reach the public market and have produced less than desirable returns. As a result, venture capitalists have opted for later-stage financing. Nevertheless, new technologies are being developed to answer the question of how to best address neurodegeneration. New tools of detection will allow for much earlier diagnosis and a much greater chance of discovering and applying effective treatments. Realizing that genetic knowledge is insufficient to produce innovative treatments for neurodegenerative diseases, scientists have begun to apply the genetic knowledge attained towards a future of individualized treatments. As these new tools of detection converge with an increased ability to create very precise individual solutions, the risk of future investments should come down and should then provide the potential for outsized returns that have traditionally governed the venture capital financial model.

Journal of Commercial Biotechnology (2014) 20(1), 28–34. doi: 10.5912/jcb629
Keywords: innovation; start-up; neurodegeneration; drug discovery; drug development

THE BURDEN OF NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are fast becoming one of the largest medical burdens in the United States and abroad. Currently in the United States, nearly 10 million people are living with some form of neurodegenerative disease.[1,2] The total yearly cost of healthcare for three of the most prevalent diseases in this category—Alzheimer's disease (AD), Parkinson's disease, and multiple sclerosis—is more than $250 billion.[2] Neurodegenerative diseases tend to strike in the middle and later stages of life, a fact that dictates that as the population of the U.S. ages, so too will the number of neurodegeneration patients increase. Health authorities believe that 1 in 4 Americans will soon suffer from some form of neurodegeneration and that nearly every family will include at least one member with one of these conditions.[1,2] Taken together, all these factors make it apparent that the cost of treatment is not likely

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to decline in the near future. By 2050, just treating AD is projected to cost in excess of $1 trillion per year,[1] a Medicare burden that could bankrupt some states.

Due to these alarming cost projections and the lack of any effective treatment, the biomedical community is now mounting a major push to leverage the resources needed to overcome the public health threat posed by neurodegenerative diseases.

The National Alzheimer's Project Act,[3] which was signed into law by President Obama in January 2011, and whose goal is to find treatments for and effectively cure AD by 2025,[3] is a sign that neurodegeneration is a medical phenomenon whose time has certainly come.

Presently, Alzheimer's disease, the sixth-leading cause of death in the United States, afflicts more than 5 million Americans; and this population is expected to rise to about 11-16 million individuals over the next 30 years.[1-3] Yearly healthcare costs for these patients are nearly $200 billion in direct costs,[1,2] but these numbers only partially describe the true costs of Alzheimer's. There are, for example, over 15 million unpaid caregivers in the U.S., providing vital day-to-day patient care for the victims of Alzheimer's. These caregivers are typically family members of working age who are holding down full-time jobs as well as meeting their caregiver responsibilities.[1,2] These unpaid caregiver hours, which must be considered as indirect costs, have been estimated to be as much as $200 billion a year, making the total yearly costs of Alzheimer's treatment nearly $400 billion dollars. While the Advisory Committee on Alzheimer's Research, Care and Services[3] acknowledge the need to optimize our long-term treatment of Alzheimer's patients, they also stress the need to increase our scientific knowledge of all aspects of Alzheimer's, including the genetic, molecular and cellular phenomena behind the disease's formation and progression. To this end, they advise that the National Institutes of Health ramp up their Alzheimer's-related funding to $2 billion per year.[3]

SHIFTS IN RESEARCH AND INVESTMENT STRATEGY

Most recent attempts by pharmaceutical companies to address the Alzheimer's market have been disappointing at best. Dimebon, for example, the drug being developed by Medivation in collaboration with Pfizer, performed poorly in Medivation's phase III CONNECTION clinical trial, failing to show any significant positive effects in patients with mild-to-moderate AD.[4,5] Furthermore, the Pfizer/Medivation CONCERT trial showed no evidence of significant benefits in patients already taking Aricept, Pfizer's already-approved Alzheimer's treatment.[6,7]

To add to these research woes, bapineuzumab, an immunotherapy treatment originally co-developed by Elan and Wyeth and now by Pfizer and Johnson & Johnson, does not appear to be panning out either. Bapineuzumab at higher dosages is known to increase a patient's risk of brain inflammation due to water retention. Although the data from the phase-3 trial are not yet public, and thus FDA approval is still pending, the story for bapineuzumab looks increasingly grim, as recent scientific findings about this drug are apparently casting doubt on the validity of brain-plaque therapy, at least as far as it being a therapeutic target. This is not to say that promising technologies and scientific breakthroughs haven't emerged that may lead to considerable progress both in our understanding of AD and in our development of new treatment methods in the coming decade. However, coinciding with these breakthroughs has been the decision of some of the largest pharmaceutical and biotechnology companies to stop large-scale neuroscience R&D aimed at the neurodegenerative diseases. In fact, Pfizer, GSK and Astra-Zeneca all decided to close down large portions or, in some cases, their entire R&D divisions devoted to neuroscience.

The general shift of the large pharmaceutical and biotechnology companies, commonly referred to as Big Pharma, away from using large R&D divisions to develop drugs has opened up an opportunity for younger, smaller biotechnology companies to emerge and bring forth new ideas and potential treatments. The desperate need for efficacious treatments, coupled with Big Pharma's shift towards using start-up biotechnology companies as a source of drug discovery, is in turn opening the door for new investors. These new investors want to make value-adding investments in these companies that may lead not only to outsized returns, but also to world-changing treatments.

And many venture capitalists (VCs) have, in fact, taken note over the past 10 to 20 years of this shift to smaller arenas, and have injected tens to hundreds of millions of dollars in capital into companies that are addressing the challenge of Alzheimer's and other neurodegenerative diseases. However the question remains—has this injection of capital born fruit in terms of both new treatments and outsized financial returns for the limited partners of these venture firms?

BIOTECHNOLOGY VENTURE CAPITAL: IS THE TREE BEARING FRUIT?

On the surface, venture investing in the biotechnology space appears to be performing admirably. True to expectations, VCs have gravitated to this space bringing much-needed capital to the formation of new companies. Venture capital firms spent $4.73 billion on 446 biotechnology companies in 2011, the highest dollar amount since 2007.[8]

One would think that a capital injection such as this would be indicative of a burgeoning group of new biotechnology companies, all attacking the risky challenges we face over the next ten years; challenges that the large pharmaceutical companies are less inclined to address. Further inspection, however, suggests that this ideal scenario is not the reality. Last year, about 153 life sciences companies—a category that includes both biotechnology and medical devices—received their first round of funding—the lowest financial backing since 1996.[8,9] In the first quarter of 2012, 80 biotechnology companies received funding, but the focus was not early-stage financing. The National Venture Capital Association reports that first-time financing for biotechnology companies in the first quarter of 2012 amounted to $93 million—the lowest it has been since 2005 ($71 million).[9,10]

As Big Pharma began to modify its research direction, venture capital firms began to shift their focus onto later-stage companies that they hoped would have less risk associated with them. But why would venture capital, the sector known for taking risk, creating value and returning outsized profits for their investors, be avoiding risk? The reality is that VCs do not avoid risk per se; rather, they are managing the risk through portfolio diversification comprised of many more late-stage companies than ever before.

The customary formula of venture investing is that very risky investments in nascent companies can lead to large returns. That is, VCs invest in risky, early-stage science and technology companies under the assumption that those few that become successful will be acquired by a larger pharmaceutical company or, more preferably, will be able to "go public" via an initial public offering (IPO) of company stock.

During an IPO, the point at which many companies canonically see their valuations increase, many early-stage investors are able to "exit" by selling their shares and getting a large return due to the increased valuation of the aforementioned company compared to when the VC first invested. Due to a number of factors (dilution of equity and amount invested in "follow-on" rounds), the amount of capital returned as a multiple of amount invested can vary; but the general rule is that the earlier you invest the higher your return on investment, or multiple, is. This reward is what drives the VC to take the risk on early stage companies.

But this time-honored *modus operandi* depends on assumptions about the public markets that are presently not being met within the biotechnology sector. Recently this paradigm has drastically changed into something much more tepid, both in terms of the number of companies that progress to an IPO and the performance of those companies in the public markets, and thus their valuations.

THE BIOTECHNOLOGY VENTURE CAPITAL PARADIGM SHIFT

Many biotechnology VCs have shifted away from early-stage companies into more late-stage companies, believing that early-stage VC investing is too time- and capital-intensive for the model. By investing in later-stage companies, the biotechnology VCs hope to lessen risks such as unproven technologies and the lack of a product to take to market.

Unfortunately, this strategy may have negative consequences that may not manifest until much later. In reality, moving to late-stage biotechnology companies as a method of "de-risking" an investment portfolio only trades one set of risks for an entirely different, and yet equally difficult to overcome, set of risks. For example, taking on later-stage companies means having to deal with FDA approval or rejection of a product much earlier in the investment timeline than before. In the case of FDA rejection, a successful IPO may be ruled out along with any possibility of a successful acquisition/merger deal with a larger pharmaceutical company. Even in the cases where a drug has been approved, this approval doesn't necessarily equate to good sales. Dendreon, whose Provenge antibody treatment for late-stage prostate cancer was and may still be the best and only late-stage prostate cancer treatment on the market, underperformed and suffered a steep drop in the stock price. While Dendreon has been a public company since 2000, its experience with Provenge has shown public investors that having a fully approved drug does not give a pharmaceutical company an automatic cash cow. Provenge, then, highlights a large barrier of entry to very new and very expensive biotechnology solutions, irrespective of disease or need. If an autologous treatment for advanced-stage prostate cancer turned off the public because of its high price, then what is the outlook for what are sure to be expensive treatments for neurodegenerative diseases?

THE FINANCIAL LANDSCAPE OF BIOTECHNOLOGY VENTURE CAPITAL: THEN AND NOW

From 2010-2011, 23 U.S. biotechnology companies went public and the numbers tell some interesting, if not potentially disturbing, tales. As of the end of 2011, the stock prices of these companies were down an average of 17% since their IPOs, and 14 of these 23 (61%) were recently trading below their initial offering price. Further, heading into the fourth quarter, only 5 of 16 biotechnology IPOs in 2011 were above their initial offering price.[12] During a 2-week period from the end of July to mid-August, the biotechnology IPO class of 2011 fell 20.2 percent and lost $1.7 billion dollars in value.[12] And while biotechnology venture investing does not expect and cannot depend on the stratospheric possibilities that the Web 2.0 VCs have achieved (i.e. multiples in excess of 50x or more), the biotechnology VCs are still hoping to make large returns more consistently, and in a relatively short period of time spanning approximately 3-7 years; short for the drug discovery and development world, however very long for the investment world.

Yet even in the instances where biotechnology companies have continued to trade above their IPO price, the returns to their investors have not been as stellar as their stock performance would suggest. For example, AVEO Pharmaceuticals—which has continued to perform well, has been as high as nearly 75% over its asking price, and has been noted as a buy candidate by analysts—also has some caveats that are worth noting.

First, AVEO's IPO didn't go nearly as well as its managers had hoped it would. Ironically perhaps, they wished to sell their stock in the very same range that it trades for now ($12-$14), but instead opened at $9 per share. These circumstances not only show that the listing raised less money than the bankers wished to during the offering but it also highlights the chilly climate that biotechnology companies are facing when going public. Clearly, when biotechnology companies go to the public markets, they are met with limited interest.

The second point regarding AVEO and the performance of biotechnology companies whose stocks are trading above their offering price, is related to the returns to their private investors. Even with its great post-IPO stock performance, AVEO's valuation is below 2x the private capital invested. This is well below the greater than 4x returns that VCs are expecting and, quite frankly, are depending on from their top-performing companies. This recent, sustained, poor performance of biotechnology IPOs has already affected the landscape of the biotechnology VC community and the effects of this low performance will be felt for some time.

Perhaps the most important, if not the most overlooked, result of VCs shifting towards late-stage biotechnology companies is an avoidance of investment in early-stage biotechnology companies. Biotechnology innovation isn't a fast process when compared to Internet innovation. Changes that we see now in clinical protocols are due to changes in the pharmaceutical space that were based on ideas funded 10 to 20 years ago. These innovations have been supported by both the private and public markets and they have been allowed the time they needed to mature. The question that then arises is, can venture capitalists innovate their business model in such a way so as to:

a. allow them to continue to invest in early-stage biotechnology companies
b. continue to financially back these companies
c. coordinate financing of new companies as the maturing biotechnology companies approach exit time
d. exit these biotechnology companies at a financial gain in accordance with the goals of the fund and the desires of their limited partners?

This multi-pronged question may also be restated as, "Can VCs utilize new technologies to make early-stage investments in novel neurodegenerative therapies with less risk than they have been shouldering to this point?"

The shift to funding later-stage products is a primer that has changed the landscape of funding biotechnology innovation and discovery**.** Ultimately, the target remains partnership with Big Pharma, although at an earlier stage than before. In reaction to its own lack of innovation, Big Pharma has increasingly turned to academic institutions by directly funding innovation in discovery research, while shelving their own in-house efforts. To add to this push-pull mix in both the Big Pharma and investment industries, patient groups have become frustrated by not seeing new treatments for their particular disease. This has led to the formation of disease-specific foundations with enough capital to advance therapeutic development. For example, the organization Accelerate Brain Cancer Cure[13] funds clinical testing for innovative approaches.

BARRIERS TO TREATMENT BREAKTHROUGHS

One of the great scientific advances of the 21st century has been the Human Genome Project (HGP). While this massive endeavor obviously provides great insight

into human biology, the application of the knowledge it provides will lead to a revolution of diagnosis, treatment and eventually the prevention of many diseases. Despite researchers having claimed the human genome nearly 90% mapped by 2001, we are just beginning to apply this knowledge to human diseases. Understanding how genetic mutations can lead to disease will be instrumental in understanding the early stages of disease and how it can be halted, reversed or completely prevented. However, genetic knowledge alone is not sufficient to deal with many of the issues we presently face.

It is worthwhile to consider a clear example of how genetic knowledge has proven useful but insufficient to create cures. Long before the HGP, we learned that Huntington's disease is caused by a mutation in the gene huntingtin. Briefly, the disease occurs when excessive repeating of the protein code leads to the production of an abnormally long portion of the protein which renders the protein unstable. The mutated huntingtin protein damages the cell through mechanisms that scientists are still deciphering. But this discovery of the genetic basis of the disease in the mid-1990s gave scientists a clear direction to take in their investigations, as well as a means to determine by genetic testing who will contract the disease, but it did not readily produce a cure.

