Volume 6

May 2008

Financial Innovations Lab Report

Accelerating Medical Solutions in Israel: Building a Global Life Science Industry

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בית הנשיא

Tomorrow
The Israeli Presidential Conference 2008
Facing Tomorrow
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We give special thanks to the Sacta-Rashi Fund and the Yeshaya Horowitz Foundation for their interest and continuing support of this work.

The Israel Presidential Conference "Facing Tomorrow" will be dedicating a special session to the translation of medical innovation in Israel into business success, based on the current report. We thank President Shimon Peres for his vision and inspiration of the process whereby the Financial Innovations Lab took place.

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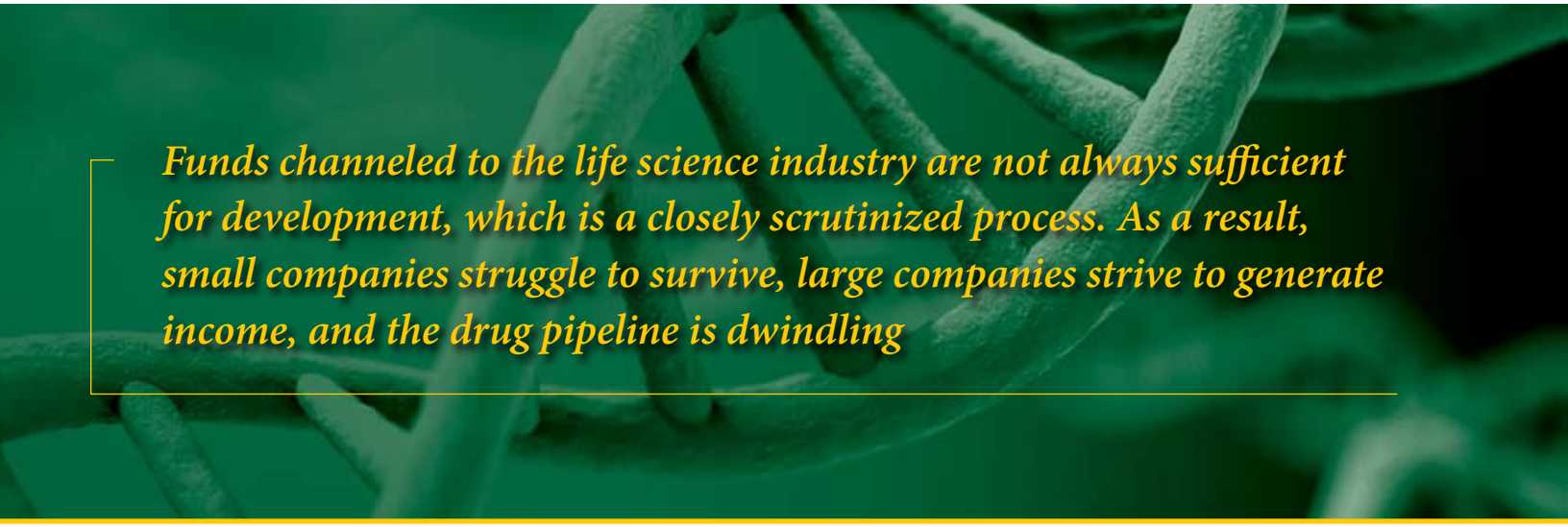

Funds channeled to the life science industry are not always sufficient for development, which is a closely scrutinized process. As a result, small companies struggle to survive, large companies strive to generate income, and the drug pipeline is dwindling

Executive Summary

Intangible Assets and Israel's Unrealized Potential in Life Science

The Israeli life science industry is at a crossroads. Having matured for over a decade, during which time academic research and industrial development initiated successful collaborations, the potential for added growth is enormous. Through its demonstrated capacity to support and generate new products and services in the life science and healthcare industry, Israel has the ability to produce leading international companies which could drive global collaborations for mutual benefit and for the purpose of solving the planet's health crisis.

Israel's life science and healthcare industry is one of its most invaluable assets for future economic growth and security. This industry develops and leverages its most valuable human capital, creating demand for education and diversifying its high tech advantage. As a foundry of intellectual capital, it achieves shorter proof of concept and faster time to market in innovating healthcare products and services than arguably anywhere else in the world. Israel is first worldwide in medical device patents per capita, fourth worldwide in biopharma patents per capita, seventh in absolute number of medical device patents, and first worldwide in the percent of life science patents of total patents; the litany of achievements is impressive. Israeli physicians and scientists are at the cutting edge of global leadership as innovators and early adaptors of technology in cardiology, neurology, orthopedics, oncology, metabolic disorders and immunology, infectious diseases, patient monitoring, emergency medicine, surgery and other fields. Among the notable pharmacological breakthroughs are Copaxone (TEVA), Interferon (Serono) and Exelon (Novartis). A range of medical device advances occurred including the innovation around the CT scanner (Elscint, later sold to GE Medical) and imaging systems (such as Given Imaging).

Lagging Behind

Despite these remarkable achievements, the life science industry is lagging behind due to serious underinvestment. Venture capital investments in the biomedical sector are falling and represent a lower percentage of new investment than in countries which Israel faces in global competition. Adequate financial resources and incentives are available to bring products to market. Israeli companies pursue outlicensing or mergers and acquisitions because they cannot raise financing for later stage development, resulting in early and undervalued exits. This report details why Israel's life science industry urgently needs financial, regulatory, and tax resources compatible with their capital requirements, long life cycle (7-15 years) and higher risk profile than the current venture capital industry alone can support. The funding challenges per development

phase as presented in Figure 5 clearly reveal the need for such a financing innovation for the Israeli life science industry.

Without becoming a clear national policy priority, the life science industry faces the threat of market failure due to the insufficient allocation of capital and inefficient resources being committed to realize the country's competitive advantage in this field. Human, intellectual and financial capital flight depletes the required resources necessary for developing medical solutions. In global terms, these resources are necessary for curing global epidemics in chronic and infectious diseases that threaten global growth and prosperity. Meanwhile, companies, patents, and people emigrate. Despite vast potential for growth and extensive investments in research and development in the life science industry in Israel, this potential is in danger without the immediate launching of the public-private partnership outlined in this report. Failing to do this would represent not only a default of economic policy responsibility by failing to respond to the market failure outlined in this report, but also a historical and generational failure in building the State of Israel.

Call to Action

The outcome of this Financial Innovations Laboratory is a call to action for a collaborative strategy combining government, philanthropic foundations, and corporate resources to:

- Create a public-private partnership to launch an Israel Life Science Financing Facility that would bridge the capital access gap for medical innovation;
- Resolve regulatory, tax, and infrastructure gaps to accelerate the industry's global position;
- Craft global collaborations to export these innovations abroad.

These measures would allow us to build the Israeli life science industry rather than solely build start up companies for quick sales. Government intervention and leadership is needed to catalyze foundation, multilateral, and private resources to achieve this inflection point of growth.

Think Global, Invest Local: Israel's Service in Addressing Global Health Problems

The current situation, as described in this report, is a striking opportunity which would enable transforming Israeli knowledge based industries into a national advantage, leveraging on the demand posed by the global biomedical industry. Worldwide, pharmaceutical companies are continuously required to enhance their dwindling pipelines of new drugs, devices, and healthcare services in order to survive. In this environment, emerging Israeli companies in primary stages of clinical development are potential bearers of new drugs, medical devices and healthcare delivery systems. These pioneering companies are struggling to survive. Adequate national organization, by means of innovative funding tools and a new policy initiative, can not only provide a solution to the local industry but would also allow it to provide essential technologies to international companies, thus encouraging the emergence of large, global Israeli-based companies. Instead of exclusively investing in early stage companies with insufficient resources to carry companies the

entire way from innovation to realization of financial and social returns, providing the financing bridge for existing and successful companies would enable them to stay independent for longer period thereby encouraging their presence and impact in Israel.

Various countries have already implemented such innovative financing programs. Members of the European community, particularly Finland and Ireland, as well as Singapore, Taiwan and many American states, have established frameworks of public funding that incorporate collaborations between private and public capital. This report calls for the adoption of a similar approach, offering an additional and innovative framework through which industry sectors and companies may be organized and financed. Namely, we encourage public private partnerships and consolidation by means of a portfolio fund and an infrastructure fund. Figures 9 and 11 provide a basic schematic of the long-term structured finance facilities to support the portfolio and infrastructure funds.

The solution described below focuses on a structured finance facility that would enable diversification of risks, mutual guarantees by underlying companies, and potentially multilateral and Israeli government, philanthropic foundation or other non-governmental organization guarantees. These would enable raising and investing $2 billion over the next three years in Israeli healthcare companies and build the Israeli life science industry to serve global markets. The enterprise would be characterized as follows:

- The structured finance facilities for healthcare development and infrastructure outlined in this report would reduce scientific risk through the diversification and pooling of intellectual property.
- Government guarantees would be matched by philanthropic foundations generally interested in healthcare development or with a specific disease focus, along with potential partnership matching by the US, UK, European, or other partner countries to enhance credit quality, lower capital costs, and attract potential investors.
- For example, a diversified pool of drugs or devices within a single company or sub-fund as outlined below would have too much financial risk. The public-private partnership would diversify risk through a structured financing vehicle which would provide financial guarantees to raise the credit quality of the pool thereby opening the investment to a significantly larger group of investors injecting fresh capital at lower cost into the underinvested life science industry in Israel.

This public-private partnership fund in life science and healthcare development and infrastructure would:

- Bridge the funding gap facing Israeli R&D and commercialization focused on developing new therapies, diagnostics and healthcare delivery at lower costs;
- Address global demand for healthcare solutions in emerging markets;
- Support Israeli healthcare solutions locally;
- Support disease specific foundation programs to leverage their grant and investment dollars by creating a mission-related investment vehicle for Israel;
- Ramp-up life science and healthcare industry funding and growth over the next three years to achieve global leadership for Israel.

The proposed financing facility would consist of a basket of sub-funds stratified by sector, disease, and stage of development. This could be an open-ended fund with a 15 year maturity consistent with the timeframe required for the life science industry. Funds would be released to underlying portfolio companies upon achievement of milestones with reinvestment of proceeds allowed for performance. Exits could occur via trade sales, IPO, free cash flow generation and would differ depending on sector, stage of development and disease. Debt and equity would combine and be raised on the basis of the diversified pool with guarantors (the Government of Israel or other governments, foundations, multilateral funds) receiving equity upside from realizations.

These funds would enable low cost capital to support infrastructure, sales and marketing, recruitment and the return of scientists, physicians and biomed managers to Israel. The stable and low cost sources of funds would provide incentive to founders to invest in and develop their businesses in Israel. This finance facility structure would enable therapies and technologies to treat specific diseases and gain support and collaboration from international disease foundations (e.g., especially addressing translational medical research in diabetes, cancer, heart disease, stroke, neurology, cell therapy and other areas of life science).

Most importantly, by developing solutions, therapies and technologies responding to the healthcare needs of specific countries and regions, a post-partisan, transboundary geo-political process could be launched to bring Israel to the world and the world to Israel while resolving global health problems.

Regulatory and Tax Initiatives to Support Israeli Healthcare

To support this effort, changes are required in Israeli regulation of the life science industry and tax incentives to support it. This report outlines key initiatives that would be part of this healthcare growth agenda:

- Establish the Israeli equivalent of the Food and Drug Administration (FDA);
- Create a National Tissue Bank for research and development for accelerating medical solutions;
- Accelerate and support regulatory and information infrastructure to support clinical trials;
- Centralize and develop health records to support health efficacy and medical research.

All of these require deploying information and communication technologies present in Israel to support the knowledge base and data infrastructure for efficient operation of the initiatives outlined above.

Information and communication technologies required to successfully obtain these goals are already present in Israel. Data warehouse and information systems need only to be deployed for efficient operation of the initiatives outlined above.

These solutions are all based on collaborations between companies, industries, and nations. It would be possible to export medical knowledge to developing countries worldwide, focusing on child and adolescent medical care. Preliminary exploration of potential target countries, such as Kazakhstan, Turkey and India, is under way. Israel has already developed similar initiatives in the field of healthcare services,

including the treatment of child cancer patients in the Palestinian Authority made possible through the collaboration of Augusta Victoria Hospital and Hadassah University Hospital. Many other models exist throughout the healthcare industry worldwide, which may be deployed in the Israeli context.

Participants in the current Financial Innovation Lab have set the following goals:

- Transform the life science industry into a means for Israeli economic growth in the next decade, while simultaneously building a foundation for the development of Israeli global leading companies.
- Create the physical, managerial, tax and regulatory infrastructure that will support the life science industry in Israel. For example, companies may be encouraged to cooperate for the purpose of receiving joint administrative or managerial services. Such associations could be organized by subsectors, without forcing mergers but rather providing adequate incentive for consolidation.
- Induce foreign pharmaceutical and biotech companies, as well as philanthropic funds, to invest in Israeli life science ventures at different stages. This may be achieved, for example, through legislation that would facilitate philanthropic funds designated to address specific diseases to invest in ventures that share similar goals. Grants from such funds could then be used to improve conditions of credit received from other sources. Israel could become a preferred location for the registration and operation of medical foundations by providing fewer restrictions for mission-related investing than other countries.
- Establish Israel as an international center for clinical trials. This could be achieved by the establishment of a tissue bank, clinical databases, and a regulatory body similar to the FDA which would regulate clinical trials and approve drugs.
- Diminish the brain drain and provide incentives to expatriate scientists and firms to return to Israel while also creating new workplaces and taking advantage of existing human capital.
- Reinforce the bond between academia and industry.

The current report declares unequivocally: capital access for the life science industry must be urgently expanded by means of collaboration in order to accelerate progress in this sector, rescue the local industry, and increase Israel's competitive advantage.

This intermediate report summarizes discussions carried out thus far and constitutes a foundation for further progress. The workgroups are expected to meet for a second phase in their discussions after the Presidential Conference.

Glenn Yago
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Ilan Vaknin

Background

The development of medical products is a long, costly process, growing longer and costlier still over the past two decades. Chances of successful completion of the process are small at the onset and during the lengthy early phases, increasing significantly only in later phases as shown in Table 1. While industry is spending billions on research, the number of FDA approved products does not appear to increase, as is shown in Figure 1. Funds channeled to the life science industry are not always sufficient for development, which is a closely scrutinized process. As a result, small companies struggle to survive, large companies strive to generate income, and the drug pipeline dwindles. The following chapters describe the life science industry in Israel and its potential interaction with global pharmaceutical industries, presenting both threats and opportunities in these industries: the funding challenges against the demand for new pharmaceutical products. Israel has the potential to supply the demand. Solutions to funding challenges lie namely in collaborative efforts of a wide range of bodies that share similar goals.

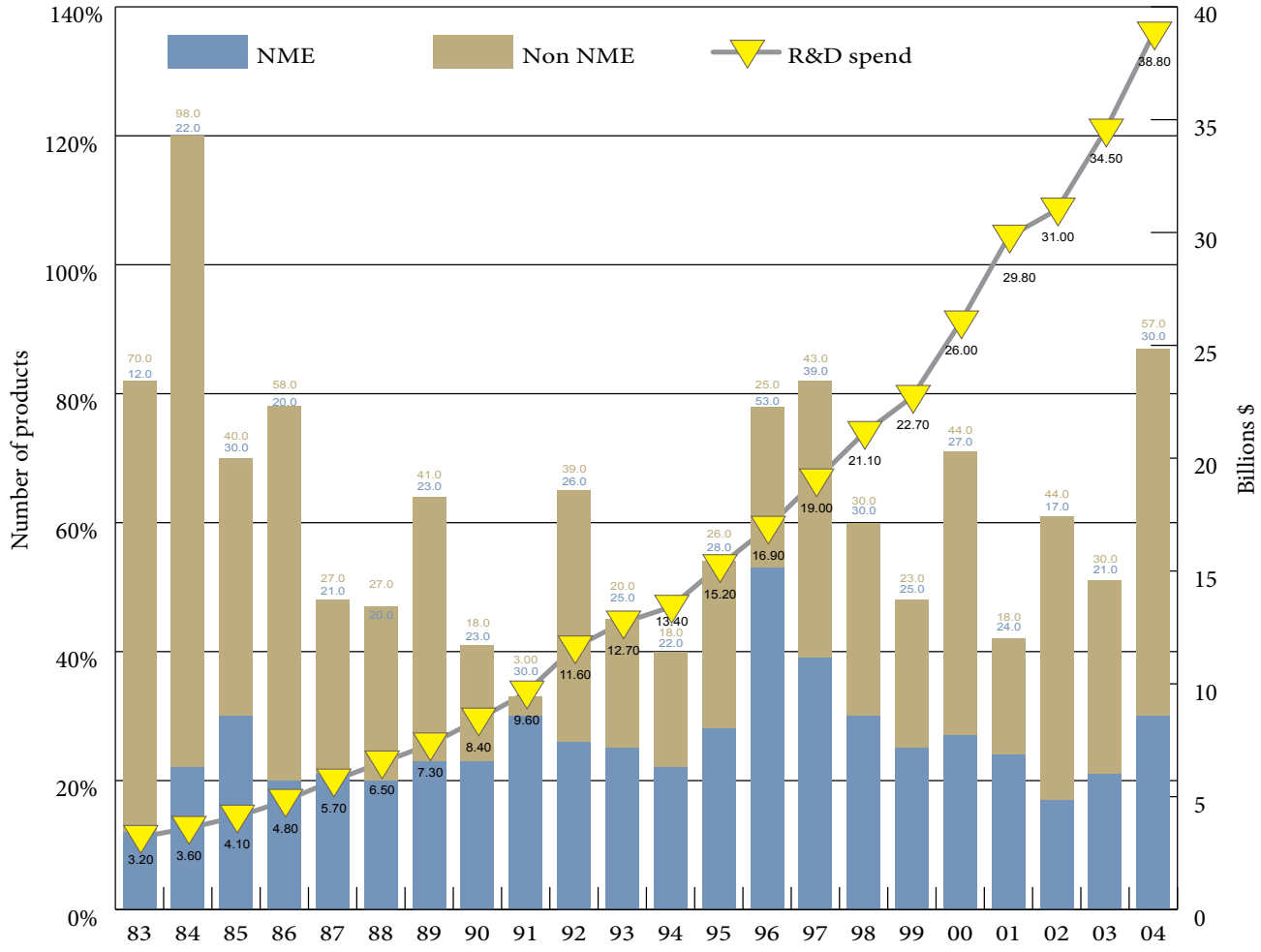
TABLE 1 *Phases of drug development and success rates*

Phase	Description	Years	Success rates to final approval
Proof of concept		1-10	
Preclinical	Preclinical (animal) testing to ensure absence of toxicity (CMC, GLP).	2.5	6.70%
Clinical trials - Phase I	The drug is tried on a small study group of 20-80 typically healthy people in order to determine absorption time and identify side effects or toxicity. Efficacy of the drug is typically not studied at this stage.	1.5	22.30%
Clinical trials - Phase II	The drug is tried on a larger study group of 50-300 people in order to evaluate effectiveness and continue to test side effects. This stage is occasionally divided between Phase IIA in which optimal doses are determined and Phase IIB in which effectiveness is studied.	2	29.30%
Clinical trials - Phase III	The drug is tried on yet a larger study group of 500-3,000. The purpose is to ascertain effectiveness and adequate dosage in comparison or in combination with other drugs while continuing to collect information concerning safety.	4	61.25%
Approval	Requesting the formal FDA approval for marketing through the New Drug Application (NDA).	1.5	90%
Clinical trials - Phase IV	Once the FDA has approved a product for marketing, the company continues to study regular use of the drug to ensure safety and efficacy		

Source: IDB Development, Research Department

FIGURE 1

Research and development expenses in relation to FDA approved products



Source: Parexel's pharmaceutical R&D statistical sourcebook 2005/2006

The life science industry in Israel

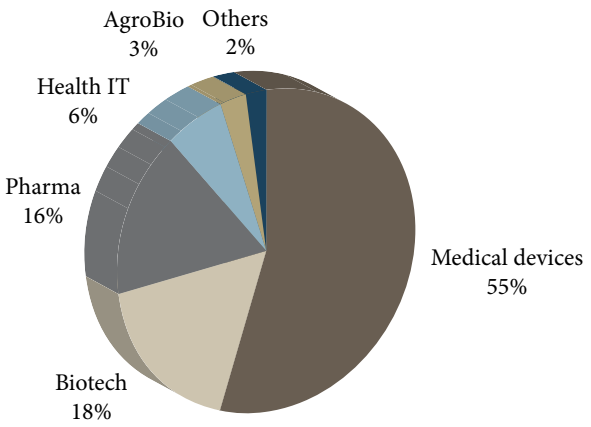
With a single notable exception, Israel's life science industry is characterized by a multitude of small companies. According to the Israel Life Science Industry (ISLI) the industry comprises over 900 registered companies, half of which were established in the course of the past six years. The exception comprises one extraordinary company, TEVA, which operates mostly in the generic pharmaceuticals market and has become an international giant.

The life science industry comprises three main sectors. Medical devices constitute 55% of the industry; biotechnology, specializing in development of products based on living organisms and biological systems, comprises 18% of the industry; and pharmaceutics, focusing on the development of new drugs, occupies another 16% of the industry. About 31% of the companies are in seed stages and 42% are in preclinical or clinical phases. The remaining 27% are revenue generating companies: 19% are at the stage of preliminary revenue and 8% at the stage of revenue growth. Figure 2 presents the breakdown of the Israeli life science industry according to these criteria. Further breakdown by subsectors is presented in Appendix 3.

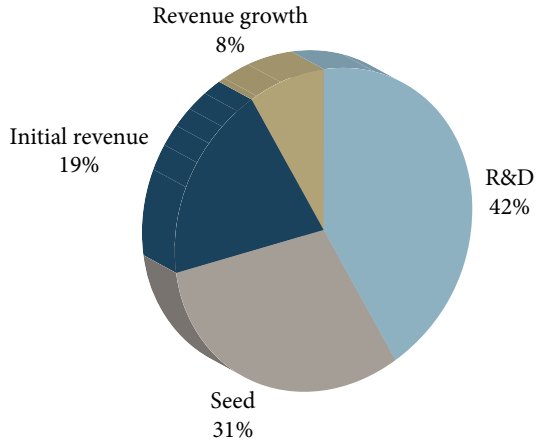
FIGURE 2

Israeli life sciences companies

Breakdown of sectors



Breakdown of development phases



Source: Israel Venture Capital, IVC

In 2005, 557 companies of the Israeli life science industry employed a workforce 25,000 strong, of which 80% was employed at companies whose workforces were larger than 50 employees. Data from 2007 show that 88% of all companies in the life science industry number less than 25 employees. Within the industry, the pharmaceutical sector is the largest employer, employing about two thirds of the entire workforce. Table 2 presents the distribution of companies according to industrial sector and employee count.

A survey conducted by Ernst & Young reveals that in life science companies numbering over 50 employees, the ratio between life science academics and other employees is 1:10. New potential employees are constantly emerging from academic institutions. As shown in Table 3, according to Israel's Central Bureau of Statistics, approximately 3,000 undergraduate students completed medical or life science programs in academic institutions in Israel in 2006; 1,600 students graduated from Masters' programs; and 300

Skyrocketing sales of Copaxone and Azilect in 2007, $1.7 billion and $120 million, respectively, in comparison to $100 million revenues of the rest of the industry clearly demonstrate the extent to which a successful drug can impact Israeli economy at large

completed Ph.D. programs. This large number of graduates is expected to strain the current workforce, emphasizing the need to increase work places in the industry. Companies currently numbering under 25 employees should be encouraged to grow in order to absorb this rising flow of academic graduates. Unless adequately organized, Israel will continue witnessing a national brain drain.

TABLE 2

Distribution of companies according to industrial trajectory and employee count

NO. OF EMPLOYEES	1-25	26-50	51-100	> 100	SUM
Agricutural Biotech	12	3	0	2	17
Medical device	365	20	9	12	406
IT	40	4	2	2	48
Biologicals	44	1	0	0	45
Diagnostics	65	5	2	1	73
Bioinformatics	8	1	1	0	10
Industrial	22	1	1	0	24
Therapeutics	149	13	5	8	175
Total number	705	48	20	25	798

Source: VentureOne/Ernst & Young 2007

The Tel Aviv Stock Exchange (TASE) currently lists 37 companies that are classified as biomed companies. Nearly half of these develop medical devices while the rest are either biotech companies or biotech project consortiums. The total market cap of these biomed companies is estimated at 5.6 billion NIS, of which 2.5 billion NIS comprise the value of four companies whose shares are listed dually both at the TASE and at NASDAQ. A financial profile including returns, indices, and market cap of Israeli biomed traded companies is presented in Appendix 4.

In global terms, the Israeli biotech is fairly young. The total sales of global companies in biotech sectors alone exceeded $70 billion over the past year. Increase in sales rate was measured in double digits, amounting to 22% in Canada and 14% in both Europe and the US. In comparison, according to the GlenRock report, the aggregated volume of biotech trade in Israel barely reached $100 million, excluding two newly introduced TEVA drugs (Copaxone and Azilect) and four additional drugs (Rebif, Doxil, Exelon, Erbitux) that, while based on Israeli research, were developed by foreign companies. The proportions are clear. Skyrocketing

sales of the newly introduced TEVA drugs are incomparable to the rest of the industry. In 2007, Copaxone generated $1.7 billion and Azilect generated $120 million. These revenues reveal the true extent of the unrealized potential of the life science industry in Israel. Moreover, they demonstrate how a small number of successful drugs may change Israeli economy at large.