Putting aside the potential ethical and moral issues, this work gives an opportunity for early symptom mitigation. However, beyond detection, even with the clear genetic connections predating the HGP by decades, there is still no available cure for Huntington's disease. Scientists continue to investigate what precisely the mutated huntingtin gene is doing to cause damage to neurons and will eventually be targeting therapies to those particular mechanisms. And, although we can't yet know what those therapies will be, we do know that the information we have managed to untangle so far—early detection of who needs what type of therapy—will be crucial to their efficacy.

Our genetic knowledge of Alzheimer's disease is not nearly as comprehensive as our knowledge of Huntington's yet they both exist within the realm of "untreatable neurodegeneration." Our understanding grows each day but with that understanding comes new questions and newer barriers to break through with regards to understanding this disease. But with the nearly completed mapping of the human genome we will see new breakthroughs in our understanding of the disease's underlying mechanisms, which will lead to a deeper understanding of what is causing this illness. This may allow clinicians, in the somewhat immediate future, to better detect who is susceptible to Alzheimer's as can be done with Huntington's. Indeed, the biomedical community has taken a turn towards the question of "*how early can we detect Alzheimer's?*" As stated above, the overwhelming majority of treatments for *late-stage* Alzheimer's have been total failures. As we begin to look toward earlier stages of AD, we first must address exactly what "early" means in this case. And so, in the absence of knowledge about the disease's genetic foundations, we must look to our advancements in medical imaging to assess the earliest signs of AD from a cellular perspective.

One of the biggest barriers in Alzheimer's treatment was deciphering when a patient truly had Alzheimer's. Until recently, it was believed that the only way to diagnose AD with certainty was with an autopsy after death. Even then, complications arose that prevented diagnosis with 100% certainty: for example, the two distinct guidelines for diagnosis, NINDS-ADRDA and DSM-IV-TR[14], were addressing two different aspects of AD as the NINDS-ARDA focused on the necessity of histopathology for definite diagnosis while the DSM-IV-TR focused exclusively on neuropsychological defects. Within the last 10 years, however, we have begun to find similarities across AD patients versus non-AD patients when we image their brains using positron emission tomography (PET) and structural magnetic resonance imaging (MRI). Indeed, researchers have stated that they believe that the diagnosis of AD from PET is now nearly statistically equal to the autopsy diagnosis.[15,17]

Thus, in spite of the fact that we still lack a standardized set of quantitative metrics to determine AD through imaging biomarkers, we have made strides. PET imaging has shown that differences in brain glucose metabolism may be critical to an early and specific diagnosis.[16] The application of imaging in evaluating the early stages of AD, mild cognitive impairment (MCI), and the possible transition from MCI to AD[17] will also aid our understanding of clinical trial efficiency and, by extension, treatments. Further, treatments that can be vetted against a standardized cellular measurement of efficacy can be invested in with less risk than the non-standardized criteria that aren't effectively universal across all MCI and AD patients.

On the clinical side, physicians still must sharpen their ability to distinguish between AD and other forms of dementia—all of which are themselves not entirely understood and are thus in need of a standard of measure. Breakthrough innovations will come in the form of new, more precise ways to accurately diagnose patients so that the treatments provided will be specific to their needs.

THE FUTURE OF OVERCOMING THE BARRIERS

The societal burden of neurodegenerative diseases is only going to increase. Presently, there is a shortage

of efficacious treatments on the market, and so financiers play a vital role in aiding the development of new therapies. As the example of Huntington's disease illustrated above, we know that simply having the sequenced genome available isn't sufficient to create breakthroughs and it is the application of genomic technology that will most likely lead to innovations in healthcare. But these medical applications are coming now. Research is presently underway that aims to increase the accuracy of high-throughput DNA sequencing and then apply those improvements to the noninvasive detection of early-stage cancer. Will this particular technology soon be applied not simply to early detection of cancer, but to other diseases as well?

The cost of DNA sequencing continues to drop, and soon a complete map of who we are and what we may be susceptible to will be available at low cost, not only to medical practitioners but also to all patients. As our detection tools improve so too will our ability to test the hypothesis that we may be able to protect against the disease if we can begin treating it early enough. Perhaps we can better treat Alzheimer's patients if we are able to begin therapy before the neurodegeneration has begun to produce symptoms. Research is being done now investigating the efficacy of failed AD drugs at earlier stages of the disease. Is it possible that we are simply beginning AD treatment too late? Could neurodegeneration be halted if it is defended against early enough? These are the questions we will soon be answering. These questions will be at the heart of the new breakthroughs and investors would do well to look forward to those new companies that are addressing these questions as they will be at the forefront of the new frontier of healthcare.

Cost-effective DNA sequencing also provides the benefit of personalized medicine. In truth, we are not able to say on a genetic level that all AD patients are suffering from the same disease. And while their symptoms by and large are the same across all groups, we do not know if they are manifesting from the same genetic pathologies. It is quite likely that different genetic mutations will have to be treated by different drugs, even if the disease looks the same on a physiological and behavioral level. Our ability to categorize the variety of AD patients by different genetic variations and to delineate how each group responds to different treatments—whether pharmacological, bioelectrical or other—will have enormous implications going forward in this battle.

Of course, simply detecting neurodegeneration is not enough. As our experiences with Huntington's disease have shown us, knowing what is wrong in no way directly translates into fixing the problem. Research must go on continuously and new agents must be developed to target these diseases. New agonists, protein inhibitors, silencing RNA and many other technologies will continue to be produced and should not be cast aside. It can be argued that the need for new innovative therapeutic agents is higher now than it has ever been. However, as our vision into the problem approaches understanding, so too will the efficacy of interventions. It is quite likely that the days when all people with a single disease will be treated with a single drug are soon to be at an end; instead, a group of people with a certain type of that disease, as defined by their particular genetic variations, will be treated by therapeutic approaches targeting disease pathology in the context of a genetically defined environment. In time, perhaps each patient will be treated by a single specific therapy tailored exactly to his or her disease as well as their specific medical and genetic history.

It is this future that VCs must begin to look towards and to place their investments within structures that can accommodate high risk, long timelines—and high rewards. While simply finding effective treatments for patients may be enough return for some, it is not a stretch of the imagination to think that with investing success comes outsized rewards for those who were willing to venture out into the new world first.

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From the Board Room

A social media manifesto

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Journal of Commercial Biotechnology (2014) 20(1), 35–42. doi: 10.5912/jcb637
Keywords: social media; apps; adherence; compliance; safe use; outcomes; OPDP; marketing

The role of marketing communications is to advance the bottom line and the public good—and not necessarily in that order. Giving back is an integral part of the New Normal. And there has never been a better tool to accomplish this mission than social media.

But healthcare marketing—and particularly of the regulated variety—is between a rock and a hard place. On the one hand, marketers understand the importance and opportunity in social media. It's where the people are. It's where the action is. But then there are all those pesky regulatory concerns.

As Walter O'Malley—the man who moved the Brooklyn Dodgers to Los Angeles once commented, "The future is just one damn thing after another."

While everyone else is using social media as a healthcare communications blitzkrieg, or "lightening war," regulated industry is digging in for a sitzkrieg, a "sitting war."

This is not good news for pharma, physicians, or patients (also known as "consumers"). Social media is the newest arrow in the communications quiver, but it's a discipline both misunderstood and frightening to those operating in the heavily regulated world of healthcare.

The Internet can be extremely useful in informing patient discussions with doctors. It can be a helpful tool to empower an individual in their medical decisions. But it is important to remember that not everything online is true. The Internet has made it easier than ever before for charlatans and quacks to spread fear and misinformation. Mark Twain wrote, "Beware of health books. You might die of a misprint." Having a website does not replace having insight.

Regulated companies mustn't feel safe behind a social media Maginot Line. Social media is a social movement and using the excuse that healthcare firms can't engage because "we're different," misses the point. Compliance issues are very important, but it's precisely because of the "special difference"—the responsibility of advancing the public health—that these companies must engage actively and creatively in social media.

There are a number of key issues relative to the use of social media by regulated healthcare entities. Let me address five:

1. USER-GENERATED CONTENT

If a consumer with no financial relationship or corporate interest posts a comment on a social media site that's supported by a regulated entity—say a pharmaceutical company—is the regulated entity responsible for the content of the comment?

User-generated content is de facto "interested" (otherwise there would be no content generation)—but does that mean that, de jure, it should be considered as regulated speech?

As they say, where you stand often depends on where you sit. And if you sit in Europe, consider a new European Court of Justice ruling that says information about medicines produced by independent third parties outside any commercial or industrial activity may constitute advertising, even though they have no connection with the product's manufacturer or marketer.

According to the court, "… even though the third party in question is acting on his own initiative and completely independently of the manufacturer and the seller of such a medicinal product."

That's carte blanche for an almost complete gag order on anyone who wants to discuss anything to do with medicines. Under such a regulatory environment—would letters to the editor become liable for an FDA warning letter? What about radio call-in comments? What about freedom of speech?

2. BLOGS

What about blogs and other social media sites that accept pharmaceutical advertising?

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Why are social media sites that accept advertising any different from publication such as the New York Times, or the Washington Post, or the New England Journal of Medicine?

When is "interest" not "conflict of interest?"

A related issue is that of "user" versus "property owner." Specifically, websites owned and maintained by a regulated entity, but whose online content is created exclusively by users without any financial "interest" behind their participation. For example, a social media site for people with diabetes that's created and maintained by a company that markets a diabetes medicine. What are the responsibilities of the "property owner" and what do they need to prove vis-à-vis "disinterest?"

Relative to "intended to promote"—How can this be differentiated from "intended to share and educate?" And whose job is it to define such differentiation?

3. SUBSTANTIVE INFLUENCE

What rules should apply when a healthcare company wants to pitch a story to a blog or some other social media site with an audience that's relevant to its marketing strategy?

As the Food and Drug Agency asked in its Federal Register notice, "Are there different considerations that should be weighed depending on the specific social media platform that is used or based on the intended audience? If so, what are these considerations?"

One thing that healthcare companies' worry about is that social media commentators will not factually report the news. A legitimate concern, but is this any different then accurately pitching a story to a reporter at the New York Times and having her miss or misrepresent a clinical data point?

Whether it's the New York Times or a blog or a social media site for caregivers, information "in" is vetted and controlled. Information "out" is not. Errors and hyperbole are, for better or worse, freedoms of the press.

4. CORRECTIVE INFORMATION

The FDA's Federal Register notice comments that: "… companies have stated that they have not corrected what they believe is misinformation in the belief that they could be viewed by such an action as being responsible for all the information on the target Web site rather than just the information that they post or submit."

This is an issue that really strikes at the heart of the matter—the unintended consequences of having responsible and regulated companies shy away from social media even to correct erroneous information.

According to the Pew Internet and American Life Project, 13 million Americans search online for answers to their health questions. Three quarters of these individuals rarely, if ever, check the sources of the material they find

Without the participation of regulated healthcare players, the social media field is left to snake-oil salesmen, Internet drug dealers, unscrupulous trial lawyers and others who operate without almost any constraints whatsoever. Nature abhors a vacuum. It is irresponsible not to correct healthcare information errors. And yet that is precisely the advice being regularly given by regulatory consultants. It is a sad state of affairs indeed that ambiguity on behalf of the FDA has led us to this dangerous state of affairs. Sad, perhaps—but not surprising.

5. ADVERSE EVENT REPORTING

A real bête noire of social media—adverse event generation. Should companies actively avoid participation—even to the degree of monitoring—lest they uncover an adverse experience? Shouldn't companies embrace social media so that adverse experiences can be found with greater alacrity? Shouldn't companies be rewarded for such behavior? If regulated industry wants the FDA to be both regulator and colleague, then it's not a leap of faith to imagine that the FDA would like industry to be proactive in its search for new ways to surface adverse events.

There's at least one large pharmaceutical company whose policy is not to monitor social media sites because they don't want to unearth adverse events. Is this responsible? Is it even supportable? If this company received a call from a reporter and was asked if they purposely avoid social media so as not to find adverse experiences, would the truth set them free? Legally they may be in compliance, but it wouldn't look good on Page One or sound very good in front of a congressional subcommittee. "In compliance" and "in the best interest of the public health" must not be mutually exclusive propositions.

As F. Scott Fitzgerald wrote, "At 18 our convictions are hills from which we look; at 45 they are caves in which we hide." Social media is still too young an adventure for us to seek shelter in the caves of caution, complacency and compliance.

Social media is communications at the speed of life. As Marshall McLuhan wrote, "At electric speed, all forms are pushed to the limits of their potential." That's a terrific challenge, to be pushed to the limits of our potential. But are we willing to be roused and animated by the new frontier that is social media and the nascent healthcare experience?

Are we up to the challenge?

Having a web site does not replace having insight. Change is opportunity.

The use of social media by regulated industry is faltering because of fear, timidity and misunderstanding.

How can the FDA be blamed for industry's reluctance to push the boundaries—even a little? Fear of warning letters? Fear of unearthing adverse events? I say, where there's a will, there's a way. If you won't blaze the path—even a little—then don't expect anyone to know where you want to go.

Unfortunately, blazing new territory through real-time learning is not, shall we say, historically a tradition of regulated industry. Everyone wants to do new and exciting things—second.

More regulatory clarity? Not likely.

What are the odds, lacking direction, expertise and experience, that the FDA will deliver some kind of *deus ex machina* solution? Expecting the Holy Grail will only lead to disappointment and frustration. And blaming the agency when that happens won't make anything better or move the social media agenda any further ahead. If industry is expecting to climb the steps of the agency's headquarters at White Oak on its knees, kiss an FDA relic and miraculously throw away the crutches hobbling their *ability* to participate in social media, well, there had better be a Plan B.

Embracing social media means embracing regulatory ambiguity. That's a paradigm shift for an industry that has been going in precisely the opposite direction.

Social media (and its game-changing opportunities) demands a move away from the cautious tactics of the Vioxx Populi toward a better understanding of the digital Vox Populi. And that means more than sponsored Google links and branded Facebook pages with the interactivity turned off.

It means mixing it up with real people in real time. It's not going to be easy, or risk-free, or inexpensive. Whatever social media "marketing models" companies build will have to be elastic, just like the media environment in which they are designed to operate.

For the past 20 years, the overwhelming majority of pharmaceutical marketing budgets have been dedicated to promoting specific products.

Due to a less robust drug development pipeline and an increase in the rates of patent expiry, the next era of pharma marketing will put a company and its corporate reputation front and center.