From a national perspective, promoting the life science industry is highly advisable. Most investments in knowledge based industries are immediately translated into growth of Gross Domestic Product (GDP), affecting not only the organic growth of the knowledge based companies, but national economic growth at large through increased demand for services from various supporting companies. In Israel, about a third of the life science companies are located in peripheral areas, 30% in the north and 6% in the south, so any growth in the industry would also increase employment in these peripheral areas, further strengthening the nation.

TABLE 3 *Distribution of recipients of academic degrees according to field and program*

Academic year of 2005/06				
	Undergraduates	Graduates	Ph.D. graduates	Total
Medical program	416	531	58	1,005
Paramedical programs	1,469	418	19	1,906
Biology sciences	1,112	683	253	2,048
Total	2,997	1,632	330	4,959

Source: Israel's Central Bureau of Statistics 2007

A relatively high number of drugs originating in Israeli research have been translated into billion dollar sales, reflecting the vast potential that has failed thus far to transform into large Israeli biotech companies

Israel offers two key qualities in the life science industry, which render this local market lucrative to international capital and which justify the establishment of infrastructural institutions such as a local Food and Drug Administration (FDA). First, Israel is a leading authority in fields such as stem cells, neurobiology, cardiology, orthopedics, oncology, immunology, and other fields. It is a world leader in the quality of its research facilities, the number of scientific publications, the flow of information from academia to industry, managerial quality of medical devices, and the accessibility to scientists and engineers. Israel holds and generates a large number of patents in the fields of biotechnology and medical devices. The ratio is high not only in relation to the local population but in more global terms as well. A relatively high number of drugs, which originated in Israeli research and have been translated into billion dollar sales, best reflect the potential that has failed thus far to transform into large Israeli biotech companies.

A second advantage offered by the local market is the speed by which new technologies are embraced and

applied at hospitals, where clinic and beta trials are conducted for both pharmaceuticals and medical devices. Manpower in the healthcare services is relatively inexpensive, presenting yet a third profitable aspect, particularly for biotech products in early stages of development and prior to advanced clinical phases.

» Funding Resources

Current funding resources in Israel are limited, comprising both public and private capital, the stock exchange, venture capital funds, private equity and financial collaborations. No structured financial instruments providing longer term debt capital exist.

The Incubator Program provides funds of $300,000-750,000 per company for a period of two or three years. The share allocated to the life science industry is rising and currently accounts for 60% of all incubator activity

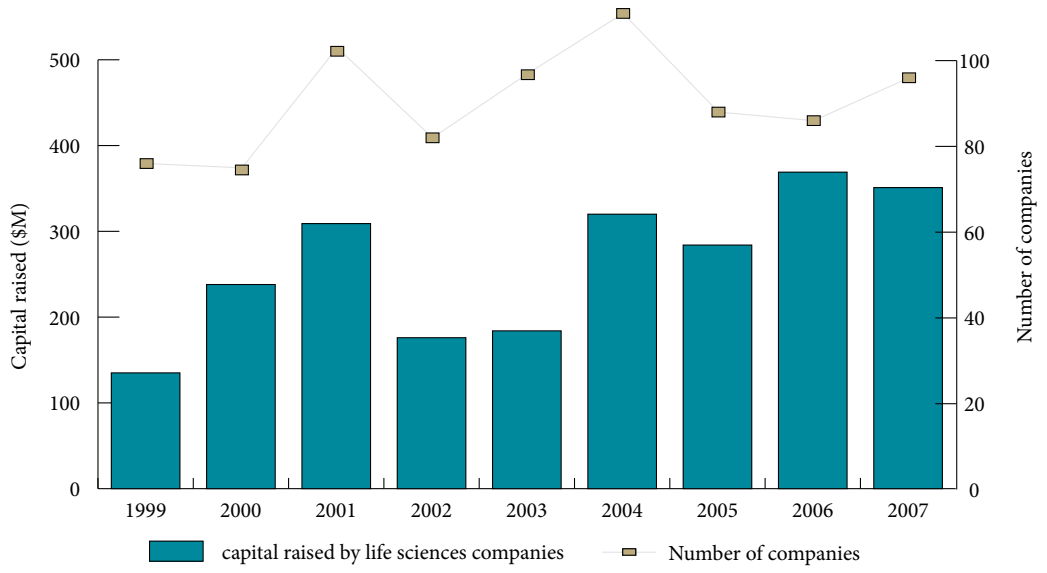
- ***Local governmental funding resources.*** Governmental support for Israeli R&D at large is managed through the Chief Scientist at the Ministry of Industry, Trade, and Labor. General funds available to the Chief Scientist in 2008 amounted to $1.4 billion, including royalties. Of these, 30% have been allocated to the field of life science. The funds are distributed through the following main channels:
  - **The R&D Fund.** According to the R&D law, funds are granted only in cases where supplementary funds have been raised from private parties that are equal to or larger than the R&D fund contribution. These grants, up to $3 million per project, have typically been granted to projects at the clinical phase.
  - **The Incubator Program**, which provides funds of $300,000-750,000 per company for a period of two or three years. The share allocated to the life science industry is rising and currently accounts for 60% of all incubator activity.
  - **Secondary funds.** The Chief Scientist also operates the Magneton program, with grants up to $800,000 and the Nofar, with grants up to $100,000.
- ***Funding by foreign pharmaceutical companies.*** Recently, several agreements have been signed through the mediation of the Ministry of Industry, Trade, and Labor, by which various pharmaceutical companies, such as Merck, would allocate financial support to technological and clinical fields for both R&D and marketing efforts as well as integrating local companies in their future development plans. Baxter has also been expressing similar interests. Notwithstanding, to date, no foreign pharmaceutical or biotechnological company provides significant funding to Israeli life science companies.
- ***Financial markets.*** In the last three years, IPOs have been used to finance nearly thirty companies, including companies from the fields of medical devices and biotechnology, consortiums as well as life science investment companies. Financial data pertaining to twenty of these companies – returns, capital listed for trading, market cap, and market makers – are detailed in Appendix 5. Most of the companies that raised funds through IPOs are in early, occasionally even preclinical, development phases. At current market conditions these companies might find it difficult to raise future funds, and worse – failure in meeting expectations set by stakeholders, would compromise prospective use of this funding channel for other emerging companies. A large majority of the biomed companies traded at TASE suffer from low liquidity. Trading volumes and stock returns are often low compared to relevant indices, as may be deduced from Appendix 4. NASDAQ, as a funding channel, does not eliminate the challenge. Seven biotech companies are currently listed at NASDAQ. While some failed advanced clinical trails, others struggle to maintain market value. Out of four dually listed companies,

two develop medical devices, a sector less challenged by capital raising prospects, while the two biotechnology companies have yielded a negative return in 2007.

- ***Venture capital funds and other private funding resources.*** According to the GlenRock report, $20-40 million of annually invested capital in the life science in Israel originates in private ownership. In 2006, 86 life science companies in Israel raised $369 million from venture capital funds, private equity, private and institutional investors; but investments were reduced to $351 million for 96 companies in 2007. Fluctuations over the past decade in both raised capital and number of companies who enjoyed these funds are presented in Figure 3.

Only a few venture capital funds invest in Israel's life science industry. As shown in Figure 4, these resources tend to be invested in medical devices rather than in biotechnology companies. In the

FIGURE 3 *Capital raised by Israeli life sciences companies 1999-2007*

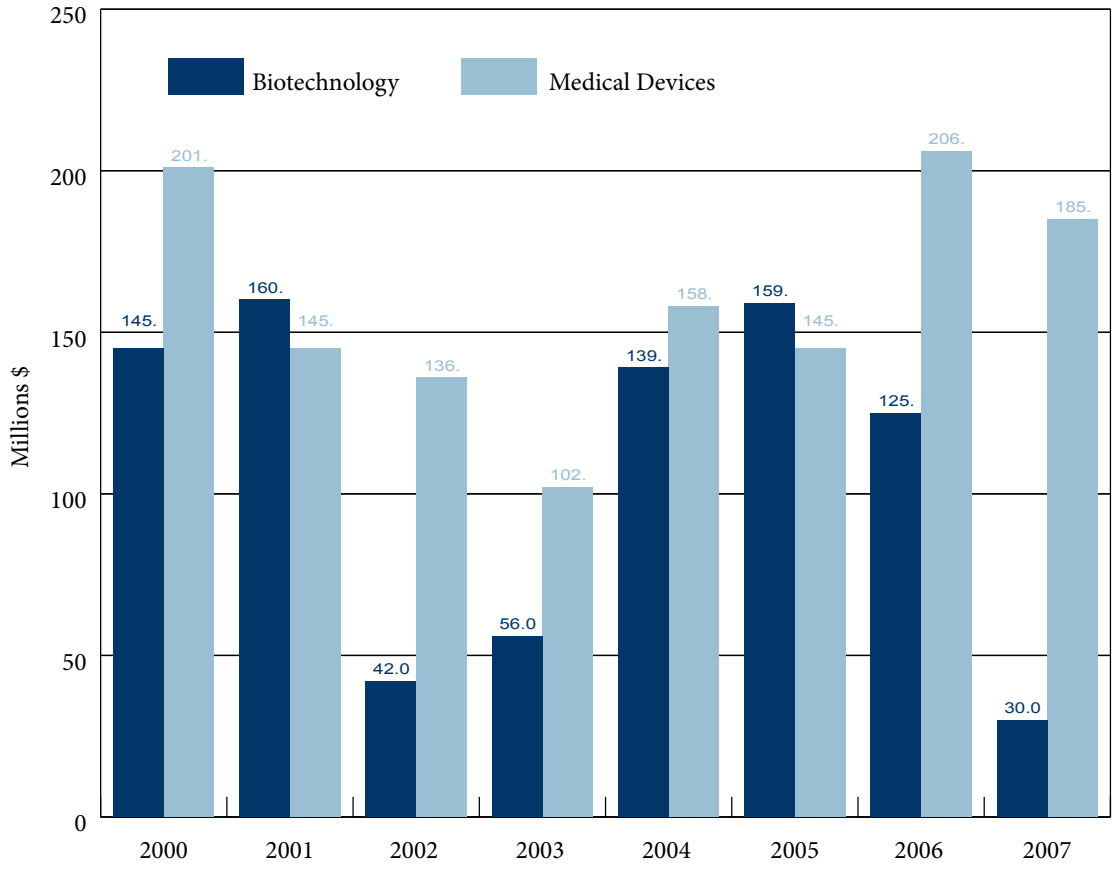


Source: Israel Venture Capital, IVC

2007, for example, medical devices obtained 86% of all venture capital budgets procured that year for the life science industry. This is perhaps unsurprising, as venture capital funds expect an early exit and relatively low valuations and risks – expectations that drug development cannot meet. A venture capital fund usually matures after ten years, whereas drug development can last up to two decades. While worldwide venture capital funds invest in Israel, no designated Israeli venture capital fund is large enough to satisfactorily distribute its resources among the various sectors of the life science industry. Thus, even when investing in biotechnology, venture capital funds tend to invest in mature companies and focus on products with proven viability.

FIGURE 4

Distribution of venture capital investments among medical devices and biotechnology, 2000-2007

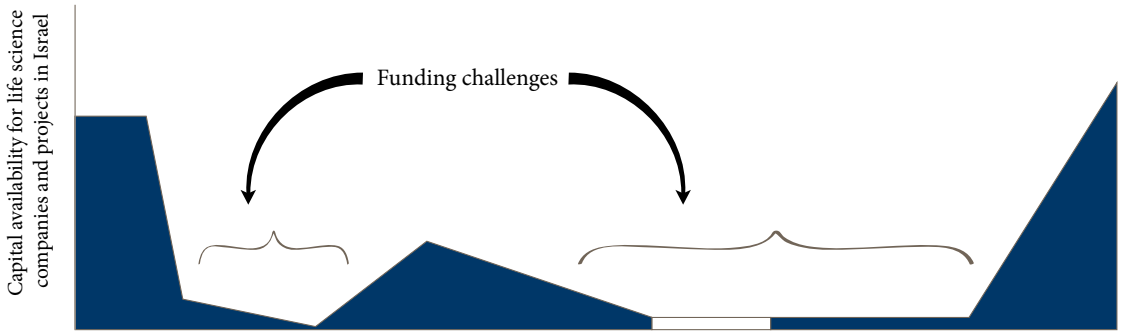


Source: Ernst & Young / VentureOne,
Incomplete data

Due to these constraints, most Israeli life science companies are unable to raise funds in their early stages and never reach clinical phases. Many companies graduate from incubator at a premature stage, before human viability has been proven, and lack an experienced management team. The financial bottleneck created at this stage, typically equivalent to the preclinical phase, accelerates the dissolution of many projects that show high potential for success. Due to its harsh nature, this bottleneck has been termed "*the first Death Valley*". A "*second death valley*" occurs within a few years, starting at Phase IIB and continuing throughout approval and marketing phases. In other words, funds are lacking during most clinical trial stages and also after FDA approval. The funding challenges per development phase as presented in Figure 5 clearly reveal the two death valleys. Collaborations with pharmaceutical companies could resolve the funding problem throughout the cycle, provide appropriate marketing resources after FDA approval, and allow these large companies access to new drug compounds.

FIGURE 5

Capital availability and projected success rates according to development phase 2005-2007



Stages	*Proof of concept*	*Preclinical Trials*	*Clinical trials - Phase 1*	*Clinical trials - Phase 2*	*Clinical trials - Phase 3*	*Approval*	*Clinical trials - Phase 4*	*Shipping*	*Sustainable business*
*Chances of success**		*30%*	*76%*	*48%*	*68%*		*90%*	*60%*	*85%*
Approximate cost (Million$)	*1-10*	*1-10*	*2-12*	*10-30*	*75-250+*				

Source: Ernst & Young / VentureOne, 2005-2007 data, *IDB research unit, market data

The Pharmaceutical Industry Worldwide

An escalating deficiency in new drugs is acutely experienced by the pharmaceuticals industry in recent years as the number of drugs in development (the drug pipeline) is too low to meet the demand. In their long sojourn for FDA approval, developing drugs must face, among others, local regulatory barriers that complicate and prolong development processes. The numbers reveal an extreme picture. In 2007, out of 64 FDA approved applications (New Drug Application) only fourteen were new compounds (New Molecular Entity). Biologically based drugs (New Biologic License application) are even scarcer. Only two such drugs were approved by the FDA in 2007.

Even a successful launch of a drug does not guarantee financial success, as many of the drugs that do reach the market cannot compensate for funds invested in their research and development phases. One catalyst in the process is safety considerations, resulting in "black box" warnings or even the withdrawal of products from shop shelves. Insurance companies also share the responsibility in creating this predicament. By limiting their part in installments made out to insured persons, they increase the pressure to lower prices of marketed drugs. Under this financial pressure, cost-benefit considerations eventually reduce potential experimentation that might have otherwise been made at the expense of highly priced drugs. In addition, due to the long development processes and painstaking efforts to obtain FDA approval,

many pharmaceutical companies prefer to invest in the promotion of existing drugs by extending labels, changing doses, or changing drug combinations in existing treatments, thus accelerating the deficiency in the drug pipelines.

Many drug patents are about to expire while few patents emerge to ensure further growth of pharmaceutical companies. This presents an additional threat to pharmaceutical companies on behalf of generic companies due to the large volume of sales involved. In 2007, for example, sales of drugs whose patents expired reached $17 billion. Sales resulting from newly launched products are insignificant in comparison to this, amounting only to $441 million in 2007. Exposed to market conditions and competition, pharmaceutical companies would have to purchase developing drugs to ensure growth, yet candidates are scarce on the horizon. Emerging companies, in early phases of clinical development, are struggling to survive. Their funding constrictions are about to affect the industry at large.

The effects of these factors are reflected clearly in the sales of pharmaceutical companies in the US:

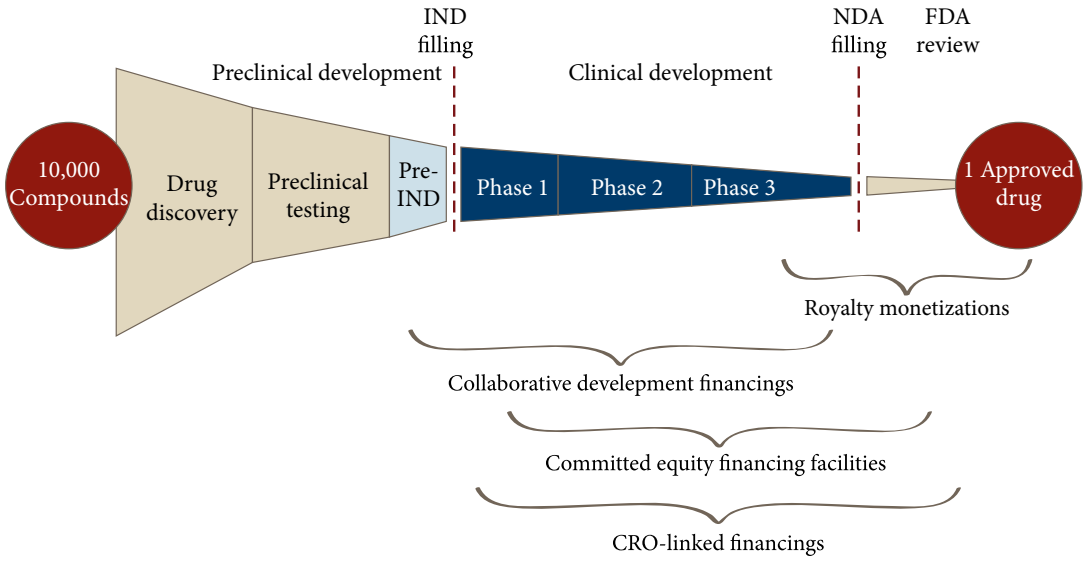
- Growth in sales of pharmaceutical companies in 2007 was not only arrested but plummeted to the lowest level since 1961, from 8% in the previous year to 3.8%, yielding the total revenue of $286.5 billion.
- Safety considerations are estimated to have reduced sales by 10% in 2007.

» Funding Resources

As with the Israeli life science industry, the global industry is faced with a growing challenge when seeking adequate funding for drug development. Funding techniques listed below have helped raise extended capital to the global biotech industry in recent years. Prominent employment of these funding techniques per development phase is depicted in Figure 6.

FIGURE 6

Funding techniques prominently employed in the US in 2007, according to development stages



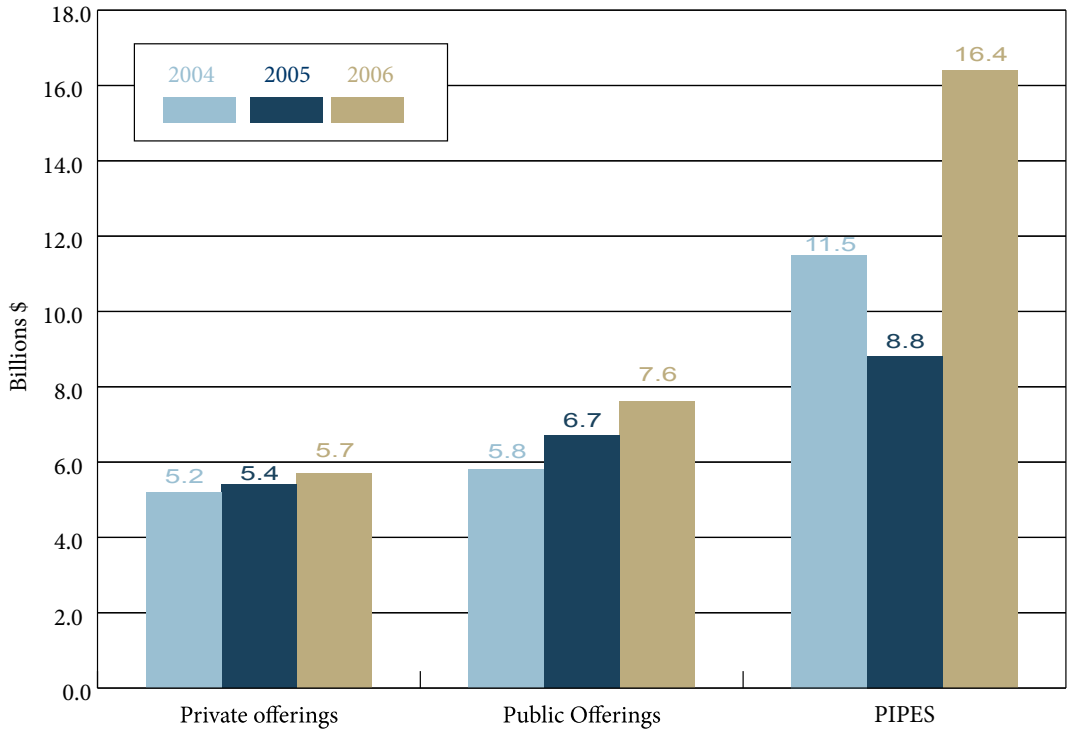
Source: Mark Kessel & Frederick Frank, Nature Biotechnology 2007

Funding techniques employed in the life science industry worldwide:

- ***Financial markets.*** After an initial IPO, secondary offerings of shares by publicly traded companies present one of two key financing techniques that have traditionally been applied in the US in biotechnological and pharmaceutical fields. However, the demand for shares in these fields in public offerings has weakened worldwide and particularly in the US, significantly affecting the field of biotechnology. Even where applicable, this funding method holds clear disadvantages for shareholders of emerging biotechnological companies as share offerings repeatedly dilute shareholders' stake in the company. At the same time, the value of the company's shares does not usually reflect its intrinsic value or the potential value of the company when acquired. In 2006, for example, 17 out of 19 issues of biotechnological companies in the US raised capital at an actual value that was lower by an average rate of 30% compared to the estimated value prior to issue. Moreover, in recent years, demand from investors has mainly been directed toward companies at advanced phases of development.
- ***Mergers and acquisitions.*** A thriving market of mergers and acquisitions has yielded numerous purchases, some at relatively early phases, including consolidation processes in the large pharmaceutical companies. Sales of promising drug pipelines, still in development, to large pharmaceutical companies seem to be a growing funding avenue in the US. Mergers between small companies and acquisition by large pharmaceutical companies both allow immature companies to finance their operations.

FIGURE 7

Funding resources of US biotechnology companies 2004-2006*



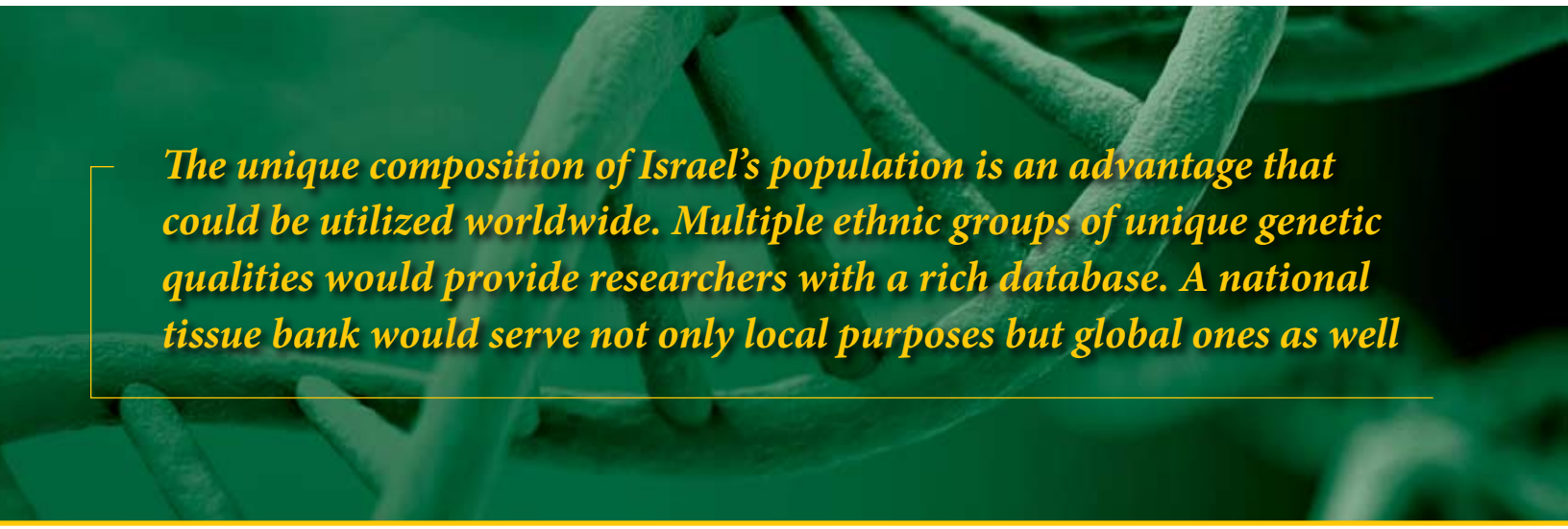
Source: BioCentury
* Data true to Dec. 7,2006.