When you think about it, it's a perfect match for social media, where transparency is the most urgent, non-negotiable, and magnificent mantra. The change will be defined not by third-party groups or KOLs (although these traditional avatars have their place), but a company speaking on behalf of itself and its products.

I believe that the blockbuster era of the pharmaceutical industry will be replaced by the era of post-patent medicine. To compete against generics and biosimilars, pharma companies will need not only a robust portfolio of lower cost medications, but also an army of brand loyalists.

Communications programs supported by social media will be crucial tools in this process because they're able to target people where they are.

It's estimated that Pharma loses $30 billion a year in patient non-compliance. True two-way social media has the potential to serve as a new and puissant health education platform that will help keep patients informed about the dangers of non-compliance by earning their trust through transparent dialogue. And that's twice as true when it's mobile-based.

As Dr. James Fowler of the University of California at San Diego, opined, "Pharma must realize their own network power."

Where there's a will there's a way.

There are a few key conundrums that are often overlooked or misconstrued when we discuss social media in the context of regulated speech:

There is a difference between online advertising and social media

When the FDA sent out the "famous 14" warning letters on sponsored Google links, many pharmaceutical regulatory review professionals said, "You can't use social media," and breathed a secret sigh of relief—another sign of an ever-growing regulatory Stockholm Syndrome.

But they were wrong; because when you read the letters it becomes quickly evident that the agency equates "sponsored links" not with social media—but with paid advertising. In the context of those letters, "sponsored" equals "paid." And there *are* rules for that.

Beware, because as Disraeli said, "A precedent embalms a principle."

There is a difference between social media platforms and social media content

FDA sent out a warning letter regarding a YouTube video where a paid celebrity spokesperson said that a drug had "cured" his disease (a decidedly off-label claim, shades of Dorothy Hamill and Vioxx). And some internal reviewers industry-wide said, "You can't use YouTube." Not so.

If the content is non-compliant, then it is non-compliant regardless of platform. On the positive side, I believe the reverse is also true.

OPDP Director Tom Abrams has made it clear that when there is guidance from the agency on social media, it will NOT include agency direction on how to use specific platforms such as YouTube or Facebook or Twitter—and that includes emerging mobile platforms too.

The fear of user-generated content and off-label conversations is real … but

There are a multitude of solutions, ranging from moderating comments (which are generally accepted by social media communities as long as they understand the necessity for such moderation) to corporate responses directing the user to a given product's PI and pre-vetted company web pages.

Who's responsible for what?

Social media is a big place. Can any single company be held responsible for what's said about itself or its products anywhere online?

Consider the current on-the-books guidance, which reads, "Applicants should review any internet site sponsored by them for adverse experience information, but are not responsible for reviewing and internet sites that are not sponsored by them."

But what does "sponsored" mean?

Consider the oft-heard TV voice-over, "This portion of the Masters is sponsored by (NAME OF ERECTILE DYSFUNCTION PRODUCT).

Nobody in the viewing audience thinks the sponsor chose the speed of the greens or the pairing of the golfers, or the height of the rough. But say, "sponsored" on interactive social media and watch the sparks fly at internal regulatory review.

Let's be blunt—expecting a regulatory Holy Grail will only lead to disappointment and frustration. And blaming the FDA when that happens won't make anything better or move the social media agenda ahead any further or faster.

At the end of the day, the issue of social media and FDA regulations was summed up nicely by another senior member of the FDA brain-trust who told me privately that, "We need to learn to talk to people the way they talk to each other—and that's going to create a culture shift at the FDA."

What Pharma wants (or should want) is permission from the FDA to guide itself. And that permission has been granted.

The December 27, 2011 Draft Guidance, "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices" offers sound counsel but not much in the area of direct guidance. Nevertheless, there are valuable lessons to be learned—if you are willing to read between the numerated lines.

The draft guidance doesn't address many of social media's (referred to in the document as "emerging electronic media") regulatory red flags such as adverse events, the question of property owner vs. property user, and a more precise discussion of what "sponsored" means.

But the giant regulatory bugaboo, not only of social media but of regulated speech writ large, ***is*** off-label communications. So those who are complaining this document isn't "comprehensive enough" don't understand what it has to offer.

Lesson #1: The agency is saying (in so many words) "if you wouldn't say it off-line, don't say it on-line." It isn't a question of platform-specific guidance (regulatory rules for YouTube or FaceBook or Twitter). Rather, the FDA is asking industry to *use their best judgment* in this new and, well, *emerging* media. That's the good news.

The bad news is many folks in Pharma find that frightening.

The agency recognizes companies are already responding to unsolicited requests for off-label information. That means the current procedures companies have in place to address these requests are (when properly followed) FDA compliant.

Lesson #2: When trying to create processes and procedures for social media communications—draw parallels to existing communications processes and procedures.

That's not, however, a get-out-of-jail-free card by any means. Just as with traditional communications, there's a great deal of regulatory ambiguity and use of the FDA's favorite tense—the conditional tense: The role of legal and medical in the review of social media communications (relative to off-label issues and beyond) is still crucial. This draft guidance doesn't lighten the regulatory burden—it just makes it more feasible.

What it also says (IMHO) is that responding to unsolicited off-label communications is, indeed, in the best interest of the public health:

> *FDA recognizes that it can be in the best interest of public health for a firm to respond to unsolicited requests for information about off-label uses of the firm's products that are addressed to a public forum, as other participants in the forum who offer responses may not provide or have access to information about the firm's products.*

The agency has, importantly, made a clear distinction between "solicited" and "unsolicited" off-label questions:

> *Unsolicited requests are those initiated by persons or entities that are completely independent of the relevant firm. (This may include many health care professionals, health care organizations, members of the academic community, and formulary committees, as well as consumers such as patients and caregivers). Requests that are prompted in any way by a manufacturer or its representatives are not unsolicited requests.*

Lesson #3: The message being sent here is, "don't get too cute." And that's worth remembering. Using social media for marketing is okay—but using it to advance the public health takes precedence.

One key area that requires greater clarification (on the part of the FDA) is the definition of an unsolicited off-label *request*." Does it have to actually be a *question* or could it also be a non-interrogative *incorrect statement* about the off-label use of a product? Independent third parties who make erroneous statements about off-label use generally are ignorant of the fact that they are making factual misstatements.

Shouldn't a company be able to respond to factual errors that aren't in the form of a question? Isn't the whole idea here *not* to play *Jeopardy* with the public health? Agency clarification is necessary so that companies can regularly and aggressively correct on-line misinformation about their products.

Lesson #4: It is the responsibility of every company to correct product misinformation that it discovers not only in social media—but it all media. After all, what would a company do if a factual mistake about one of its products appeared in the pages of the New York Times?

The draft guidance also offers some very sound and practical tactical advice. For example, when dealing with off-label questions:

> *Information distributed in response to an unsolicited request should be provided only to the individual making the request directly to the firm as a private, one-on-one communication.*

And:

> *If a firm chooses to respond to public unsolicited requests for off-label information, the firm should respond only when the request pertains specifically to its own named product (and is not solely about a competitor's product).*

Lesson #5: Take conversations about off-label use (and, IMHO, adverse events) off line and into existing processes and procedures.

The FDA requires some additional assistance in understanding social media. Specifically:

> *FDA is also concerned about the enduring nature of detailed public online responses to off-label questions because specific drug or device information may become outdated (e.g., new risk information may become available).*

While it's good to be concerned, it's also important to recognize that any piece of information ever written on social media (generally speaking) is going to be available forever for those who know how to find it. Perhaps a better way to address this concern is:

Lesson #6: Companies who respond to posts on independent third party sites should continue to regularly monitor those sites for future legitimate interventions.

Another questionable statement in the draft guidance concerns the use of "brand.com" sites as an *inappropriate* way to address unsolicited public off-label questions:

> *The public response should include a direct link to the current FDA-required labeling, if any, but should not include links to any other information (e.g., product websites, product promotional materials, firm websites, third-party websites).*

Why shouldn't a product website, assuming that every word on the site is appropriately compliant, be used? Isn't this where the most comprehensive, up-to-date, and accurate product information resides?

If the agency is concerned about the legacy of "old" on-line information, they should support options that are regularly (and factually) updated—such as brand.com sites and apps.

The draft guidance also raises the issue of communications with health care professionals and formulary committees. For both of these constituencies, seeking a regulatory parallel is useful. For healthcare professionals, the current guidance on Good Reprint Practices is as clear (and useful) for a social media interaction with a physician (or nurse-prescriber) as it is for a one-on-one office visit by a pharmaceutical company representative.

Lesson #7: Social media means more than marketing products. It means using this "emerging electronic media" to advance the public health by communicating factual and timely information. In short—sharing

knowledge with those who want it, when they want it, where they want it.

Lesson #8: Not just when *a marketer* wants to. Strategic use of social media can put the pharmaceutical industry back in the public health business in the eyes of physicians and patients.

Lesson #9: It's about judgment. If a company can make a strong case (internally and honestly) that a social media engagement truly advances the public health, it's a strong foundation for ensuring compliance.

Lesson #10: Pharma, Guide Thyself.

When it comes to social media, the FDA wants companies to do what's in the best interest of the physician and the patient (really!).

But there's an unfortunate disconnect—the regulatory go-forward proposition of many companies is to avoid *any* regulatory ambiguity. The result is a vast regulated healthcare wasteland.

What about social media and the crucial public health issue of adherence/compliance?

Zig Ziggler once said, "If what you're doing isn't working, try something else. If what you're doing *is* working, try anything else." While there are certainly success stories and validated methodologies in the battle for better adherence/compliance, we're losing the war. It's time to reconsider what we're doing—and social media is a logical tool.

As I see it, there are six issues we are trying to impact — and they are linked:

1. *Sub-optimal patient outcomes* (the Big Kahuna).
2. *Sub-optimal physician pay-for-performance metrics.* (More important today than ever and back at the top of strategies to control costs. Alas—one of the unintended consequences of pay-for-performance is that some physicians will try to game the system by not seeing those patients who they see at high risk for non adherence/compliance.)
3. *Lower healthcare costs for payers.* Not surprisingly, all of the big private payers are in the adherence/compliance game with both feet.
4. *Sub-optimal profits for pharmaceutical companies.* (The sale doesn't end once the script is written.)
5. *Impact on safe-use.* The way to make drugs "safer" is to ensure they are used appropriately. Safe use begins with adherence/compliance. (Hear that FDA?)
6. *Lower healthcare costs for society.* (You might have heard of this issue—it's been in the news a lot.)

Alas, there are no magic bullets in the fight to improve adherence/compliance. News articles feature talking pillboxes that offer bells and whistles, rings, buzzes, and flashes, and that's all to the good—but they only combat forgetfulness (purposeful or otherwise). It's a part of the solution—but, just as in the battle against counterfeit medicines, it's only a piece of the puzzle.

Some think that (as with REMS), the FDA should insist that new drugs have adherence/compliance plans that can be monitored and improved through iterative learning. Should sales reps (or, better yet, MSLs) "detail adherence/compliance programs and share validated tools for adherence/compliance "triage?" The only thing that's currently on the table is that the FDA has promised to make MedGuides more user-friendly. (We can do better.)

Others talk about behavior modification through gamification—and that too is a useful pathway. We talk about carrots—but what about sticks to address bad patient behavior (particularly sticks of the financial variety)?

All of these are important. But talking pillboxes and better MedGuides are only making existing tools better. And trying to "regulate" adherence/compliance is a slippery slope indeed. To really make a difference, to change the game, what we really need are solutions that impact social conditioning and *address patient responsibility*—and that means using innovative platforms such as social media and, specifically, apps.

Not apps that are medical devices (although those play an important role in 21st century healthcare), but apps that remind, cajole, educate, praise, incentivize, and assist patients in their quest for better health. Apps are at the nexus of sage use, treatment outcomes, and patient satisfaction. And it's not science fiction.

At present, there are some 17,828 healthcare and fitness apps and 14,558 that can be deemed "medical." While some are better than others, these numbers tell us one thing—this is not a fad or a trend. It is reality.

And as Philip K. Dick wrote, "Reality is that which, when you stop believing in it, doesn't go away."

Will our socio-economic "technology gap" lead to a more pronounced "adherence/compliance gap?" It's an important question. That's why it's crucial we remember there is no one-size-fits all solution. But that's mustn't mean we disregard the reality of the growth and

pervasiveness of apps, *mobile* apps. Let's face it, when it comes to mobile phones, any gap is rather narrow.

Apps for adherence/compliance are "safe use" apps. Apps that can be "prescribed" by physicians to their patients are the wave of the present. Adherence/compliance "app-ens" and patients, physicians, payers, pharmaceutical companies—and society benefit.

Mario Andretti said that *If everything seems under control, you're not going fast enough.*

As social media participation by regulated healthcare companies continues its slow slog forward, here are some issues to ponder:

* **Intent.** Internal company debates often focus on responsibility for what happens after a corporate comment is posted. And that's important. But what's more important is what drove the company's decision to make the post in the first place. What was the *intent*? Was it marketing-driven or was it done in the best interest of a patient or the broader public health? Intent counts. Just as the FDA has asked whether or not the speaker and the audience matters when it comes to the issue of "scientific exchange," so too is this relevant in helping to determine "responsibility" for what takes place on a social media site.

Does this mean that (at least initially) regulated healthcare speech in social media will be more corporate (vs. product) driven?

* **Control.** When it comes to the "property owner vs. property user" question—what is the difference between "sponsorship" (generally defined by an exchange of money) and "control" (a more ambiguous but no less important concept)? If you control something, then can you be considered able to prevent something from happening—such as a discussion of off-label use?

* **Environment.** If you buy a banner ad on Google, that's advertising. But if that ad appears above an organic search that you do *not* either sponsor or control—are you responsible for the broader environment of that page? Perhaps the best way to approach that question is to offer this thought experiment—If you decided to run a commercial for a statin on the evening news and, during the course of the program, there was a feature on off-label use of statins—would you be responsible for the environment?

* **Safety Information.** Is it a good thing or a bad thing for consumers to spend more time interacting with important safety information? Of course it's a good thing.

Here's a question that's calling for some solid research—do consumers spend more time with ISI via the traditional off-line "brief summary" and patient package insert, or on-line via click-throughs? Inquiring minds want to know. If it is the latter, then that would further strengthen the argument that its important for regulated healthcare companies (on both corporate and product fronts) to participate in social media for the public good.

* **Commitment.** Perhaps the one thing that is the toughest to internalize is that social media is a commitment—not a tactic. Obvious financial and FTE implications here, but more frustrating is the fact that participating in social media means playing with irrational actors—like patients.

Is social media about "collaborating" with consumers or "cooperating" with them? What's the difference? Cooperation happens when both sides want to survive. Collaboration happens when they want to thrive.

Collaboration means interacting honestly and transparently. And Pharma's opportunity (within the context of social media) is to be the first among equals.

Success for Pharma in social media will come through collaboration. And that doesn't mean, "selling."

Transparency (via social media) is leading to erosion in trust of once sacrosanct gurus such as physicians, corporate spokespeople (and their avatars) and other "experts" (not the least of which is the mainstream media).

It's been a painful and swift denuding of influence. Rather than being slowly disrobed, yesterday's unquestioned experts have been roughly stripped of their influence and authority. You can't airbrush social media.

While various "emperors" are being exposed as having no clothes, the void is being filled with robust and real-time peer-to-peer communications.

Alas, there are also many ascendant false prophets. The Internet is full of them. Some are well-meaning (but still dangerous) idiots, others are pure charlatans.

Social media is a wonderful "green field of opportunity." But to maximize the opportunity, we must accommodate the reality of a messier world. Social media, almost by definition, is messy—and the regulatory framework (or lack thereof) is equally so. And it's not likely to get much better.

Nobody said it was going to be easy. If we need to change our national healthcare paradigm we must also change the way people learn, discuss and address healthcare issues. And that means social media.

Social media is interactive—and it is interactively egalitarian.

Social media requires interactive engagement in real time. It requires you to play rather than purchase. And that's a wonderful opportunity—because you cannot purchase passion.

Regulated healthcare industry must participate in social media –not because of its potency as a marketing vehicle—but because it's the right thing to do. That being said, here are 11 principles that must serve as the basic substrate of regulated social media participation.

1. We engage in social media to help improve the lives of patients and advance the public health of our nation.
2. We will thoughtfully engage in social media while remaining in compliance with both the letter and the spirit of FDA regulations.
3. Our social media engagements will have both strong public health themes and appropriate marketing communications.
4. All social media messages and partnerships must be accurate, appropriate and transparent.
5. We believe that social media presents multiple opportunities to learn more about how our products impact the lives of patients.
6. We believe that social media engagement allows us to correct errors and misperceptions about both our company and our products.
7. We believe in using social media discover adverse drug experiences, which will then be addressed off-line.
8. We will strive to interact in a timely manner, appropriate to the general expectations of social media.
9. We believe that social media must be regularly monitored and our programs measured in real time to gauge effectiveness.
10. We respect but are not responsible for user-generated content that resides on sites we do not control.
11. We believe the path to engagement is through useful and thoughtful content and commentary.

One principle that runs as a red thread throughout all of these 11 principles is transparency. Real, honest transparency—not the usual translucency that "in compliance" often brings.

NIH Director Francis Collins recently said, "We are living in an awkward interval where our ability to capture information often exceeds our ability to know what to do with it."

Collins' comment was directed at the complete human genome sequence—but is equally germane to an equally complex human proposition—social media.

It's time for action. As Friedrich Engels said, "An ounce of action is worth a ton of theory."

Case Study

A biological battlefield: The potential applications of using remote sensing technology and biomarker organisms for identifying, tracking, and differentiating persons of interest within an area of operations

Jason Rivera
is a captain in the US Army.

ABSTRACT

Since World War II, the majority of American wartime engagements have been characterized by a series of low-intensity, asymmetric conflicts. These conflicts have increased the importance of understanding the dynamics of individual actors within complex battlespaces which in turn has led U.S. military commanders, intelligence professionals, and wartime decision makers to seek a variety of means for identifying, tracking, and differentiating persons of interest. From the jungles of Vietnam to the mountains of Afghanistan, the process of understanding the movements and activities of hostile actors has become paramount to successful military targeting and combat operations. Over the last 50 years, the military and intelligence communities have developed a plethora of technologies capable of accomplishing this task to include overhead satellites, infrared imaging, unmanned aerial vehicles (UAV), advanced biometrics, and host of other personnel identifying and tracking technologies. While these technologies have closed the gap in enabling U.S. military and intelligence professionals to understand the human aspect of the battlespace, there are still significant challenges in uniquely identifying the movements and activities of specific persons or groups of persons.

Given the above outlined challenge of understanding the battlespace, this article will explore an alternative means of identifying and uniquely tracking individuals. Specifically, this article will explore the combined use of remote sensing technologies and genetically engineered biomarkers in order to uniquely identify, track, and differentiate persons of interest. Such a combination of two disparate technical fields would be technologically challenging both within the biological and remote imaging scientific fields, thus emphasizing the paramount importance of combining biological markers with distinct signatures that are detectable by specific and technologically matching visualization means. In addition to discussing the technical challenges associated with such a combination of technologies, this article will also discuss both the potential military benefits and negative implications this process could have in ethical, legal, and diplomatic terms. At the conclusion of this article, the reader should have a fundamental understanding of how remote sensing technologies and biomarkers can be combined to better understand the battlespace as well as the possible implications of this technological pairing.

Journal of Commercial Biotechnology (2014) 20(1), 43–48. doi: 10.5912/jcb643
Keywords: biomarkers, remote sensors, m13 virus

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INTRODUCTION

Between 1961 and 1971, the United States and Republic of Vietnam military forces employed a herbicidal 50/50 mixture of trichlorophenoxyacetic acid and dichlorophenoxyacetic acid, otherwise known as "Agent Orange" in order to defoliate key forest/jungle areas used by the Communist Vietcong forces for food supplies, logistical routes, and military staging operations.[1] After 20,000 herbicidal spray missions, five million destroyed acres of forests and agricultural lands[2], and the emergence of several pervasive illnesses to include soft-tissue sarcoma, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, and chloracne[3], the U.S. still failed in its endeavor to shape the battlefield in favor of understanding the movement of hostile Vietcong actors. Over a half-century later, the United States security apparatus has made leaps and bounds in terms of surveilling the human geography of the battlespace to include advances in overhead satellites, infrared imaging, unmanned aerial vehicles (UAV), and advanced biometrics.

The need for increased understanding of human movements and actions throughout the battlespace became increasingly apparent during the United States' engagements in Iraq and Afghanistan. This need resulted in the implementation and widespread use of the Biometrics Automated Toolset (BAT), a system of laptop computers and networked peripherals designed to uniquely identify individuals by cataloging photographs, scanning irises, and collecting fingerprints.[4] This system enabled the nation-wide tracking of individuals throughout both Afghanistan and Iraq and facilitated limited progress in allowing coalition forces to understand the movements of individuals throughout the battlefield. Unfortunately, BAT achieved limited success as it relied heavily upon compliance of the target populous. Enemy combatants are notoriously and obviously non-compliant; this implies a great deal of difficulty for a biometric system that requires its subject to be in close proximity and remain still.

While the use of biometrics may not hold all the answers to identifying and tracking persons of interest, there may be yet other possibilities that could be enabled via the biological sciences. This article refers specifically to the use of biomarkers combined with the use of remote sensing technologies in order to provide a standoff solution capable of remotely identifying and differentiating individuals. In using the term "biomarker", this article specifically references an organic substance capable of emitting a measurable action via the biological processes, pathogenic processes, or pharmacologic responses.[5] In regards to the term "remote sensing", this article references a method of measuring an object's properties and acquiring data from that object without coming into direct contact with said object.[6] More specifically, these two technologies must possess the following characteristics:

Biomarker:

1. A biomarker used in this process would have to exhibit a remotely detectable and measurable substance such as heat, electricity, a chemical reaction, light, etc.
2. The biomarker must be capable of being paired with a human host via a microscopic biological delivery mechanism such as a bacteria, virus, fungus, parasite, prion, etc.
3. The biomarker's detectable and measureable effects would have to minimally diminish over time.
4. Scientists and military practioners would have to be technically capable of altering the biomarker such that it would exhibit distinguishable signatures when applied against different target populations, i.e., different levels of heat, voltage, types of chemicals, intensities of light, etc.
5. For moral and ethical reasons, this biomarker should not cause adverse side-effects within human beings.

Remote Sensor

1. As the name implies, a remote sensor must be capable of operating at a significant standoff distance and, ideally, would be undetectable by the target population.
2. The remote sensor must be equipped with a specific algorithm capable of paring with and quantifying the specific emission of the biomarker. For example, a biomarker that emits heat should be paired with a sensitive infrared sensor whereas a biomarker that emits a chemical signature should be paired with a device known as a FM-DIAL sensor, a sensor designed to detect chemicals by interpreting the spectral features of that specific chemical.[7]
3. The remote sensor must be capable of being employed in combat environments, must be usable by military service members or co-deployed scientific augmentees, and must be able to interpret results with a certain rapidity that is necessary for a fluid and complex combat environment.

Given the above outlined possibility, this article shall now explore the practical and technical applications of

this methodology using a specific example of a recently developed virus.

THE ELECTRICITY EMITTING VIRUS KNOWN SIMPLY AS "M13"

The technology necessary to deploy a biological marker designed to track human beings could potentially be available within the immediate future. The recent synthesis of the M13 Virus in May of 2013 by a group of Berkeley scientists is one of the potential candidates for a biomarker that could be deployed given today's available technology. The M13 bacteriophage is a piezoelectric* virus capable of allowing the bacteria within human beings to emit a small, electric charge through the mechanical motions of the human body.[8] This virus is a potential candidate for leveraging a capacity to use biomarkers and remote sensing technology as it meets most of the five criteria previously mentioned within this article:

1. M13 emits electrical voltage and is thus quantifiably measurable due to the piezoelectric process.[9]
2. The M13 virus achieves human host pairing by infecting the bacteria on a person's skin.[10]
3. The half-life of the M13 virus is currently unknown, which implies difficulties in predicting how long a selected strand of M13 virus would infect its host bacteria.
4. Byung Yang Lee, one of the scientists in this project, demonstrated that the virus' capacity to be genetically engineered in order to increase or decrease the piezoelectric strength by adding or detracting negatively charged amino acids the coat the helical proteins of the virus.[11]
5. The virus has no known negative effects on a person as it only infects the bacteria on a person's skin and not the person's cellular structure.[12]

When tested, the virus proved capable of lighting up a small LED screen and emitted a quantity of electricity equivalent to approximately one quarter of the voltage of a AAA battery.[13] At varying intensities, the M13 virus could be used to differentiate members of a population from members of other populations. Combined with a powerful infrared remote sensor, it could be possible to detect the piezoelectric effect of an individual as the infected bacteria on their body produces an electric field. For use in a combat scenario, a remote sensor applied with the M13 virus would have to possess the following qualities:

1. An infrared optical payload capable of being mounted on a UAV, infrared goggles, wireless recording device, or some other type of apparatus capable of achieving an acceptable standoff distance.
2. The infrared remote sensor would need to be capable of differentiating electrical heat signatures by accurately detecting and depicting varying quantities of voltage and/or heat. One method of accomplishing this would be to implement an algorithm within the infrared device capable of calculating the concentration of pixel intensities[14] produced by the M13 virus' piezoelectric effect. Another method would be to implement an algorithm that calculates the qualitative/quantitative effects that heat diffusion has on soil temperature distribution[15] as a M13 affected person takes steps, thereby determining the population center origin of that particular person.
3. The infrared remote sensor must be able to upload the results of its calculations into a sort of "intelligence cloud" apparatus capable of being accessed and utilized by military and intelligence personnel within the battlespace. An example of such a cloud is the Army's Distributed Common Ground System (DCGS), a computer network system capable of sharing relevant information, calculating data, and providing intelligence estimates across great distances[16], thereby improving battlespace command and control.

The M13 virus along with an infrared remote sensing apparatus that met the above requirements could prove extremely useful in the conduct of counterinsurgency operations in environments where it is necessary to differentiate hostile actors from the ambient noise of the surrounding population. Let us take the NATO coalition's current endeavors in Helmand Province, Afghanistan for example.

According to the United Nations Drug Control Programme, southern Afghanistan represents the single most prolific source of worldwide opium production.[17] Opium production is particularly pervasive within Afghanistan's southern province of Helmand, which also happens to be the province where coalition

* An electric charge that accumulates in certain solid materials as a result of applied mechanical stress.

forces have suffered the most casualties due to Taliban led insurgency operations. Through opium production and trafficking, the Taliban manage to continue funding their combat operations[18] and therefore continue to impose terror upon the local populous as well as the Afghan military and police forces. Drug traffickers, who play a key part in the Taliban's opium operations, rely on the civil infrastructure of the local population in order to obtain sustenance, housing, transportation, and a host of other necessary services while trafficking opium product from point A to point B. In order for coalition forces hamper the Taliban's drug trafficking operations, they must interdict and detain those involved in the trafficking process; but first, coalition forces must differentiate opium traffickers from the local population. This is where a benign virus such as M13 would come in useful.

The intended goal of introducing strains of the M13 virus into battlefield affected population centers would be to facilitate the technical capacity to differentiate population center members from other population centers as well as to detect the presence of outsiders. Given this objective, consider a scenario where NATO coalition military and intelligence forces operating out of Camp Leatherneck are responsible for conducting counterinsurgency operations within the local area. With the help of Berkeley's M13 virus, NATO forces use three different strains of the virus to infect the bacteria of three local population centers shown above in figure 1[19]: Laškar Gāh, Gereshk, and Sangin. The three different strains would possess three substantially different levels of the piezoelectric effect and would thus emit three different quantifiably detectable voltages. In this scenario, the M13 virus would have to pair with its human host through some type of means that would discourage unintended transference of a particular strain from one population center to another. Bacteria infected with the M13 virus could be introduced via aircraft or aerosol. A preferred method of entry would be if the M13 virus infected bacteria in the population's water source or locally derived food source; this would ideally make human-to-human transference of bacteria unlikely.