- ***Private investments in public equity (PIPE).*** Public biotechnological companies also experience funding constraints, in light of a significant increase in funding from private sources, aka Private Investments in Public Equity (PIPE). Lacking other funding alternatives, PIPE allows companies to issue shares at a price that is considerably lower than the market price and has become an increasingly common financing tool, as shown in Figure 7.

While most raised capital still relies on the above sources, the continuous search for alternative funding resources has resulted in several additional techniques:

- ***Financing by projected royalty streams.*** Future royalty streams from expected product sales are sold in exchange for immediate capital, required for early phases of drug development, by means of debt or investment.
- ***Collaborative development financing.*** According to this model, biotechnology company A grants license and access to its promising drug development pipeline to company B, who has suitable resources to bring these to their final phases of development and acquire FDA certification. In return, company A receives rights of first refusal to repurchase the drugs from company B at a pre-established price. Company B assumes the risk of development costs in the case of failure.
- ***Contract Research Organization (CRO) linked financings.*** An organization that provides pharmaceutical research and development services to biotechnological companies, supplying required funding and resources at a relatively inexpensive price, such as skilled manpower or infrastructure for clinical trials as well as other services required for FDA approval, in return for future royalties of drug sales or ownership in the companies it serves. In addition to lowering expenses, overheads may be written off as variable rather than fixed costs, rendering the services even cheaper.
- ***Committed Equity Financing Facilities (CEFF).*** This model proposes a financing commitment, for a limited timeframe, during which publicly traded companies may sell a predefined amount of stock at a price lower than market price, thus securing funds over longer periods of times.
- ***Designated funds.*** Funds designated to promote treatment for specific diseases occasionally finance research and development phases up to Phase II. Although this funding channel is typically insignificant in relation to general funds required by the industry and is available for only a few named diseases, it may be an interesting vehicle to apply in the Israeli context.
- ***Incubators promoted by large pharmaceutical companies.*** Worldwide large pharmaceutical companies associate with venture capital funds to raise funds for drug development and promote incubators to support emerging biotechnology companies. Approximately 40% of funds invested in emerging biotechnology companies in the US are raised this way. As a means of funding, then, it is vital to encourage the growing presence of global pharmaceutical companies in Israel.

Israel holds a key to transform these global challenges in the pharmaceutics industry into an opportunity. Adequate organization by means of innovative funding techniques and new policy making can assist the local life science industry by providing long-needed technologies for large international pharmaceutical companies while also providing opportunity for local pharmaceutical companies to grow.



The unique composition of Israel's population is an advantage that could be utilized worldwide. Multiple ethnic groups of unique genetic qualities would provide researchers with a rich database. A national tissue bank would serve not only local purposes but global ones as well

Financial Innovations Lab and Workgroups

The adverse effect of insufficient funding in the life science industry as a barrier for growth is obvious.. In order to identify underlying barriers, devise applicable solutions, and define pragmatic goals to the life science industry in Israel, high-ranking Israeli industrialists, scientists, and policymakers were brought together by the Milken Institute to a series of discussions and workgroups to consider infrastructures and tools for accelerating medical solutions in Israel. At workgroup meetings new financing models, requiring collaboration between investors, companies, and countries, were presented. However, in order to implement such collaborations, regulatory changes are mandatory.

A brief listing of the chief barriers faced by the Israeli life science industry would include:

- Funding issues. This includes both long term funding and lack of international relations with companies that could potentially finance early phases of development;
- Insufficient relations between academia and industry. Although the bond between these two entities is one of the advantages posed by Israel to the global industry, it is limited to early stages of patent registration and must be extended to advanced phases, typical of mature companies.
- Lack of professional personnel. Israel's scientific brain drain is resulting in a lack of management and adequate organizational infrastructure;
- Lack in industrial infrastructures through which life science research can be promoted;
- Lack of regulatory know-how needed for adequate regulation, legislation, and supervision concerning various fields.

Consequently, the workgroups have suggested the following recommendations:

- Design creative solutions that would leverage governmental support in developing and financing research infrastructure and commercialization for the life science industry.
- Formulate the necessary regulatory framework regarding clinical and genetic trials that would assist in establishing Israel as an international center for the development of medical solutions based on Israeli research. The barriers resulting from the current state of regulation, as well as operational recommendations for their removal are presented in detail in Appendix 1.
- Employ the IT advantage Israel currently holds to develop and use medical databases for research as well as supervising clinical trials.

Following is a brief summary of recommendations to promote research and development in Israel while simultaneously creating the required physical and regulatory infrastructures.

BRAIN DRAIN AND WORKFORCE

The brain drain has severely strained Israel's economy and available driving workforce the life science industry in particular. It is imperative not only to resolve this issue but to increase the number of physician scientists who regularly contribute to research.

- The brain drain has already been recognized by Israeli government. The workgroup recommends expanding existing efforts in order to accelerate the retrieval of outstanding expatriate researchers, who must be enticed to return to Israel, regardless of field of research. To promote this goal, a committee should be established to find these outstanding researchers and provide them with work places at Israeli research institutions or hospitals by opening new positions and securing additional grants aimed to promote applicable medical research. The committee itself should comprise excelling researchers and practitioners who can professionally evaluate candidates and their potential for success, while the program could be funded by the government or philanthropic organizations.
- Development of a centralized database, accessible to researchers and practitioners abroad, has yet to be produced to assemble easily accessible information concerning available posts and required professionals in Israel.
- Economic considerations currently restrain practitioners from conducting medical research while working. An incentive mechanism must be established to encourage practitioners to contribute to research.
- The low rate of doctors in Israel relative to population generates enormous pressure on practitioners, significantly reducing available time for research. The number of practitioners must be increased as research is advanced. It is hopeful that the expected establishment of a fifth medical school in the Galilee would help resolve the issue.
- Designated training programs should be developed for researchers and practitioners in the life science industry in order to promote applicable research and medical solutions in this industry.
- Promote expertise through providing practitioners and Ph.D. graduates limited financed training opportunities in leading companies or research institutions, conditioned by their return to Israel, in order to establish future leadership in the rising Israeli life science industry.

ACADEMIA AND INDUSTRY

Knowledge transfer between Israeli academia and industry should be intensified. The vital promotion of collaborations between academic and industrial institutions may be achieved through grants sponsored by philanthropic or private funds.

Tissue bank and clinical database

A national tissue bank and clinical database that could serve all relevant fields of research are the most acutely lacking from physical infrastructural institutions in Israel.

- ***Tissue bank.*** Although tissue and tissue-related data are currently collected at various institutes in the country, Israel lacks a national tissue bank that would centralize tissues and information. Tissue would be collected from patients and be clinically documented while treatment would be monitored in order to identify genetic and molecular characteristics of diseases at their different stages. Identification of such characteristics would not only facilitate pathogenesis and optimization of treatment, but also allow for the research of preventive methods. A local tissue bank would promote collaborations between pharmaceutical and biotechnology companies for the purpose of drug development and diagnostic markers. In addition, the field of medicine at large is currently in transition from a generic approach to a personalized approach in both diagnostics and treatment. Progress in this personalized approach would be further accelerated by means of an easily accessible tissue bank.

  The unique composition of Israel's population is an advantage that could be utilized worldwide. Multiple ethnic groups of unique genetic qualities would provide researchers with a rich database. A national tissue bank would serve not only local purposes but global ones as well.

- ***Clinical database.*** Clinical data is typically stored in computerized databases. Under the Israeli patients bill of rights and the genetic information law, it might be possible to use such databases for purposes of general research or clinical trials.

The tissue bank and clinical database would be regulated under Israeli patient's bill of rights and the genetic information law as well as under international laws and regulations.

Regulation and legislation

Proper regulation could assist in promoting several causes simultaneously.

- ***Leveraging public funds.*** The National Forum for R&D (TELEM) has decided to support centers of infrastructural equipment servicing the biotechnological R&D community in Israel. Funds allocated for this program amount to $10 million for three years. It would be advisable to leverage this governmental support in order to secure additional funds for this purpose.

- ***Designated funds for specific diseases.*** Legislation must be changed to encourage philanthropic funds, promoting research for treatment of specific diseases, to invest in Israel by establishing branches and designated research centers. Specifically, modifications in the law of philanthropic foundations would allow foreign nonprofit organizations, and particularly from the US, flexibility in their investments in research of particular diseases. Currently, nonprofit organizations in the US are unable to invest freely in businesses that are directly related to the purpose for which they were founded. The proper alteration in Israeli law might draw such international organizations to invest in Israeli research and encourage the establishment of new research and development centers aimed at providing medical

solutions for specific diseases. In addition, an administrative center should be established to liaison with prospective investment funds and centralize requests for grants and guarantees provided for the financing of relevant life science companies.

- ***Healthcare service centers (Israeli equivalent of health maintenance organizations – HMO) and hospitals.*** The ties between these two healthcare bodies should be strengthened and regulated, and information flow between them should be encouraged. For example, through proper incentives, community practitioners could provide data concerning patients on a regular basis (while maintaining patient's rights of privacy). This may be a part of the clinical database that needs regulation. The efforts should be concentrated to encourage parties send information to the database rather than to each other. Such information would also be useful for clinical trials and the tissue bank.
- ***Israel as a world center for clinical trials.*** The advantages for local patients are up-to-date medical care and treatment by latest technologies. The advantages for researchers from an international perspective would be in the quick assembly of patients and the complex nature of the ethnic heterogeneity of the population. The main barriers in promoting this goal would be bureaucratic, for example, length of time for trial approval by the regulator and additional local demands.

Funding

Workgroups considering economic and financing policies for the acceleration of the development of medical solutions in Israel discussed the following alternatives as potential means to promote the life science industry and its potential collaboration with the global pharmaceutical industry.

» General reforms

- Declare the life science industry and the biotechnology sector in particular a national priority industry, upon which national economic growth may be based.
- The current policy encourages funding of new projects within technological incubators, limiting this support on the basis of time. However, many mature projects that exceeded the time limit and are no longer eligible for incubator support are faced with a funding challenge. It is therefore advised to extend support within the framework of the incubators to a period of up to five years taking into consideration the readiness of the company, technological maturity, and chances of success.
- Improve credit conditions through public and philanthropic funds. For example, programs of the Chief Scientist could be extended so that government support may be leveraged to procure additional private funds or to encourage international collaborations.
- Successful Israeli companies may be encouraged to re-invest in the community by investing in basic research, as is customary in the US.
- Encourage local and foreign institutional investors to support the life science industry in Israel. This may be achieved by creating a relevant life science shares index or an Exchange Traded Fund (ETF), which would increase liquidity and encourage future IPOs.

» Financially specific reforms

In addition, a financial reform may encourage research, product development and commercialization within the life science industry. Specifically:

- Employ tax breaks and exemptions, similar to those that are currently employed in Israeli film industry and oil explorations to encourage private investors, on the one hand, and venture capital funds specializing in biotechnology, on the other hand, to invest in the life science industry in Israel.
- Revise regulation over reporting requirements (such as J-curve exposure) to increase asset allocation of institutional investors into private equity at large and in funds specializing in life science in particular.
- To prevent early exists at lower valuations while encouraging the formation of large mature companies, companies may be offered incentives to reach the end of Phase II by partial funding (over 50%) in more advanced phases of development.