The military applications of introducing three uniquely quantifiable strains of the M13 virus would be a game changer in enhancing the hostile actor targeting process. Intra Afghan/Pakistan Taliban border crossing and smuggling operations would be made substantially more difficult as coalition forces would be able to detect the presence of outsiders due to the absence of the piezoelectric effect. Furthermore, the ability to track individuals moving to and from various local population centers would help intelligence personnel develop patterns and thereby gain additional information about insurgent and/or opium trafficking activities. Most importantly, unlike the BAT system which requires the compliance

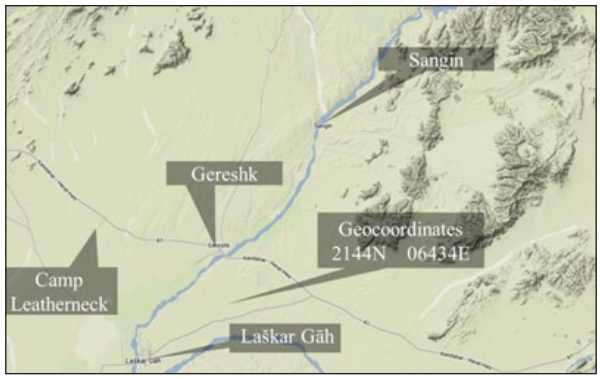

Figure 1: Helmand Province, Afganistan

and awareness of the targeted individual, bacteria could be infected with the M13 virus without the awareness of the local population and, more importantly, Taliban insurgents.

While the M13 virus is one example of how a biomarker could be used to track individuals in the battlespace, it may not be the most effective or durable method. Other biological biomarker identification methods should be considered as well to include chemical reaction inducing organisms or organisms that have bioluminescent properties. One potentially promising application would be the combination of low light imaging systems that could image bioluminescent bacteria and detect anomalies in spatial distribution[20], thereby potentially being able to detect anomalies and differences between individual people. However, in addition to considering the effectiveness of using biomarkers to understand the battlespace, it is dually important to consider the moral considerations of their use. The next section of this article will consider the ethical, legal, and diplomatic implications of using biomarkers on human populations in the context of combat and intelligence operations.

ETHICAL, LEGAL, AND DIPLOMATIC CONSIDERATIONS

While though the potential application of biomarkers in conjunction with remote sensing could yield tremendous military advantages, the use of organic material to mark and track individuals would likely face a plethora of ethical, legal, and diplomatic consequences. International laws and norms would carry tremendous amounts of weight in terms of the ethical and legal parallels that would be linked to the term "biological warfare". Specifically, such methods would be heavily scrutinized under the United Nations' Biological Weapons Convention, which strictly prohibits the development,

production, and stockpiling of biological and/or toxic weaponry.[21] While though the use of biomarkers in a non-weapon context does not strictly meet the definition of a biological and toxin weapons defined as weapons that "disseminate disease-causing organisms or toxins to harm or kill humans, animals or plants,"[22] it would be difficult to verify that deployed biomarkers would not have dual-use applications and thereby be designed to cause death and/or physical harm to human beings. Additionally, policy-makers and military commanders would have to consider the possibility of mutation. Microscopic organisms, especially potent viruses, have a notorious reputation of mutating in order to adapt to their environments. Clinical testing of biomarkers used for tracking individuals would likely undergo limited or potentially even no human trials prior to their deployment, thereby raising the probability of unintended consequences. These same consequences would become even more severe if their use were to become public knowledge.

Public knowledge of the United States sponsoring biomarkers for personnel tracking purposes could have potentially negative effects on international diplomacy. The nation's military leaders and policymakers would likely be seen as hypocrites given the United States' posture against biological and chemical warfare over the last two decades to include condemnation of the former Soviet Union's biological weapons programs, the U.S. military's intervention as a result of Saddam Hussein's chemical weapons stockpile, and the United States' current posture against the Syrian military's most recent use of chemical weapons. Furthermore, public discovery of the United States using biomarkers to track individuals of interest could potentially derail the nation's efforts to hinder Weapons of Mass Destruction proliferation.

CONCLUSION

The United States military, intelligence, and policymaking communities would have to carefully deliberate the possible outcomes and second/third order effects of using biomarkers to track human beings. Over forty years later, the U.S. still bears the scars of having used Agent Orange in Vietnam and dealing with the decades of consequences that followed. On the other hand, use of benign biotechnologies that could identify, track, and differentiate individuals could make a tremendous difference in the conduct of wartime operations. Counterterrorism professionals and intelligence targeteers alike have come to understand the value of predicting the movements of high value persons as they transit the battlespace, the countryside, and the urban environment. The implementation of biological signatures could greatly aid in the discovery of enemy networks, trafficking routes, safe houses, and other enemy patterns that could prove invaluable if better understood by the U.S. security apparatus.

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Case Study

How a large biotechnology company teamed with a translation service provider to define best practices

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ABSTRACT

According to the World Intellectual Property Organization, nearly 100,000 pharmaceutical and biotechnology patent applications are filed each year around the world, and the trend is increasing. These companies have very little room for error in the work they conduct each day. As a result, the translations of these patent applications need to be completely accurate, which requires a translation service provider who follows best practices. These best practices include centralized processes, highly specialized teams, quality control, terminology management and advanced technologies.

By following them, they will ultimately reduce office actions and litigation risks, as well as decrease time to grant.

This case study will highlight how a large biotechnology company worked with its translation service provider to develop a series of best practices for the translations of its intellectual property, focused primarily on its patent applications. Readers will come away with an understanding of how their multinational enterprises can leverage these best practices to get improved quality, reduced time to grant and more filings for the budget.

Journal of Commercial Biotechnology (2014) 20(1), 49–53. doi: 10.5912/jcb638
Keywords: foreign patent filings; international patents; intellectual property; IP translations; patent translation provider

According to the World Intellectual Property Organization,[1] nearly 100,000 pharmaceutical and biotechnology patent applications are filed each year around the world, and the trend is increasing. These companies have very little room for error in the work they conduct each day.

Market trends (and personal discussions with Global 500 legal departments) show filing demands increasing while budgets are not. Many multinational enterprises spend millions of dollars in R&D and thousands of hours creating source documents in their native language to protect their intellectual property (IP). They then hand off the source documents to domestic counsel or disparate foreign agents in various countries, who use disconnected translators with no incentive to collaborate. They're unclear on the qualifications, timelines and processes of these agents.

Enterprises filing foreign patents strive to reduce office actions and litigation risks, as well as decrease time to grant by engaging with translation service providers to manage IP translations and patent filings.

Proven best practices can protect an enterprises' best ideas around the world by managing their unique terminology and establishing deep collaboration between scientific linguists in the languages that matter most for their patent filings—resulting in improved quality, reduced time to grant and more filings for the budget.

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HOW TO MAKE THIS POSSIBLE?

One of the world's largest commercial biotechnology companies *(which asked not to be named)* has research facilities in North America, Europe and Asia and spends billions of dollars a year inventing procedures, chemical compounds and products such as detergents, soaps, cosmetics and cleaners. It then files hundreds of patents annually in 30+ countries and holds approximately 35,000 patents, which makes it one of the world's largest patent portfolios.

In 2001, the company faced a major decision: find ways to cut costs or reduce the number of foreign patent filings. A critical component of patent filings is translation, which at the time accounted for nearly 40 percent of the company's international prosecution costs. These costs were rising, while markets and foreign jurisdictions continued to expand. The company knew it needed to make some dramatic changes.

Until this point, the biotechnology company sent its patents to foreign agents, independent translators and other administrative personnel around the globe. This resulted in non-uniform and decentralized processes associated with relying on an ever-expanding network of in-country patent law firms for patent translation. These firms often justified high fees based on the sensitivity of translation projects, and the rarity of translators with the specialized technical education and expertise required for the subjects being translated.

The complexity of using multiple law firms added to the company's administrative overhead, and increased error risks associated with too many people handling documents.

With the goal of reducing cost, risk and complexity, the company required the following:

- Translators must be in the target country, native speaking and vetted for subject matter expertise and quality
- Translators must have patent specific experience and technical knowledge in the technical subject matter area being translated
- The company must own and control its language IP and terminology must be managed from a centralized location
- The company must reduce overall patent prosecution costs by 20 percent

Other factors considered during the company's search for a translation provider: a centralized point of contact with highly a network of highly specialized translation experts; terminology management capability for the proper and consistent use of company- and industry-specific terminology across all languages; translation memory for the reuse of previously translated text; and, coordinated quality assurance oversight.

At the end of an exhaustive search and an intensive vetting process, the company chose a translation service provider specializing in IP translation services and other foreign patent filing related services to translate and manage its language IP. The company valued the translation service provider's uniquely efficient centralized model that incorporates five elements vital to multinational IP translation: specialized teams, centralized processes, terminology management, quality control and advanced technology.

By consolidating its patent translation providers to only a few vendors, and working with the translation service provider to streamline its internal processes, the pharmaceutical company found it could not only reduce its translation costs and improve quality, but it could also reduce the associated risk of translation errors, substantially decrease internal administrative costs, and increase human efficiency throughout the entire process.

SUCCESSFULLY INCORPORATING A NEW PROVIDER

As the translation service provider became a trusted partner, the biotechnology company gave its service provider online access to its patent information, eliminating the need for the biotechnology company to notify its service provider when a patent was ready for production. Now, as soon as a translation request arises, the service provider is electronically informed and can immediately start the translation process. With targeted translation software and 24/7 online access, the service provider schedules and tracks the lifecycle of each project and the biotechnology company receives status updates in real time.

Over the past six years, more than 300 dedicated translators have translated more than 83 million words related to more than 2,500 cases filed in more than 30 countries. Since 2002, the service provider has captured more than 100,000 unique concepts in its language database, which provides the biotechnology company with high visibility, usable data for making decisions and absolute control over its language IP.

OUTCOMES

The multi-year, large-scale project (performed by both the biotechnology company and its service provider) streamlined the company's patent translation and foreign

filing process. Specifically, this process has reduced time-to-grant and litigation risk, as well as:

- Produced approximately twice the number of international filings due to increased efficiencies, while budgets remained relatively flat—40 percent of this efficiency was directly attributed to the service provider
- Reduced administrative, maintenance, and data handling costs
- Shortened turnaround time through leverage of previous translations— the client has never missed a filing deadline due to a translation
- Reduced risk of errors: error rates exceed ISO standards
- Increased employee satisfaction: translation docket management was eliminated and two full-time employees have been reassigned to higher value work
- Eliminated soft costs such as translation-related office actions
- Reduced Foreign Agent review of translated claims—the client demonstrated that if the English source document is correct, the target language translations will be accurate
- Exceeded its goal of lowering overall patent prosecution costs by 20 percent

In summary, more patents are being filed internationally at significant savings to the client, with higher quality, lower risk and less burden on its staff.

TRANSLATION "BEST PRACTICES"

The service provider and its biotechnology client worked together from the beginning to create what are now proven best practices for IP and patent filing translations. These best practices include centralized processes, highly specialized teams, quality control, terminology management and advanced technologies.

1. **Specialized Personnel**
   Every person who comes in contact with a patent should be specialized in the target language, the technical nature of the patent and the filing requirements of each individual country. Ideally, translators should be native speakers of the target language with education in language translation or linguistics, and have knowledge of the various technical fields. They should also keep up to date with the terminology and developments relevant to the customer market segments in question and understand multinational patent translation requirements and rigid translation and documentation processes. This ensures that a company receives the most accurate, specialized, secure and timely translations.

   The service provider working with the biotechnology firm has highly specialized IP translation teams that include project managers, translators, legal specialists and desktop publishers for IP translation and related services for foreign patent filings. Its network of translators is comprised of native-speaking, in-country experts, more than half of who hold doctorate or master's degrees in scientific fields relevant to its Global 500 clients.

2. **Centralized Processes**
   Even with all the latest technologies on the market, some patent firms persist with the inefficient and often frustrating decentralized model comprising dozens of translation teams around the globe—each managed locally, without coordinated project management or cross-team collaboration. This often leads to higher costs, increased human errors, lower productivity and a general absence of transparency in project advancement and deadlines. Service providers that consolidate translation tasks from independent teams and agents to interactive teams that report to the project owners at the company streamline the translation process and reduce costs, since translations are produced by fewer employees and external agents.

   The translation service provider's centralized processes streamline translation and other foreign patent filing tasks to interactive teams that report to enterprise project owners. Working in partnership with the service provider, Global 500 legal teams experience increased patent filings, decreased office actions, reduced invalidation risk and faster time to grant.

3. **Terminology Management**
   Establishing a common terminology database across all countries and languages relevant to the enterprise is vital to improving quality, meeting deadlines and maximizing ROI.

Without terminology management, the risk of patent errors and omissions is increased. Translation providers should be willing to coordinate development of glossaries and dictionaries, research and develop terminology databases, and edit, review and update terminology on a consistent basis. They should then integrate these terminology databases into their systems, and develop and implement style guides.

Before beginning any translation, the translation service provider should work closely with the legal teams to streamline the consistent use of predefined terminology specific to their internal vernacular, as well as that of their target industries and geographies.

4. **Quality Control**

For translation, quality should be defined as the degree to which the work product achieves the purpose for which it is created. When discussing the need to increase IP translation quality, this quality can be measured by technical and scientific accuracy. This can have certain specific benefits, including fewer U.S. Patent and Trademark Office actions related to translation or clarity problems, reduced time to grant, and the absence of opposition or invalidation due to translation and clarity issues.

The translation service provider should drive rigorous, redundant quality control, delivered by both advanced technology and skilled team members at multiple steps in the translation process. This service provider, for example, has patented its own for quality assurance with the Translation QA Evaluator (US Patent 7653531). This translation review technology increases the objectivity in translating and reviewing translations.

There are also a variety of quality standards and certifications that translators can receive to highlight expertise in language, location or industry. Ones to consider when looking for a translation service provider include:

- *European Standards (ENs) 15038 Global Certification:* This certifies the translation process according to the European and German standard. It demonstrates a translation company's effort to establish the best procedures for creating a high-quality translation. The standard defines the requirements of the translation service provider in regards to personnel and technical resources, quality control, project management, client contract parameters and management methods for providing service.
- Society of Automotive Engineers (SAE) J2450: SAE International established this translation quality metric for subject matter expertise in the automotive industry.
- Localization Industry Standards Association (LISA): This quality assurance model is designed to promote the best translation and localization methods for the software and hardware industries. While LISA is no longer active, their standardization methods are still widely used as the benchmark for quality translations.
- ATA Metric: This method was developed by the American Translators Association to be used as an evaluation tool to test the quality of a translated text. A "strong" or "standard" score on the text correlates with an International Language Roundtable (ILR) Professional Performance Level 4 or 5, respectively, which indicates the highest level of professional performance for a translator.
- ISO 9000: The translation service provider should adhere to — or be working towards adherence — to the management system of ISO 9000, which is designed to help organizations ensure that they meet the needs of customers and other stakeholders.