TABLE 4

Probability of inclusive portfolio failure in relation to number of products in the portfolio

No. of products	Probability of inclusive portfolio failure given these chances of success						
	20%	25%	30%	35%	40%	45%	50%
1	80%	75%	70%	65%	60%	55%	50%
2	64.00%	56.25%	49.00%	42.25%	36.00%	30.25%	25.00%
3	51.20%	42.19%	34.30%	27.46%	21.60%	16.64%	12.50%
4	40.96%	31.64%	24.01%	17.85%	12.96%	9.15%	6.25%
5	32.77%	23.73%	16.81%	11.60%	7.78%	5.03%	3.13%
6	26.21%	17.80%	11.76%	7.54%	4.67%	2.77%	1.56%
7	20.97%	13.35%	8.24%	4.90%	2.80%	1.52%	0.78%
8	16.78%	10.01%	5.76%	3.19%	1.68%	0.84%	0.39%
9	13.42%	7.51%	4.04%	2.07%	1.01%	0.46%	0.20%
10	10.74%	5.63%	2.82%	1.35%	0.60%	0.25%	0.10%
11	8.59%	4.22%	1.98%	0.88%	0.36%	0.14%	0.05%
12	6.87%	3.17%	1.38%	0.57%	0.22%	0.08%	0.02%
13	5.50%	2.38%	0.97%	0.37%	0.13%	0.04%	0.01%
14	4.40%	1.78%	0.68%	0.24%	0.08%	0.02%	0.01%
15	3.52%	1.34%	0.47%	0.16%	0.05%	0.01%	0.00%

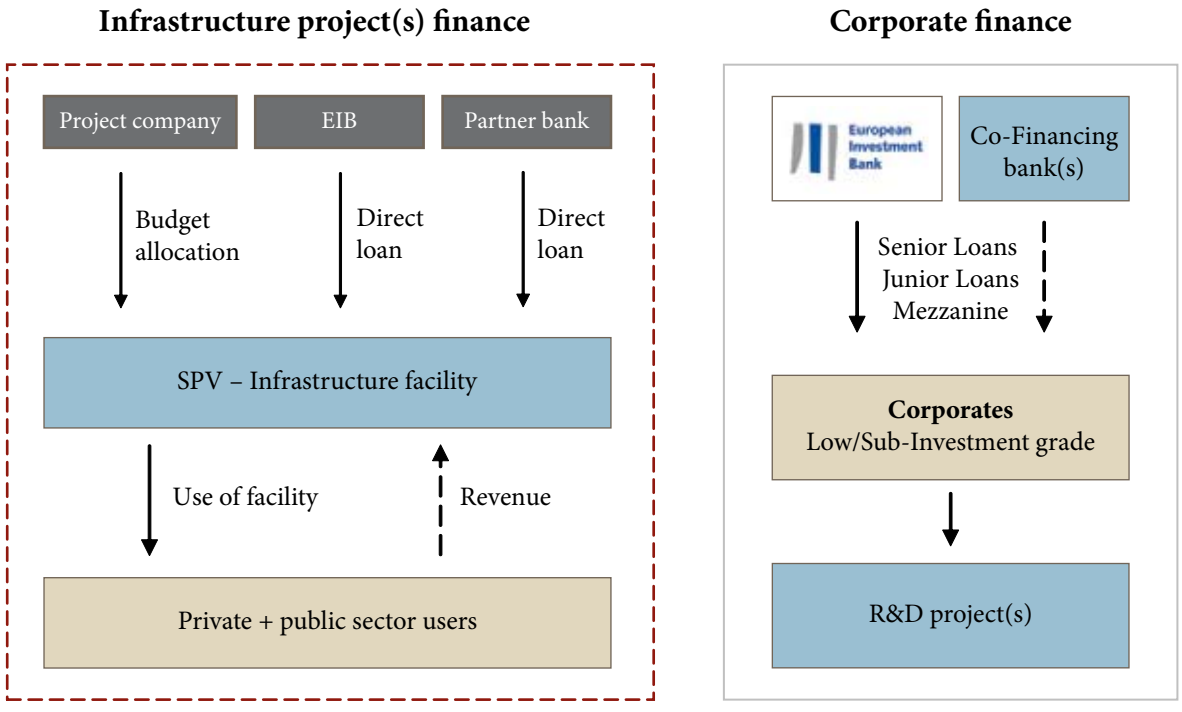
Guarantees are required from governmental institutions in partnership with other parties such as insurance companies, sovereign wealth funds, multilateral institutions, disease-specific designated foundations and other philanthropic organizations in order to lower funding risks thus attracting prospective investors both locally and globally

Innovative Financial Models

This chapter presents financial facilities proposed to fund and support Israeli healthcare and life science companies as they advance through the development phases as well as improve their exposure to strategic partners and to additional funding resources that could assist the life science sector in Israel at large. These models originate in different sources and are presented in detail in a previous report published by the Milken Institute. Several models were developed in latest Financial Innovations Lab while others were designed in a financial program, applied by the European Investment Bank (EIB), aimed at funding research, development, and infrastructures in the life science. According to these models, EIB sponsors up to 50% of the loan based on due diligence and no external rating is imposed on the debt, thus enabling funding through debt for companies with low credit rating. Two of EIB's models are presented in Figure 8.

FIGURE 8

EIB financing for research, development and innovation in life sciences
The risk sharing finance facility (RSFF)



Source: www.eib.org/rsff

A brief introduction of six of these models is presented below. The first two are particularly pertinent to the case at hand and will be further discussed later.

- ***Portfolio fund.*** A fund dedicated to support development of an assortment of products or companies at early developmental stages, particularly seed to Phase II companies. Several portfolio companies might be adjoined, leveraging on size that would allow diversity of investments, decreased risks, increased rating for funding purposes, ability to draw highly professional management, and the ability to increase success rates through other means. This structured finance facility provides longer-term, fixed rate debt capital to the developing life science industry.
- ***Infrastructure fund.*** A fund aimed for long term investment in the development of infrastructures for the life science industry that are expected to resolve barriers resulting from the funding deficit described earlier. The fund would establish publicly-privately funded centers of infrastructural equipment servicing the biotechnological R&D community in Israel, similar to the National Forum for R&D (TELEM).
- ***Grants and credit enhancement through philanthropic resources.*** Credit enhancement can be achieved through various means, including securities, insurance, and guarantees. Both local and international funds, supporting the development of medical treatment for specific diseases, may be employed to procure guarantees or credit insurance. These credit enhancements would lower substantially the overall costs of financing the structured finance facility discussed above. Moreover, it would leverage government participation and lessen budgetary concerns about this initiative. The financial involvement of such funds in the life science industry is relatively new, reflecting the growing funding challenge in the industry. Consequently, such funds invested $75 million in 2007 in biotechnology companies in the US supporting the development of new pharmaceutical and medical treatment, in comparison to $6 million in 2000. To name a few examples, the Cystic Fibrosis Foundation invested over $300 million in research and development over the last decade and the Juvenile Diabetes Research Foundation invested nearly $25 million in 22 companies developing treatment for the disease. Funds supporting research of treatment for cancer, multiple sclerosis, Parkinson's, Alzheimer, and other degenerative diseases have all contributed to the funding efforts. In the life science industry in Israel, this is currently an unutilized funding channel. Companies sharing similar fields of interests may be encouraged to associate and liaison regularly with relevant international funds, in order to centralize grant and guarantee applications that could fund diverse projects.
- ***Trade in intellectual property.*** It may be possible transform intellectual property into financial assets by aggregating an assortment of patents or technologies at early development phases. Based on the estimated value of their intellectual property, capital may be raised, in the form of equity or debt, in exchange for future royalty streams. Israeli credit rating agencies (Midrug or Maalot) would have to develop the required and specialized skills for this financing method. This financing model may be particularly interesting to academic technology transfer arms as well as funds specializing in the life science industry.
- ***Securitization of loans.*** Collateralized Loan Obligation (CLO) may be a recommended avenue for companies seeking to reduce financing costs. A dedicated fund would invest in diverse companies at different stages, allowing for positive cash flow in the form of debt. The fund would then sell its

loan portfolio to a special purpose vehicle (SPV), which in turn would issue securities to investors at different risk rates (hedge funds, institutional investors). Cash flow from the portfolio companies would be used to repay outstanding debt according to risk rates. As some of the funded companies would be in early phases of development, and therefore not expected to generate returns, governmental or philanthropic funding may be utilized to improve their credit.

- ***Funding contracts.*** A commitment for future purchase is typically used to fund drugs, vaccines, and other medical products that have a relatively small market, unattractive to large pharmaceutical companies. Governmental and philanthropic incentives may induce and enable companies to allocate resources for such drug development, selling the drugs at cost value in developing countries and for profit in developed countries. This model may be employed to encourage development of drugs whose main markets are in developing countries, drawing funding resources from foreign governments and philanthropic funds.

As mentioned, two models in particular are applicable for the Israeli life science industry: the portfolio and infrastructure funds.

Proposed model: Portfolio fund

Two phases in drug development are particularly challenging: the preclinical phase, prior to proven human viability, and a later stage starting at the end of Phase II. A portfolio fund is based on the notion of investment in an aggregate of products or companies. As described earlier, Israel's life science industry, rich in potential money-making ideas, is abundant in such immature and inexperienced companies. A portfolio fund would add value by creating an organizational and financial structure that would not only assist in advanced development stages but could also guide the companies and products up to later stages. Such a fund would be complimentary to existing governmental financing programs, particularly the incubator program, which are essential for the ripening of new projects. Moreover, this fund would provide support for companies struggling in existing venture capital portfolios that are running out of funds. Essentially, this model may be extended to comprise a portfolio fund consolidating matured companies. Such a fund would help improve overall chances of success for these mature companies and may stimulate consolidation of companies at advanced stages of developments; while simultaneously increasing accessibility to funds sponsored by government or other agencies. Although any portfolio fund would be able to invest only in a select number of companies and products, potential accessibility to it should constitute an incentive for companies to reach advanced stages in their product development. In today's market, lack of potential resources available for the funding of advanced development stages deters investors from financing early development phases. Any success, even at a low rate, would draw additional investors and increase the presence of large biotechnology and pharmaceutical companies in Israel, which, in turn, would allow for the implementation of a new instance of this funding model.

» A dedicated fund for emerging companies

The fund's characteristics are determined by the sector in which it invests (e.g., biotechnology, medical devices). The sector which shows the highest unrealized growing potential is that of biotechnology, which,

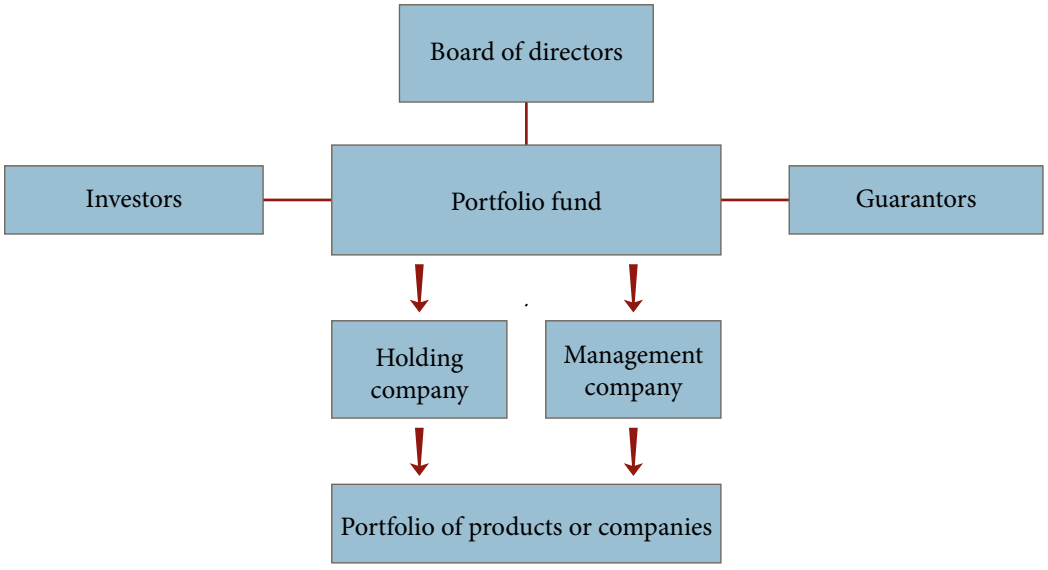
in Israel, is comprised of a large majority of small emerging seed companies with little experience in drug development and lacking in financial and professional managerial resources. To a certain degree, a dedicated portfolio fund, focusing on highly promising products, would build on existing infrastructures offered by the incubators, offering an organizational, managerial, and financial infrastructure that would allow the incubators to support developing products from preclinical trials and until the end of Phase IIB, in which drug efficiency is determined.

» A dedicated fund for mature companies

The same model can also be applied to companies at more progressive stages of product development in order to eliminate funding barriers and lack of professional management typical of these stages. Portfolio funds could be formed on the basis of common interest, such as nature of products (biotechnology, diagnostics, medical devices), field of research (infectious diseases, auto-immune diseases, cancer), or specific diseases.

As in the context of emerging companies, here, too, funds would be raised to develop a range of products, emphasizing the deployment of common infrastructures, physical and managerial, as a basis to grow Israeli life science companies, thereby avoiding early exists. Companies induced to collaborate in this way may also significantly reduce operating costs, and information shared by companies of a single portfolio may help overall progress. From the national perspective, the incentive is that such large companies induce the build out of technology-based production facilities and plants while increasing workforce demand both in-house and in supporting sectors.

FIGURE 9 *Rudimentary structure of the suggested portfolio fund*



» Fund structure

The suggested structure of the fund, presented in Figure 9, would allow access to funding resources at lower costs as well as managerial support. The various structural elements are further described below.