5. **Advanced Technology**

Advances in machine translation regularly refresh the debate about whether humans or machines should be translating documents. In the case of highly technical IP translations, however, humans win every time. Only humans can fully understand the nuances of source text and target languages.

Consider this example in a 2010 Reuter's article focused on pharmacists who provided medicine labels in Spanish to customers. According to the article,[2] 90 percent of these pharmacists used computers to translate labels from English to Spanish. The reporters looked

at 76 computer-generated labels, comparing them to the originals, and concluded that half of the labels contained serious mistakes. One such error translated the instructions "once a day" to "eleven times a day." In a situation that involves taking a drug, one with potentially lethal side effects if taken in the wrong dose, accuracy counts for more than convenience.

The same is true for patent translation: accuracy matters. However, this does not mean that technology should not play a significant role in IP translations. There are indeed translation-related technologies that can ensure greater accuracy and quality for the rigorous requirements of patent filings. For example, translation memory software allows translators to leverage past translations. This saves time and cost for both translators and the enterprise client.

Project management tools allow project owners to coordinate even the most formidable portfolio of patent prosecutions across a global network. A translation company's project management and tracking tool should be specifically designed for translation processes, creating schedules and following each project task from start to finish. Centralized management improves project transparency and enables project managers and team leaders in a global, distributed work environment to work collaboratively and effectively on translation projects. All parties can monitor the status of each project, along with its actual expenses and projected cost estimates.

Technology systems help manage translation workflow and recognize the source language, target languages, document attributes and other project-specific items, and will automatically associate the source files with the most pertinent translation memories and dictionaries.

Technology to help manage a client's specific terminology also improves accuracy and manages costs. This translation software captures repeat text and uses these captures to build out a terminology database devoted to that enterprise's patent documents. Translators are then able to check existing terminology or build other databases for new projects.

Terminology management software also provides translators with suggestions and allows updates to the database throughout the translation process. Using this technology, translation companies develop extensive glossaries and style guides based on their client's preferences. Many of the world's largest patent filers clients have more than 100,000 terms captured and stored. These glossaries and guides that help eliminate possible inconsistencies that result from multiple translators collaborating on the same project.

While the software ensures the integrity of existing terminology, it also builds new terminology databases for individual language translation projects. As the software captures terms, it tracks the source of the term, the date the term was entered, who entered it and other related information. Terms can even be suggested "on the fly" and new terminology databases will be updated while translation occurs.

A translation service provider should be strategically investing in technologies for translation services, project management and even desktop publishing. As a result, these technologies will significantly contribute to process transparency, increased patent filings, decreased office actions, reduced invalidation risk, faster time to grant, improved translation quality and reduced errors.

By ensuring that your translation service providers meet these five best practices, you will help reduce your enterprise's risks, increase the value per patent translated and protect your intellectual property throughout the patent filing process.

A company's patent applications are the headwater of its documentation, and when translated with the high degree of accuracy that these projects demand, the investment can be leveraged for all other communications, including clinical trials, protocols, case reports, dossiers, product inserts and labeling.

ENDNOTES

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Legal & Regulatory Update

Raw materials intended to be used for gene, cell and tissue therapies: Legal and regulatory considerations

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ABSTRACT

This paper offers some insights on the European regulatory situation with respect to raw materials used in production of gene, cell and tissue therapy products, including advanced therapy medicinal products. By focusing on the existing EU and French rules, the purpose of this paper is to review the content and scope of the measures restricting their placing on the market and/or use, the legal implications and hence key challenges ahead. Also known under the specific term "ancillary products" in France, raw materials are subject to a fragmented regulatory environment that could indirectly hinder innovation in this rapidly evolving area. Taking account of contamination risk that could originate from such materials, the question as to whether it is necessary to assure their quality and safety by means of one or various regulatory instrument(s) does not arise. Nevertheless, it is vital that, in a sector as innovative as this one, an appropriate and more predictable regulatory regime applies in Europe, which requires undertaking a constructive work aimed at harmonising the rules in relation to production of and trade in raw materials intended to be used for advanced therapies while ensuring the EU objective of public health protection: a work already in progress.

Journal of Commercial Biotechnology (2014) 20(1), 54–60. doi: 10.5912/jcb633
Keywords: raw materials; ancillary products; placing on the EU market; free circulation; restrictions of use; harmonisation

INTRODUCTION

Regulation (EC) n°1394/2007[1] has unquestionably contributed, over the last few years, to achieving an effective opening-up of the EU market of gene, cell and tissue therapies (hereinafter referred to as "advanced therapies"). Even if this market sector is becoming a reality through marketing authorisations issued progressively, the fact remains that "*a large number of products are still in early clinical development*"[2] and that developers involved in advanced therapies face many more regulatory challenges than in any other field. As a matter of example, all the final products of these therapies are manufactured utilising materials that are commonly used for cell procurement, separation, cultivation, differentiation and expansion. From a regulatory standpoint, such materials are neither framed by any specific EU legislative act nor covered—since intended for professional use—by the general provisions of Directive 2001/95/EC.[3] At best, they are lumped together under the same concept of "raw materials", which is specifically defined for the purpose of Annex I to Directive 2001/83/EC[4] and thereby covers any "*substances used for manufacturing or extracting the active substance(s) but from which the active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives*", including any biologically active additives. They differ from starting materials from which the active substance of the medicinal product is manufactured or extracted.[5] Although no other specific definition is given outside the EU pharmaceutical legislation, it is clear that, within the framework of the latter, the notion should be understood in its widest sense. Article 15 of the Regulation indeed refers to raw materials in "*including all substances coming into contact with cells or tissues [the ATMP] may contain*", the notion of contact being here determining. Whereas they are distinct from starting materials, raw materials may, in residual amounts, become part of the final product that is administered to patients, and hence raise public health concerns. As expressed at a Symposium dedicated to raw materials used in the sector

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of advanced therapies,[6] they have recently emerged as a real issue in regulatory discussions. Despite the role that the above Regulation plays in this sector, on which the European Commission is expected to publish a report soon,[7] it should be borne in mind that the sector taken as a whole covers not only advanced therapy medicinal products (ATMPs), but also all human tissues and cells that are used for therapeutic purposes and fall, since not manufactured by a method involving an industrial process and not substantially manipulated, within the scope of Directive 2004/23/EC.[8] For the sake of clarity, materials intended to be used for the production of all the above products (hereafter "gene, cell and tissue therapy products"), but not to form part of the active substance shall be considered, without any distinction, as "raw materials" in this paper. The purpose of the latter is to review the origin, scope and content of the existing legal and regulatory requirements with respect to safety and health protection of such materials, with a particular focus on the EU and French rules, and to see the extent to which they restrict their free circulation within the EU.

RESTRICTIVE RULES IN THE CONTEXT OF ADVANCED THERAPIES: A PATCHWORK

Rather than falling into a single legal category, raw materials constitute a wide range of products from culture media to biologically active additives that are not uniformly addressed in the EU law. The concept of "raw materials" is not assimilated to a completely independent legal status. In the absence of harmonisation of legislation, the EU principle of free circulation of raw materials shall be ensured, unless they are subject to national specific measures (see the French example below) or deemed to be approved, for instance, as medicinal products in the Member States of destination. It should be recalled here that, contrary to some assertions, it does not infer from the Manual on borderline and classification in the Union regulatory framework for medical devices that there is a harmonised position according to which the provisions of Directive 93/42/EEC[9] could, prior to their placing on the Union market, apply to reagents and culture media intended to be used in the context of advanced therapies. Indeed, the manual was amended in 2009 only to include into the scope culture media used for *in vitro* fertilisation (IVF) and assisted reproductive technologies (ART) and agents for transport, nutrition and storage of organs intended for transplantation. They may be qualified as medical devices and subject to certification within the context of these specific medical procedures on a case-by-case basis only, taking into consideration their principal intended action and intended purpose.[10] The European Medicines Agency (EMA) excludes, by implication, in the guideline on human cell-based medicinal products the application of certification processes and CE marking to raw materials used for their manufacture.[11] Conversely, this guideline provides that "*when*" raw materials have a marketing authorisation (e.g. human albumin to be approved as a medicinal substance) or are mentioned in a Pharmacopeia, *"appropriate references may be given"* and thus highlights the EU regulatory patchwork in this area. It follows that raw materials are not all subject to the same regulations—and in some cases are not regulated at all prior to being made available on the Union market. Whereas they are not—or cannot be—subject to unified conditions for the placing on the market, their use is partly harmonised through the EU pharmaceutical legislation. Directive 2001/83/EC and the GMP Guidelines[12] provide for some requirements with respect to raw materials intended for the manufacture of ATMPs. Once implemented into the different national legal systems, the said requirements are, however, binding on every applicant who is in charge of the quality part of the dossier supporting the application for a marketing authorisation for an ATMP. Module 3 of part I of Annex I to Directive 2001/83/EC requires, for instance, detailed information on the quality and control of the starting and raw materials used during the manufacturing operations of the active substance. Commission Regulation (EC) n°668/2009[13] imposes, in more revealing terms, the same obligation on "*micro, small and medium-sized enterprises, which develop an [ATMP]*", this information being, from a regulatory viewpoint, not required at the time of placing such materials on most national markets. Where a raw material is the subject of a monograph of the *European Pharmacopeia*, it is, again, the applicant's responsibility to obtain a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines (EDQM), replaces the relevant data required in Directive 2001/83/EC.[14] Likewise, noteworthy is that, within the terms of Article 15 of the ATMP Regulation, it is the responsibility of "*the holder of a marketing authorisation for an [ATMP]"* to ensure that the individual product and its starting and raw materials can be traced from their sourcing. In consequence, where raw materials are not approved for marketing—due to the absence of a recognised legal status—the regulatory burden is only placed on developers. Albeit mere users of the raw materials intended to be used during the manufacturing process of ATMPs, they are thus more liable to be subject to restrictions likely to create practical obstacles to their activities. By contrast, it infers from the GMP Guide that only raw material suppliers who provide manufacturers with animal sourced products are subject to "*regular audits*", even if "*source, origin and suitability of [all] biological of*

starting and raw materials should be clearly defined" in dossiers supporting applications for marketing authorisations.[15] Although, in practice, "*some raw material companies have started qualifying their products,*"[16] that is to say determining suitability based on their characteristics, it is clear that suppliers are not under the regulatory obligation to comply with the provisions laid down in the EU pharmaceutical legislation and hence cannot predict all rights and responsibilities they are given. In that context, they can legitimately fear that compliance with the relevant GMP requirements on a voluntary basis entails contractually shifting, in the supply chain, the responsibility for risk of contamination.

SCOPE AND CONTENT OF THE RESTRICTIONS OF USE LAID DOWN IN THE PHARMACEUTICAL LEGISLATION

In light of the foregoing, raw materials are subject to clear sourcing restrictions when used during the manufacturing operations of ATMPs. According to point 4.2.1 of the guideline on cell-based medicinal products, "*it is recommended to keep the use of [biologically active additives in culture media] to a minimal and to avoid use of reagents with sensitisation potential.*" Moreover, "*when applicable, the use of animal reagents should be avoided and replaced by non-animal derived reagents of defined composition.*" It is also noteworthy that the use of synthetic alternatives to reagents of human origin is encouraged. The sourcing of materials is therefore not flexible. They shall be selected, taking into account their quality and their real or potential risk of transmitting spongiform encephalopathies. In addition to complying with these stringent sourcing requirements—the above guideline being unequivocally considered as the harmonised Union position—developers should identify, document and even control the quality of raw materials, with a particular emphasis on viral safety aspects. As proof, some documentation requirements with respect to raw materials apply to applicants for marketing authorisations in pursuance to point 3.2.1.2 of part I of Annex I to Directive 2001/83/EC. Likewise, as regards human cell-based medicinal products, "*quality of biologically active additives in culture media, such as growth factors, cytokines and antibodies, should be documented with respect to identity, purity, sterility and biological activity and absence of adventitious agents*" (point 4.2.1 of the EMA guideline). While the terms "qualified raw materials" are not expressly referred to in the relevant provisions laid down in the pharmaceutical legislation and the related guidelines, it is unquestionable that raw materials should be appropriately selected, "*evaluated*" as to their suitability for their intended use and that the whole manufacturing process should be described and "*validated*".[17] It is, however, apparent from the guidelines, when examined more closely, that quality requirements are referred to in specific contexts, but not sufficiently detailed. For instance, materials and reagents used for the transduction process should be of "*appropriate quality […] in order not to compromise the quality, safety and efficacy of the final product*" containing genetically modified cells. Rather than a very distinct objective, this here constitutes a legal standard subject to interpretation.[18] It can arguably be contended that, the "*intended purpose*" being a key notion, raw materials are never reintroduced into the human body, and thereby do not require the same acceptance criteria as those applicable to starting materials from which the active substance is manufactured under Directive 2001/83/EC.[19] For instance, the regulation considers biologically active molecules differently, depending on whether they are liable to become part of the final product in residual amounts or are part as "components" (see point 3.3.2.3 of part IV of Annex I to the Directive). The fact is, yet, that decisions are based upon quality criteria with regard to raw materials. Indeed, "*recurrent objections raised during the evaluation of ATMPs [are related to] quantitative and qualitative information of the raw material composition*". Moreover, albeit not clearly banned in the pharmaceutical legislation, the EMA, which is in charge of centralised marketing authorisations for ATMPs, finds that "*raw materials of 'research' or 'in vitro' grades*[20] *[are] not acceptable*".[21] Taking account of these implicit limitations and their significant impact, the direct link of cause and effect between the use of raw materials and conditions for the marketing of cell, tissue and gene therapy products is all the more crucial to foresee. In addition to defining quality requirements for key raw materials, as was expressed at the above Symposium, it would be needed to provide a more predictable regime for all potential recipients in making positive and negative obligations more explicit and in specifying obligations as to results to be achieved.