- ***Board of directors.*** The board would comprise relevant research professionals, highly experienced industry professionals, representatives of the investors, and a representative of the government as an observing member. Subsequent to the receipt of guarantees sufficient for initial fundraising, the board, with the assistance of relevant professional as needed, would take responsibility over the initial evaluation of candidates according to predefined criteria. The extent of risk, from both the technological and business aspects, would be evaluated in light of projected costs of development, the products' potential for successful completion of development and market penetration, projected size and share of the market, and degree of innovation compared to competitors. The board would periodically report progress to guarantors and investors.
- ***Guarantors.*** Guarantees are required from governmental institutions in partnership with other parties such as insurance companies, sovereign wealth funds, multilateral institutions (e.g., European Investment Bank), disease-specific designated funds and foundations, and other philanthropic organizations in order to lower funding risks thus attracting prospective investors both locally and globally. The extent of necessary public and private guarantees depends on the fund's composition – the earlier the development phase, the grater the risk, requiring larger guarantees. To draw investments, guarantees will provide investors with a provision to return part of their investment should the fund, upon maturity, be unable to cover its debt principle and due interest by its assets. Clearly, as the number of products or companies in the portfolio increases, so would the securities provided by the guarantors. It is thus important to set adequate criteria that would stimulate sponsorship, particularly governmental, such as:
  - Available managerial and organization infrastructure that could escort products to progressive development stages;
  - A minimal number of products;
  - Potential success rate based on projected size and share of the market, degree of innovation compared to competitive bodies, and the projected cost of development;
  - Detailed work plan, including defined milestones;
  - Projected extent of manufacture and estimated contribution to the national industry;
  - Potential to attracts investors, assuming collateral has been secured;
  - Minimum and maximum levels of fundraising.
- ***Management company.*** To increase success rates a management company, financed by the fund, would supervise development stages and provide professional support to funded companies, including legal services, preclinical trial design, interactions with the regulatory bodies, the FDA and EMEA, formulation of third-party agreements, and any other pertinent service. The management company would periodically report progress in product development to the board of directors.
- ***Investors.*** Debt principal will be prepaid to investors subject to the value of assets backing the non-

recourse part of debt and extent of the guarantees received. Coupon rates may be lowered by offering investors the option to receive a percentage of the funds' future profits if and when they are realized.

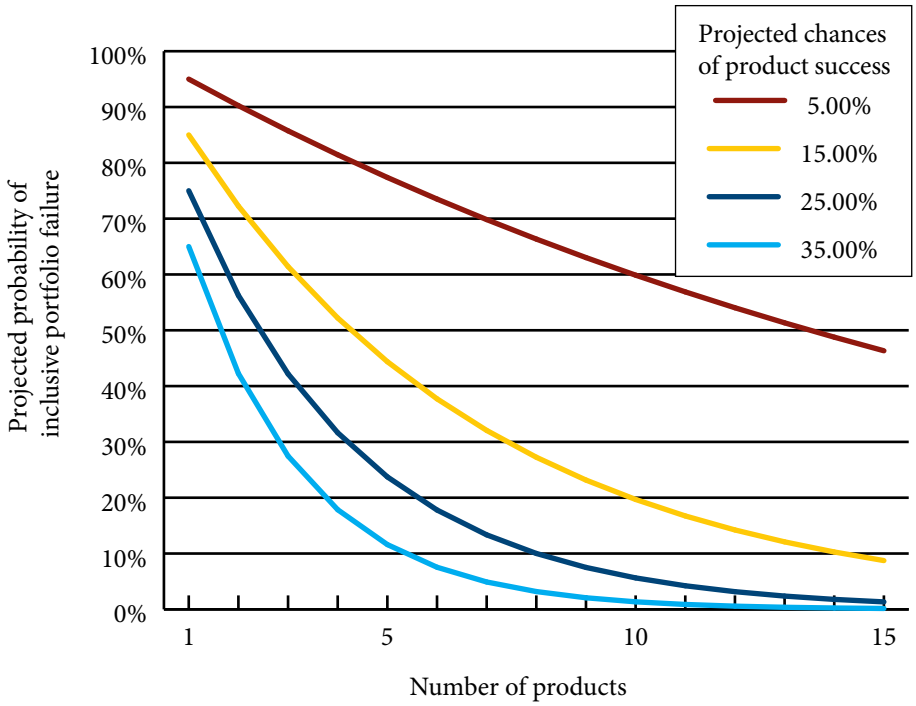
» Financial structure

The chance that all portfolio products would fail decreases in inverse proportions to the number of products within the portfolio. The lower the projected rate of success, the more products are required to secure the successful development of one product. To reduce the risk, the fund would support 15-25 products in the hope of bringing 3-6 products to their target phase. For a portfolio of emerging companies this would mean the end of Phase IIB, while mature companies would attempt to either obtain FDA approval or, if already obtained, reach the market. Given the minimum of 15 products, at a projected 40% probability rate of success the chances of a total failure of all portfolio products amounts to 0.05%, while at a 20% probability rate for success, the chances of overall failure amount to 3.5%. Table 4 and Figure 10 detail overall failure probabilities in relation to the number of products in the portfolio.

The fund may raise capital from local and foreign investors by issuing bonds. The size of the placement and interest rates would be determined according to estimated value of products and companies in the

FIGURE 10

Probability of inclusive portfolio failure in relation to number of products it comprises



portfolio at the end of the period (7-15 years). Subsequently, a first series of bonds would be issued at fixed rate. Any cash flow generated by the portfolio, based on royalties or sellout, would be used to return invested loans. In early years, when cash flow is not expected to be generated, coupon interest would be accumulated to be paid at a later installment.

The extent of required funds depends on scientific and technological complexity as well as on the nature of the proposed products (pharmaceuticals or medical devices). The development costs in Israel are considerably lower than those characteristic worldwide, mainly due to relatively low employment overhead. Based on data presented in Figure 5 above, the development of 25 biotechnological products from preclinical to Phase IIB stages requires $300-1,050 million over five to seven years, whereas the development of the same number of products in Israel amount only to $100-200 million over seven to ten years, as is shown in Table 5.

These sums may be raised over a long period of time, as they are required only incrementally. In contrast, it would be possible to invest money in additional promising products during the first three years. Should the final development costs of any phase or product be lower than projected, funds may be diverted to other products or reserved for additional, more advanced, development phases. Raised capital would be invested incrementally in the company, based on successful achievement of predefined milestones in return for shares or options. In the case of investment in a specific product in the portfolio, an SPV will be formed within that company.

Proposed model: Infrastructure fund

The infrastructure fund aims to create infrastructures required for long term development of the life science industry in Israel through collaborations between public and private funding resources and specifically public-private partnerships (PPP).

» Designated projects

Projects – centers or large facilities – sponsored by the infrastructure fund would be elected according to criteria set by the Steering Committee, prioritized by their ability to provide a large number of services. Such centers or large facilities would be operated by skilled personnel who may also serve in advisory capacities concerning technological and regulatory requirements posed by the life science industry. The list of potential projects is long, yet the emergence of some institutions is more pressing than others, for example:

- National tissue bank;
- A regulatory body supervising clinical trials, similar to the FDA;
- Expanded GMP compliant production facilities;
- Centers for commercial application of technologies such as academic technology transfer arms;
- Centers of excellence in biotechnological research and development;
- Management training centers focusing on research, development, regulation, and clinical development

TABLE 5 *Projected costs of Israeli product portfolio*

Stages	Approximate cost per product (Million$)	Chances of success	No. of products	Total cost (Million$)
Pre-clinical	1-2	30%	25	25-50
Phase I	2-5	76%	8	16-40
Phase II	10-20	48%	6	60-120
Phase III	75-250+	68%	0	
			SUM	101-210

as necessary for deployment in the life science industry.

A committee chaired by Prof. Haim Aviv in 2007, and the TELEM forum, have declared the following fields to be particularly in need of attention:

- Recombinant protein;
- Medicinal chemistry (lead compound synthesis);
- Animal imaging;
- DNA sequence mapping.

» Organizational and financial structure

The suggested structure of the fund, presented in Figure 11, would allow service and infrastructure providers access to funding resources at lower costs while also allowing supervision over projects. The Steering Committee should consider policy guidelines previously set by the TELEM Forum when planning plants and facilities required for continuous progress in the Israeli life science industry, particularly in the biotechnology sector, as well as when proposing standards expected from service and equipment providers (for example, responsibility over the training of skilled personnel). Subsequently, detailed specifications would be defined jointly by the candidate infrastructure providers and third party experts. The infrastructure fund would eventually finance the infrastructural equipment centers by means of debt bearing interest at a fixed rate.

Initial capital would be raised by issuing interest bearing bonds to investors. Periodic interest payments would be insured by the government or philanthropic institutions, which would regularly pay the service provider a commission equal to the interest while returning the principal at the predefined ending period. Upon full payment of the debt, ownership of facilities and equipment would be transferred to the State. The service provider would further enjoy exclusive access to the equipment or facility and to revenues

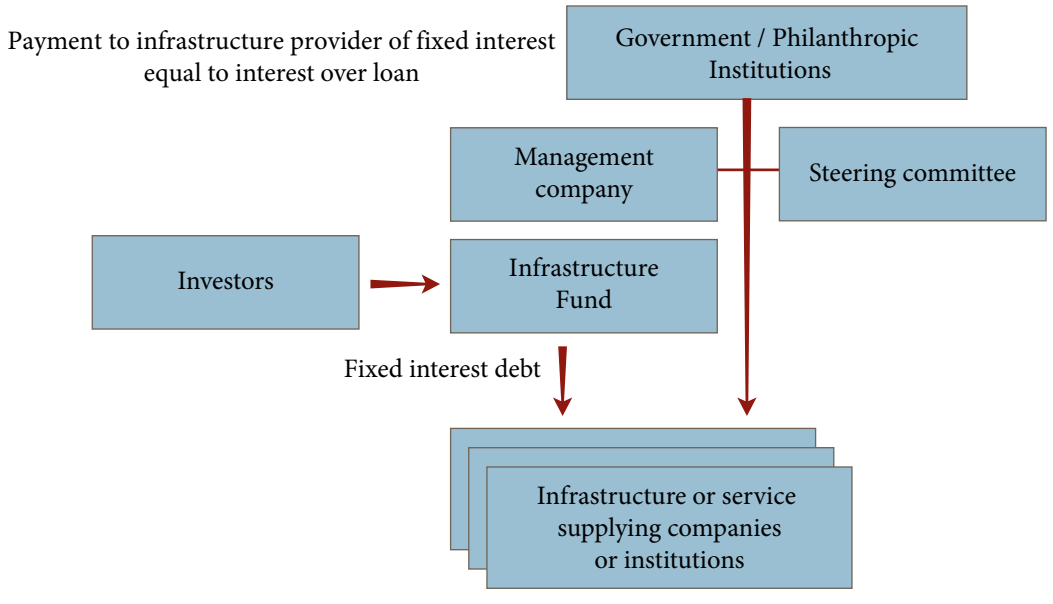
resulting from continued service provision. A management company, operating on a designated budget or as a partner, would oversee financed companies, ensuring their compliance with the criteria set by the Steering Committee. The management company would report periodically to the government and investors. The fund would be required to raise about $100 million, the estimated costs of equipment and selected projects, over a period of five years.

» Successful Deployment of the Financial Models

For successful deployment of the suggested models the following should be considered:

- Services of an international investment house with proven expertise will be required in order to create the financial structures necessitated by the fund and in order to reach foreign investors;
- To improve credit, a designated center should be established to regularly liaison with international institutions and centralize requests for grants or guarantees for projects sponsored by either of the suggested funds;
- To increase the number of sponsored products and their rate of success, experienced candidates from both Israel and other countries should be recruited as part of the managerial staff of the management company of the various portfolio funds;
- To encourage investment in either fund and encourage Israeli R&D, tax benefits in the form of deductions or exemptions are required. Current legislation does not allow for sufficient incentive in drawing such capital.

FIGURE 11 — *Organizational structure of the suggested infrastructure fund*



Global Collaborations

Accelerating medical solutions while democratizing access to health services is critical for both Israeli and global economic growth. Over the next few decades, the developed world will age and weaken demographically. Meanwhile, demographic trends in the developing world, from resurgent youth booms in the Islamic Belt to premature aging in China and population implosion in Russia, will give rise to daunting global threats. Medical solutions may play a key role in resolving this dim vision and their geopolitical importance is ignored at great risk: potential health crises from both chronic and infectious diseases resulting from chaotic state collapse or authoritarian reactions.

Several specific models for global collaboration were discussed at the Lab and subsequently found worthy of further development. Others may still need to be identified and explored. The search for collaborative models, in which other countries may participate, continues. For example, several initiatives include:

- ***Teijin (Japan) Hobart Home Healthcare Fund.*** This fund targets development of Israeli-related innovation for Japanese home healthcare market. Teijin, the leader of Japanese home healthcare therapies, a long time partner of Hobart group, built the joint venture to take advantage of the abundance of healthcare innovations in Israel and the soaring demand for novel home healthcare products in the rapidly aging Japanese population.