MORE STRINGENT MEASURES FOR RAW MATERIALS PLACED ON THE FRENCH MARKET

In the absence of harmonisation of legislation relating to certain risks associated with the storage, preparation, transformation, packaging or transport of organs, tissues and cells, France adopted in 1998 measures aimed at regulating them specifically. Hence, all chemical and biological products used during the production of gene, cell and tissue therapy products, including ATMPs, meet the

French definition of "*produits thérapeutiques annexes*" (hereafter, in English, "ancillary products"). This legal status, which is neither recognized at EU level nor in any other Member State, covers any products that, with the exception of medical devices referred to in Article L. 5211-1 of the French Public Health Code, come into contact with organs, tissues and cells of human or animal origin for their storage, preparation, transformation, packaging or transport prior to being used in patients for a therapeutic purpose.[22] The products concerned, including both culture media and biologically active additives, are uniformly and specifically regulated under Articles L. 1261-1 to L. 1261-3 and Articles R. 1261-1 to R. 1261-9 of the French Public Health Code. Therefore they are all subject to a national authorisation process, unless they are approved for marketing in another Member State and can receive mutual recognition under EU law. Interestingly, the implementation of the French legal framework for "ancillary products" relies upon two determining criteria that emphasise the special nature of this regulatory status. The definition not merely provides that all materials coming into contact with organs, tissues and cells are covered, but also that the latter shall be intended, whatever their degree of preparation, to be used for a therapeutic purpose. Where products of cell therapy are intended for therapeutic uses, developers have thus, in principle, no choice but to purchase and utilise materials approved as "ancillary products" or under any equivalent legal status. Purchasing criteria depend upon the purpose for which the cells and tissues are to be prepared, knowing that the notion of "therapeutic purpose" covers use for clinical research in pursuance to Article R 1243-1 of the same Code. Contrary to the EU rules, the French legal framework sets out a clear distinction between raw materials intended for research use only and those used in clinical development, on the understanding that only the latter fall within its scope. The problem is that, in the field of advanced therapies, the majority of raw materials, such as growth factors and cytokines, are initially intended and commercially available for research use only. Conversely, they cannot be made available on the French market after being approved as "ancillary products" by the competent authority, i.e. *Agence nationale de sécurité du médicament et des produits de santé* (hereafter "ANSM"). In that case, it is the developer's responsibility, according to the ANSM, to provide the information on the quality, safety as well as claimed *in vitro* efficacy of the product, in collaboration with the manufacturer.[23] As a result, a wide range of "ancillary products" is evaluated as part of the clinical trials applications submitted during the development of gene, cell and tissue therapy products. This has led to a situation where the requirements laid down in Articles of the French Public Health Code, which apply in principle to persons responsible for placing "ancillary products" on the French market, should be fulfilled by developers, who are, by implication, under the obligation to complete information that is not expressly required elsewhere (i.e. innocuousness, *in vitro* efficacy), in addition to that on quality of the raw materials and each of its components. Such a situation has indirectly the effect of limiting access to the French market and, because of regulatory divergences with the other Member States, partitioning national markets. As the consequence of applying more stringent requirements to raw materials coming from the other Member States, where they are lawfully marketed, the French rules hinder their free movement within the EU. They constitute, in EU terminology, measures having equivalent effects to quantitative restrictions on intra-Union trade, which, under the EU Treaties, may be justified on grounds of public health reasons.

MEASURES LEADING TO A PATCHY REGULATORY SITUATION WITHIN THE EU

Without going into all details of the public health considerations, it is clear that viral contamination and toxicity issues originating from raw materials may have an impact on the quality, safety and efficacy of the final products. The likelihood that materials become part in residual amounts of the final product destined to be administered to patients therefore raises public health concerns, the protection of which may be set forth as an overriding requirement of general interest authorising a Member State to apply restrictive measures or, as a specific objective, in an EU legislative act. Knowing that a large number of gene, cell and tissue therapy products are from now on in clinical development, this likelihood requires taking into account more than ever their safety for patients participating in clinical trials. As stated above, raw materials are, nevertheless, not regulated in the same manner, depending on the purposes they are intended for and the final products produced. Despite the objective of ensuring the protection of public health, no sufficient justification could support this patchy regulatory situation within the EU. With regard to the French measures for ancillary products, it is significant that they should not only be justified on grounds of public health reasons, but also objectively considered as proportionate and non-discriminatory under EU law. Considering the substantial discrepancies between the EU Member States, the question thus arises as to what extent requirements with respect to quality, innocuousness and *in vitro* efficacy of raw materials could be justified without any distinction criteria as to their composition and level of criticality. It is in particular difficult to see how such measures could

fulfil the "proportionality test" required under EU law, knowing that they are, moreover, much more stringent than the other national rules aimed at implementing the relevant provisions laid down in the EU pharmaceutical legislation.[24] In this instance, noteworthy is that the French measures were inserted into the draft law *on the increase of sanitary supervision and sanitary control of products for human use* within the framework of parliamentary debates, and that the reports written on behalf of the committees did not explain why an authorisation scheme had been considered as the most appropriate for ancillary products.[25] Despite the perceived safety concerns, it should additionally be noted that the French legal framework, which applies to all raw materials without any distinction, contrasts with a two-tier regulatory approach tied to the disparity of the relevant EU rules. Indeed, raw materials that are intended to be used during manufacturing operations of advanced therapy medicinal products are subject to the requirements laid down in the EU pharmaceutical legislation, while developers of gene, cell and tissue therapy products that only consist of minimally prepared human cells or tissues, in line with Directive 2004/23/EC, are not obliged to comply with—but may refer to—these requirements. What is more, it is important to remember here that the regulatory context, as described above, has led to a situation where raw material suppliers respect technical requirements that do not primarily apply to them, from a EU perspective, and developers of gene, cell and tissue therapy products have to take over tasks from the persons responsible for placing ancillary products on the French market. Unmistakably, the wide variety of legal and regulatory requirements aimed at answering the challenges in relation to the above raw materials used is not satisfactory. This regulatory environment, which is neither appropriate nor cohesive, suffers from a clear lack of harmonisation and stabilisation within the EU.

DEFINING A REGULATORY PATHWAY FOR CRITICAL RAW MATERIALS

As shown above, raw material producers and developers of gene, cell and tissue therapy products have to navigate a regulatory maze in order to carry out their respective activities. This is not—we can suppose—the surest guarantee to ensure a high level of public health protection while avoiding too burdensome administrative, financial and legal constraints likely to hold back the development of advanced therapies. That is the reason why it would be useful to strike a better balance between these different constraints. Certainly, the creation of the EDQM/EMA working party constituted a first step towards better quality standards for key raw materials used in the sector of advanced therapies. None the less, all the issues related to the relationships between suppliers and users and mutual communication of contamination risk would remain unsolved if not addressed at EU level. Also, there is a perceived need to harmonize definitional elements and procedural aspects that would level the playing field and thus benefit both the private sector and regulators. From the EU perspective, it is, moreover, significant that the content and scope of the laws, regulations and administrative provisions in force in the Member States with regard to safety and health protection of raw materials are distinctly different. Therefore, the question as to whether a EU legislative act would usefully contribute to harmonizing the provisions related to raw materials does not arise. Given the existing loopholes and disparities between legal frameworks, which constitute barriers to trade within the Union, the approximation of the relevant national provisions would, by virtue of the application of Articles 26 and 114 of the Treaty *on the Functioning of the European Union* (TFEU), guarantee the functioning of the internal market of raw materials, while pursuing the objective of public health protection. It should be noted that harmonised measures might have the effect of limiting the free movement of raw materials "*only*" where such a limitation is necessary for ensuring any higher objective, in line with the case law of the Court of Justice of the European Union.[26] In this perspective, the highly innovative nature of the sector of advanced therapies taken as a whole underlines the need to start discussions to explore regulatory pathways by taking into consideration the "level of criticality" of raw materials. It would be probably worthwhile considering all critical aspects—to be further defined—of raw materials in the same way as "*critical points*" related to the manufacturing process or the quality of medicinal products under Directive 2001/83/EC. Finally, the real question is not whether it is necessary to attempt a more comprehensive harmonisation, but to what extent the institutions could undertake such a work in this area, taking into account differences in raw materials as to their composition and their principal or ancillary action, and also potential complications associated with combined raw materials. In this regard, it would be worth investigating how the regulatory loopholes can be closed and whether, for instance, culture media containing ancillary medicinal substances, such as human albumin, can be subject to an appropriate certification process based upon specific acceptance criteria in terms of quality, safety and *in vitro* efficacy, and established in conjunction with the GMP requirements.

CONCLUSION

Although it is still necessary to examine ways to streamline regulatory procedures, developers and suppliers would surely benefit from a legal harmonisation aimed at ensuring the proper functioning of the internal market of raw materials intended to be used in a context of advanced therapies and, where necessary, a high level of public health protection. Currently, there are no indications for believing that an appropriate and well-defined certification process could not adequately apply to reagents and culture media, even if they contain medicinal additives. Nor is there any real reason for considering that the French regulatory framework is not capable of being harmonised at EU level. While regulatory discussions, which could finally lead to an alternative solution based upon a centralised evaluation, are at their very early stages, it has already been made clear that such a work cannot be accomplished without better identifying safety and quality requirements for these products and concurrently providing a more predictable regulatory regime for all the economic operators concerned. What is indeed important is that suppliers are willing to sell appropriate raw materials, whatever the purposes they are intended for and independently of the nature of gene, cell and tissue therapy products produced. One of the main challenges ahead is to strike a balance between specific financial constraints and heightened requirements of regulatory compliance in order to level the playing field.

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Legal & Regulatory Update

EU Legal & Regulatory Update — November 2013

ABSTRACT

UK and European content is compiled and written by Bird & Bird LLP, an international law firm which advises Life Sciences clients on:

- licensing intellectual property and know-how
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This section is intended to be a synopsis of recent legal developments and is not intended to be exhaustive. If any issue referred to in this section is to be relied on, specific advice should be sought.

Journal of Commercial Biotechnology (2014) 20(1), 61–66. doi: 10.5912/jcb640

ITALY: RECENT DECISIONS ON SPCs FOR COMBINATIONS OF ACTIVE INGREDIENTS

In the last few months, the Court of Milan has issued several decisions and orders[1] fitting within the framework of the European-wide litigation concerning Sanofi's combination supplementary protection certificate ("SPC") on irbesartan and hydrochlorothiazide ("HCTZ").

Background

Sanofi was the owner of the European Patent No. EP 0454 511 claiming the anti-hypertensive drug irbesartan. The patent expired on March 20, 2011 and in Italy Sanofi obtained two SPCs based on this patent: one for irbesartan and one for the combination of irbesartan + HCTZ. The latter is based on claim 20 of the basic patent claiming irbesartan in combination with a diuretic.

All the generic companies who were brought into different infringement and preliminary injunction ("PI") proceedings by Sanofi tried to dismiss the claims of the

1 Decision of the Court of Milan, 29 December 2012 in *Doc Generici vs Sanofi*; decision of the Court of Milan, 29 December 2012 in *Sanofi vs EG*; first instance PI order of the Court of Milan, 22 December 2012 in *Sanofi vs Teva*; first instance PI order of the Court of Milan, 22 December 2012 in *Sanofi vs Mylan*; first instance PI order of the Court of Milan, 20 April 2013 in *Sanofi vs Sandoz*; appeal PI order of the Court of Milan, 6 March 2013 in *Teva vs Sanofi*; appeal PI order in *Mylan vs Sanofi*.

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originator, challenging the validity of the combination SPC.

In particular[2], they alleged that the SPC for irbesartan + HCTZ would have been invalid on the grounds that:

(i) the combination was not specified in the wording of the claims in compliance with Article 3(a) of Regulation 469/2009/EC ("SPC Regulation") as interpreted by the ECJ decision of the European Court of Justice ("ECJ") of 24 November 2011 in *Medeva* (C-322/10 — "*Medeva*");
(ii) only one SPC is allowed per patent in compliance with Article 3(c) of SPC Regulation.

Furthermore the generic companies asked for the Italian proceedings to be stayed in anticipation of the decision on a referral by Arnold J in September 2012 to the ECJ in parallel UK proceedings. This concerned Actavis' invalidity action relating to the corresponding UK SPC and Articles 3(a) and 3(c) of SPC Regulation (C-443/12).

The Court of Milan, both in the first instance and in the appeal filed against the grant of the PI orders, rejected all the arguments of the generic companies and confirmed the validity of the enforced SPC on the combination product. The Court granted the injunction requested by Sanofi.

Grounds of the first instance decisions

At first, according to the Court of Milan in the first instance decisions, the staying of the proceedings was not necessary since the rules of the SPC Regulation, as well as the case law of the ECJ, are sufficient to decide the issue.

As a matter of fact, the Judge pointed out that "*Article 3(a) of SPC Regulation provides that the combination of active ingredients of the 'product' has to be protected by a valid basic patent, without setting as requirements* ad validatem *also the express individuation and description of any single active ingredients*".

The Court of Milan highlighted that, by reading the SPC Regulation (in particular Articles 4 and 5), the strict correlation between the basic patent and the extension of the protection granted by the SPC was evident. The latter was not subjected to further requirements not provided by the patent law.

The reference to *Medeva* was considered irrelevant for the case at issue according to the Judge at first instance.

Firstly *Medeva* concerned a different case since the SPCs at issue were based on a patent which protected an active ingredient constituted by the combination of two different substances. The relevant marketing authorisations (MAs) also referred to medicinal products containing different active ingredients which did not fall in the scope of protection of the basic patent.

Secondly *Medeva* stated that the claims have to identify the invention claimed by the basic patent in compliance with the patent law and that, in any case, if the patent protection is conferred to a sole active ingredient, an SPC for the combination of different active ingredients cannot be granted.

The Judge concluded: "*there are no indications by the ECJ providing that any element of the product (i.e. the active ingredient or the composition of active ingredients of a medicinal product) has to be expressly and nominally individuated in the claims, in case the patent is valid in compliance to the patent law*".

By so doing the Court of Milan seems to have broadly interpreted the ECJ principles.

As to the objection of invalidity to Sanofi's SPC under Article 3(c), the Court of Milan highlighted that this rule excludes the grant of a further certificate if it has been already granted for the same product but not the grant of a further SPC for the same patent.

As a matter of fact: "*if a patent can claim more products or more compounds* [in compliance with Article 82 EPC[3]], *on the basis of a sole patent more marketing authorizations may be granted and therefore also more SPCs, provided that such different SPCs refers to different products 'as medicinal products' (all included in the scope of protection of the basic patent), which are authorized through different MAs*".

Furthermore the Court pointed out that the word "*product*" of Article 3(c) of the SPC Regulation corresponds to "*the medicinal product as authorised by the MAs*", i.e. the "*product as a medicinal product*" and not to the term "*patent*" (which, as seen above, may legitimately claim more products).

Otherwise the alleged invalidity of the SPC could be easily avoided by the owner by simply filing two different patent applications.

Moreover, according to the Court of Milan, even the ECJ decision in *Biogen* (C-181/95) does not state that a patent can be the basis only and exclusively for one SPC

2 The other objections relate to the invalidity of the basic patent for lack of inventive step and insufficiency and the invalidity of the SPC for violation of Article 3(c) of SPC Regulation.

3 And the possible sanction for having claimed two different inventions in a patent is the obligation to file a divisional application and not the invalidity of the patent.

but affirms that a sole SPC can be granted for the same "*product*".

In the case at issue Sanofi's SPCs covered two different "*products*", i.e. "irbesartan" and "irbesartan + HCTZ", which had been authorized by two different MAs, both "*first authorization*[s] *to place the product on the market as a medicinal product*" in compliance with Article 3(d) of the SPC Regulation.

Grounds of the appeal decisions

In the appeal proceedings filed by various generic companies against the PI orders, the Panel of Judges of the Court of Milan confirmed the decisions of first instance.

In their reasoning, with reference to the validity of the SPC on irbesartan + HCTZ according to Article 3(a) of SPC Regulation, the Judges highlighted the peculiarity of the case at issue where the basic patent claims the combination of irbesartan and a diuretic.

In particular, according to the Court of Milan, the person skilled in the art, reading claim 20 of Sanofi's basic patent, would have immediately understood that the diuretic could be HCTZ. As a matter of fact: "*one of the active ingredients of the composition is indicated as belonging to the class of substances (diuretics) but in reality it could be directly identified by the person skilled in the art on the basis of his common knowledge and through* routine *operations*".

Conclusions

These decisions provide an important and interesting overview of the interpretation of the SPC Regulation and ECJ case law regarding combination SPCs carried out by the Italian Judges.

Nevertheless, it seems that such an interpretation is not the same across Europe[4].

All we can do is wait for the ECJ decision in the parallel *Actavis* case, in the hope that this will produce some clear and unambiguous principles.

Evelina Marchesoni Milan

4 For example, very recently, by decision dated 27 August 2013, the Court of Appeal of The Hague has decided in the parallel Dutch irbesartan case that *Medeva* should be read as "one SPC per patent" and not "one SPC per product per patent".

HUNGARY: STRICTER OBLIGATIONS FOR PHARMACEUTICAL COMPANIES AND WHOLESALERS

On 6 July 2013 significant amendments to Act 95 of 2005 on Medicinal Products for Human Use (Medicines Act) entered into force. The new provisions introduce an obligation for pharmaceutical companies to supply Hungarian wholesalers and also an export ban for certain medicines if it is likely that this is necessary to satisfy the demand of Hungarian patients. The amendment also provides the National Institute of Pharmacy (NIP) with strong investigation tools, including powers to impose a fine of up to HUF 500 million (approx. EUR 1,650,000), conduct a dawn raid, search any premises (including private homes and cars of company representatives), seize a wide range of evidence and clone computer hard drives and other storage media.

The supply obligations aim to tackle the recurring problem of medicine shortages of Hungarian wholesalers and healthcare providers. The increased supply obligation and the export ban are jointly aimed to serve this goal. The strengthened investigative powers of the NIP are also intended to enhance the efficiency of actions against counterfeit medicines (as also required by European legislation including Directive 2011/62/EU).

New supply obligations

The amendments to the Medicines Act were motivated by wholesalers who reported on several occasions that they struggled to supply the needs of Hungarian patients because pharmaceutical companies refused to supply them with medicines. Therefore, the amended provisions state that if a wholesaler notifies a holder of a marketing authorisation (MA) that a given product is necessary to satisfy demands that have arisen on the Hungarian market, then the holder of the MA is obliged to ensure that this product will be supplied to satisfy Hungarian demands. However, this obligation is irrespective of the existence of any contractual relationship — i.e. a distribution agreement — between the holder of an MA and the respective distributor. This may harm the business of certain wholesalers as other wholesalers may also then serve the market. The amending act remains silent on the possibility of pharmaceutical companies asking a wholesaler to provide evidence that the alleged shortage on the Hungarian market actually exists. This seems to remain a task of the NIP as wholesalers must keep separate records of all medicines received under this provision. The new provisions also make it clear that medicines provided

under these provisions must be supplied to Hungarian healthcare providers and must not be exported.

There are some uncertainties in relation to the new obligations. The supply obligation is subject to notification by the wholesaler, who is not required to prove or even demonstrate the likelihood that a demand actually exists. The duration of a supply obligation is also not determined, nor are wholesalers required to report the ceasing of any extra demand on the Hungarian market.

Export ban

As mentioned above, medicines which are supplied to satisfy Hungarian demand must not be exported. There is however another obligation to mitigate the risk of supply shortages. The NIP is entitled to order wholesalers to cease and desist from the exportation of a medicine intended for Hungarian patients if it has been notified that the amount of export is so high that it triggers a risk to continuous supply of the Hungarian market. The export ban shall last as long as it is necessary to guarantee supply safety, but no longer than one year.

While the Medicines Act does not address who is obliged to make such a notification, from a practical point of view holders of the MAs may be in a position to do so. They are aware of the quantities of the medicines provided to the distributors, and they are also obliged to report if they are unable to maintain adequate and steady supplies of specific pharmaceutical products resulting in a (potential) shortage of supplies.

It is important to note that the ban applies to a certain product rather than just the distributors who are engaging in excessive exporting activity. This may also create uneven market positions.

Stronger investigation powers for the NIP

The NIP as the supervisory authority of the Hungarian pharmaceutical market is vested with a broad range of regulatory instruments. Pursuant to the new amendments to the act, during official investigation it will be entitled to request declarations, any data and copies of files of any company or organization for the clarification of the matter in hand and may acquire and process the personal data of the party or persons related to a party to the investigation. Furthermore, subject to the prior approval of the public prosecutor, the NIP may conduct a dawn raid, i.e. enter any premises even without the owner's knowledge or authorisation, including private vehicles or property of or used by present or previous representatives, employees or proxies. An approval from the public prosecutor for such actions is valid for 90 days. The NIP is also entitled to clone hard drives and other storage media if it is suspected that these contain relevant data and it can also access information collected by other authorities in separate proceedings. These significantly stronger investigation powers are also intended to facilitate actions against counterfeit medicines. While the new Hungarian Criminal Code imposes a sentence of imprisonment for up to eight years for drug counterfeiting, police and prosecutors may not have the necessary experience to identify and analyse counterfeits and medicaments not authorized in Hungary. Therefore the amendment entitles the NIP to take action on its own, subject to prior approval from the public prosecutor.

The minimum fine imposed by the NIP for the violation of obligations conferred by the Medicines Act, including mandatory supply of pharmaceutical products to satisfy Hungarian demands and the export ban, remained unaffected by the recent amendments and is still HUF 100,000 (approx. EUR 350). However, the amending provisions introduced a cap for the maximum amount which is currently HUF 500 million (app. EUR 1,650,000). The NIP must consider all circumstances of the case when determining the level of fine to impose.

Bálint Halász & Bettina Kövecses, Budapest

POLAND: POLISH PHARMACEUTICAL CHAMBERS HAVE NO RIGHTS TO VERIFY COMPETENCIES OF PHARMACY DIRECTORS

On 5 June 2013, the Supreme Court overruled the resolution of the District Pharmaceutical Council on the procedure for approving candidates for the position of pharmacy director (file no. III ZS 8/13).

Based on Polish Pharmaceutical Law, District Pharmaceutical Councils participate in the assessment of a pharmacy permit application by issuing an opinion on the grant or refusal of the pharmacy permit. The Council's opinion includes inter alia assessment of a candidate for the position of pharmacy director.

One of the District Pharmaceutical Chambers adopted a resolution by which it introduced a new procedure for candidates' assessment involving some additional requirements. Firstly, each candidate was obliged to pass a test on knowledge of the responsibilities of a pharmacist, including those of a pharmacy director. Secondly, a professional experience questionnaire had to be completed by each candidate. Thirdly, each candidate had to attend an interview conducted by the opinion committee. Finally, the candidate was required to evidence his/her efforts to improve their qualifications.

The above-mentioned resolution was challenged by the Minister of Health who claimed that District Pharmaceutical Chambers should issue their opinions based exclusively on the information submitted in the pharmacy permit application. No provision entitles them to introduce additional proceedings which require additional verification of candidates' competencies.

As a result, the Supreme Court overruled the resolution indicating that it imposed requirements on candidates that exceeded the obligations provided under pharmaceutical law. Justice Kiryłło of the Supreme Court restated that the Chambers' opinions are not binding as Regional Pharmaceutical Inspectors are the only authorities authorised to grant pharmacy permits. Hence, if candidates fulfil the educational requirement and possess a minimum of five years' pharmaceutical experience, the Chambers are not entitled to additionally verify their competencies.

The Supreme Court judgement is important for the future practice of Chambers. Moreover, the decision is another chapter in the on-going dispute over pharmacists' guarantee of their compliance with the total ban on pharmaceutical advertising.

Cassation available to all punished doctors

On 20 July 2013, the amendment to the Medical Chambers Act dated 2 December 2009 became effective. It has unified the appeal procedure for disciplinary judgments against doctors.

The amendment implemented the Constitutional Tribunal's judgment of 29 June 2010, which confirmed that the Medical Chambers Act was partly inconsistent with the Polish Constitution. Under the old regulations, doctors could lodge a cassation only if they were punished with the most severe types of penalty, i.e. suspension or deprivation of the right to practice. In the case of a warning or a reprimand, doctors had no right to appeal the judgment.

The amendment applies to medical chambers, veterinary-medical chambers, pharmaceutical chambers, nurses and midwives' chambers, as well as the National Chamber of Laboratory Diagnosticians. Practitioners of the above-mentioned professions are entitled to file a cassation against second instance disciplinary court judgements with the Supreme Court. The term for lodging a cassation has been unified and is now two months from delivery of the judgement.

Cassation is a type of extraordinary means of appeal. Regardless of the type of penalty imposed, cassation is available on the grounds of the irregularities listed in the Criminal Procedure Code, or gross violation of the law. It is also possible to submit a cassation due to the disparity of the penalty imposed.

Marta Koremba, Marcin Alberski Warsaw

FRANCE: BEST PRACTICES FOR THE ONLINE SALE OF MEDICAL DRUGS IN FRANCE

The online sale of medical drugs has been officially authorised in France following an ordinance of December 19th, 2012 (the "Ordinance") and its regulatory decree of December 31, transposing Community Directive No. 2011/62/EU of June 8th, 2011.

A decree of June 20, 2013 published on June 23, 2013 specifies the operating conditions of websites selling medical drugs. This decree, which came into force on July 12, 2013 places strict rules on these sites.

The website must be operated by a registered pharmacist owning and running a physical pharmacy. The website is a virtual extension of the pharmacy. The site must be authorised by the territorially competent Director of the Regional Health Authority (*Agence Régionale de Santé).* The French Chamber of Pharmacists must also be informed. The e-pharmacy website must contain information establishing a link between the site and the pharmacy's owner. The site must have hyperlinks to the websites of the French Chamber of Pharmacists and the Ministry of Health which maintain an up-to-date list of authorised pharmacy websites.

The Ordinance allows for access to the online sale of medical drugs, but only those that are not subject to mandatory medical prescription and that are sold over the counter. However, over the counter drugs represent a residual share of medical drugs that are not subject to mandatory medical prescription. This substantially limits the earning potential of an e-pharmacy. On February 14, 2013, the French Administrative Supreme Court, in an expedited proceeding, suspended the application of this limitation to over the counter medical drugs due to the fact that the EU Directive covers all medical products that are not subject to mandatory prescription. We have to wait until the French Administrative Supreme Court rules on the substance of the Ordinance to determine the fate of this limitation.

As required by the French Competition Authority, the decree establishes that an e-pharmacy site can sell medical drugs alongside other products (cosmetics or

medical devices). A specific section must be dedicated to the sale of medical drugs.

It is recommended that the name of the pharmacist and perhaps even the pharmacy name be made part of the website's domain. The site must not contain any hyperlinks to pharmaceutical companies' websites. Discussion forums are prohibited. Subcontracting to a third party is prohibited except for the design and technical maintenance of the site. However, these services cannot be provided by companies that produce health products. Paying search engines and price comparison sites for indexation is prohibited. Information on medical drugs that may appear on the website is exhaustively enumerated by the Ordinance. Price is determined by the pharmacist; it is displayed inclusive of VAT and exclusive of delivery charges.

Upon the first order, the patient must fill out a questionnaire. The site must suggest that the questionnaire be updated whenever a new order is placed. The site must provide interactive communication between pharmacists and patients (e-mails or instant messaging). In addition, the site must have a private personal space that logs patients' orders and their interactions with their pharmacist.

The decree establishes maximum recommended delivery amounts in order to prevent overmedication. Similarly, no minimum order can be imposed. Given the specificity of health products, patients have no withdrawal right. The lack of the withdrawal right must be clear and legible to the patients before the confirmation of their order.

Conclusion

The implementation of medical drug online sales has not been without tribulations. France has caught up with its European counterparts, which, for the most part, have already accepted the online sale of medical drugs not subject to a mandatory prescription.

Anne-Charlotte Le Bihan and Enora Baron Paris

Journal of
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Journal of Commercial Biotechnology is published quarterly in Washington, DC by thinkBiotech LLC.

Journal of Commercial Biotechnology is available online at *http://CommercialBiotechnology.com*. Visit the journal's website for focus, scope, and policies; submission guidelines; sample papers; and staff contacts. The website may also be used to order subscriptions.

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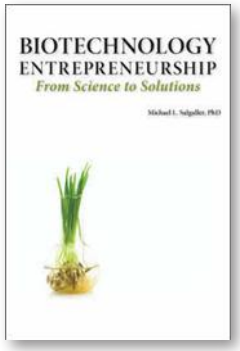

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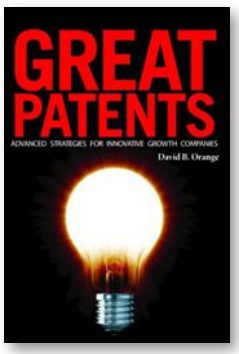

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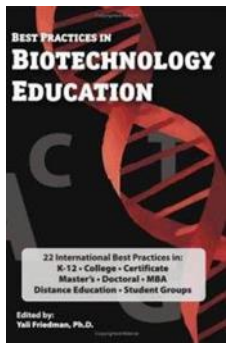

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