- ***Turkish-Israeli Healthcare Park.*** This initiative aims to develop a high tech healthcare industrial park based on Israeli-related innovations to be exploited in the Turkish healthcare market. The Turkish-Israeli park will be focused among other areas in development and production of drug delivery solutions, healthcare IT, telemedicine products, and medical device production.

- ***Kazakhstan-Israel Healthcare Park and Fund.*** This initiative aims to develop a high tech healthcare industrial park in Kazakhstan based on Israeli-related innovations to be exploited in Kazakhstan and adjacent countries. The Kazakhstan-Israeli park will have a dedicated investment fund earmarked to companies active in the park.

- ***India Hobart Rural Health Care Fund.*** A joint venture developing healthcare technologies for rural healthcare in India. The joint venture between Hobart and the Indian group is to leverage Hobart's activities in developing healthcare solutions for rural populations with the development and clinical testing capabilities of the Indian group. A dedicated fund will support investment in companies with efficacious and affordable solutions for diagnosing, preventing and treating specific disease states common in rural populations.

- ***Israeli-Palestinian Pediatric-Hemato-Oncology Collaboration (Peres Peace Center).*** A point-to-point telemedicine linkage between the newly operating Palestinian Pediatric Hemato-Oncology Department at August Victoria Hospital and its counterpart at Hadassah University Hospital. The system will have three components:

- ***Teleconferencing*** – allowing daily joint discussions at pre-determined times.

- ***Teleradiology*** – allowing joint examination of X-rays, CT, MRI and Ultrasound, as imaging is essential to the oncology diagnosis and treatment. Facilitating consultations between Palestinian and Israeli clinicians and radiologists will greatly contribute towards appropriate clinical decisions.

- ***Telepathology*** – facilitating joint examination of pathologic specimen originating in blood and bone marrow will allow for accurate diagnosis and thorough discussion of pathologic findings.

Conclusions

Participants in the Financial Innovations Lab have offered several tracks for action that may help overcome the growing funding challenge in Israel's life science industry. This report describes the barriers impeding progress in the life science industry and suggests structural and financial models through which it might be possible to accelerate medical solutions in Israel while leveraging on outstanding and leading expertise in the field.

Promoting the life science industry in Israel would enhance national economy at large, while also increasing workplaces in the life science industry as well as supporting sectors. As other high tech sectors lose their advantage, the government must acknowledge the life science industry as key player in the enhancement of Israeli economy, declaring it a favored industry.

While devising the models and strategies proposed in this report, it became clear that it is possible to resolve the acute failings of fundraising by means of public-private partnerships. Financial technologies, securitization and structured finance should be employed to ensure continued growth of this promising sector of Israel's economy.

Participants in the current Financial Innovation Lab have set the following goals:

- Transform the life science industry into a means for Israeli economic growth in the next decade, while simultaneously building a foundation for the development of Israeli global leading companies.
- Create the physical, managerial, tax and regulatory infrastructure that will support the life science industry in Israel. For example, companies may be encouraged to cooperate for the purpose of receiving joint administrative or managerial services.
- Induce foreign pharmaceutical and biotech companies, as well as philanthropic funds, to invest in Israeli life science ventures at different stages. This may be achieved, for example, through legislation that would facilitate philanthropic funds designated to address specific diseases to invest in ventures that share similar goals. Grants from such funds could then be used to improve conditions of credit received from other sources.
- Institute Israel as an international center for clinical trials. This could be achieved by the establishment of a tissue bank, clinical databases, and a regulatory body similar to the FDA which would regulate clinical trials and approve drugs.
- Diminish the brain drain and provide incentives to expatriate scientists and firms to return to Israel while also creating new workplaces and taking advantage of existing human capital.
- Reinforce the bond between academia and industry.

The current report declares unequivocally: capital access for the life science industry must be urgently expanded by means of collaboration in order to accelerate progress in this sector, rescue the local industry, and increase Israel's competitive advantage.

Appendix I

Clinical and Genetic Trials: Regulation and Legislation

Liza Ireni-Saban

Accelerated developments in biotechnology pose novel regulatory problems for state governance not only in the public policy initiatives that have been adopted, but also in their levels of public intervention and the structures of economic and governmental interaction. The forces behind policy in this area have been to a large extent national competitiveness, technological innovations and increasing commercialization of research products and services. The regulatory framework has undergone a major transformation: the traditional reliance on state operators has been replaced by regulatory designs that promote market competition among multiple actors. In this case, commercial companies often rely on public sector institutions to get access to genetic data and tissue samples, while the public sector relies on those companies for commercial exploitation of the research benefits. Indeed, the role of public authorities in this policy sector has evolved in response to technological change with new means of public intervention being developed and objectives being redefined.

Even though we must appreciate the role of private funding in the development of therapeutic products from genetic research - without the involvement of private companies, important therapeutic products may not reach the market, private companies may not be able to develop these therapeutic products without the initial basic research provided by public research organizations. Consequently, the participation of individuals and social or ethnic groups in genetic research raises major concerns, such as discrimination, stigmatization, and breaches of privacy. It is argued that a balance must therefore be found between the financial investment of the private companies involved and the public investment, be it in the form of voluntary participation or be it the medical infrastructure in large-scale genetic database without which the research could not exist. Moreover, economic globalization and increasing commercialization of science has made it even more difficult to achieve this balance in small countries like Israel where biotechnology companies do no yet have the scope to master worldwide markets.

The Israeli regulatory system generally restricts genetic and medical application of biotechnological research while in the US, Canada, and European countries such as the UK and Iceland, biotechnology companies conduct their operations against a single authority responsible for all relevant regulation and legislation, which it adapts according to the industry's needs. Most of the members of the Financial Innovations Lab feel that it is both a national and social priority to accelerate practical and moral solutions for clinical trial regulations in Israel that would be based on a wide consensus while balancing conflicting interests engrained in the decision-making process of the issue at hand. These conflicts arise from the multitude of governmental bodies currently involved in the design and application of clinical trial regulations, which are required to meet rather vague normative ethical standards. At the end of this appendix, we propose certain institutional and normative keys by which the decision-making process may be examined and designed, while also proposing recommendations by which public policy may be enhanced in relation to the life sciences industry.

Genetic trials: Israeli legislation

Regulations of clinical trials in the West have significantly transformed following the Declaration of Helsinki. A clinical trial in human subjects is defined in Israeli regulations as the use of medicine, radiation, or chemical, biological, radiological, and pharmaceutical material that are designed to have health-related outcomes.

Israel, has been updating its regulatory framework, typically by means of non-legislated regulations and procedures applicable to those fields of research in which clinical trials are conducted. Procedures concerning clinical trials are elaborate and additional regulations concerning genetic information that is revealed through trials are published by the Ministry of Health. Guidelines also exist in new fields of research that involve clinical trials, such as experimental products that employ use of living cells or tissue.

The necessity for specific legislation addressing genetic data has long been debated as both the right to privacy and the consent to provide blood samples are clearly defined in two laws: the right to privacy (1981) and the patient's right act (1996). Notwithstanding, the past decade has witnessed several legislative efforts concerning genetic trials and information in Israeli parliament, the Knesset. Attempts to formulate legislation concerning genetic trials in human subjects have begun a few years ago, but to date, Israel's only legislation regulating clinical trials concerns animals, while a second law prohibits genetic intervention in reproductive cells for a period of five years. Worldwide, for example in the European Community, clinical trials in human subjects have begun to be orderly organized in primary legislation.

Since March 1997, the Knesset attempted to address legal aspects biotechnological research through several law proposals, two of which have subsequently been accepted. Proposals that have been considered include the genetic trials law to prevent cloning[1], prohibition of human genetic cloning law[2], the law of supervision over medical trials in human subjects[3], and protecting individuals' privacy of genetic-related information[4].

A genetic information law was passed in 2000. Sections 15 and 24 to 28 reflect legislative intention to balance between the protection of individual participants in research and public interest resulting from the potential of genetic research to promote public health. The obligation to confidentiality of genetic information is clearly endorsed by the law as criminal sanctions are defined to parties violating its instructions. By law, due to the high sensitivity of genetic information, consent is required not only for participation in the research but also to record storage. DNA-related information must be stored separately from the contributor's identifying data, unless explicit written consent was given to store identified samples.

Regulating clinical trials: The Helsinki declaration and committees

Israeli regulations define bodies authorized to approve clinical trials in human subjects, the first of which is the Institutional Helsinki Committee, operating under the public health regulations (1990) and the Guidelines for Clinical Trials (2006). Membership, composition and appointment of the Institutional Helsinki Committee were defined only in the second addendum of the regulations, which determines the committee comprise at least seven members among which will be a representative of the public (religious persona or law professional), three senior doctors – either heads of departments of at the rank of associate professor at a known university – of whom at least one must specialize in internal medicine, and an additional doctor as representative of the hospital in which the trials would-be conducted. In addition, regulations advise that the committee represent both sexes. An additional requirement was added in 1990, by which the committee must also comprise a senior pharmacist, who would represent pharmaceutical aspects and skills. A second committee defined by the regulations is the **Supreme Helsinki Committee**. Its membership, composition, and appointment were defined in the third addendum. This committee is responsible to address distinctive issues, such as genetic trials, or particularly sensitive social issues, where an extensive policy, which all institutional committees abide, is required. The Supreme Helsinki Committee comprises ten members of diverse disciplines, not all of which are medicinal, such as genetic or ethic experts. The final authority in the approval of clinical trials in Israel is the **Director General**. Over the years, some of the responsibilities of the Director

1 No. p1245, submitted on 1997.
2 No. p1379, submitted on 1997.
3 No. p1309, submitted on 1997.
4 No. 2786, submitted on 1998.

Appendix I (continued)

Clinical and Genetic Trials: Regulation and Legislation

Liza Ireni-Saban

General have been delegated to key persons in the Pharmaceutical Administration of the Ministry of Health as well as in hospitals, in which officially appointed Helsinki Committees operate.

Helsinki Committees are currently operating in 24 hospitals. Their role is to balance between financial and healthcare interests of the individual patient. These committees operate independent and disassociated of each other, regulating clinical trials within their own institutions only, rendering it advisable to appoint regional Helsinki Committees, or perhaps even a national committee.

Clinical trials aimed for the development of new pharmaceutical or other medicinal technologies, are typically initiated and sponsored by commercial companies, often international, manufacturing the tested products. Applications for clinical trials are submitted to the Institutional Helsinki Committee by the physician in charge, and must include the research program (protocol) as well as other details required by the Director General. The regulations do not define the specific details required for the application, nor do they state any fundamental considerations to guide the Helsinki Committee while it evaluates an application. They do, however, state that trials would not be conducted against regulations or against the Declaration of Helsinki. Responsibility, authorities, roles, and proper conduct of trial originators, issues that have never been defined by Israeli Ministry of Health, are also defined in the declaration. While the Ministry adopted these guidelines in late 1990s, any inconsistency between international and local regulatory demands is typically resolved in favor of the latter.

Ethical regulation for clinical and genetic trials

Regulating clinical and genetic trials through the Helsinki Committees raises an increasingly growing problem. The Helsinki Committees are responsible for trials aimed to contribute to medicinal research and their responsibility is limited to the hospitals in which they operate. The committees refuse to address genetic trials of non-medicinal character or who are initiated by researchers who are not doctors of the hospital. Many Israeli academic institutions and particularly universities, accustomed to self-imposed regulatory systems, were thus resigned to draw independent guidelines for genetic research, regulated by means of hierarchical ethics committees within these institutions. Faculty ethics committees regulate research of relevant fields while operating under the guidance of a supreme ethics committee appointed by each university. Among its purposes, this self-imposed regulatory system aims to protect the institutions for potential legal proceedings concerning abuse, injury or violation of privacy. At the same time, through their self-imposed regulation, these publicly supported institutions maintain autonomy that prevents any political intervention in research conducted within and by these institutions.

A body intermediating between academic ethics committees and national institutions is the Bioethics Advisory Committee of the Israeli Academy of Sciences and Humanities. Despite lacking a binding statutory status, the committee actively publishes position papers and its chair frequently appears in Knesset committees. In 2001 IDgene Pharmaceuticals raised the issue of DNA-related databases and genetic trials among large ethnic groups among the population. The issue was addressed by both the Bioethics Advisory Committee[5], chaired by Prof. Michel Revel of the Weizmann Institute of Science, and the Israeli Medical Association' (IMA) Ethics Board, chaired by Prof. Avinoam Reches of Hadassah Hospital[6]. Many

[5] Bioethics Advisory Committee, Israeli Academy of Sciences and Humanities, "Large collections of DNA samples and genetic information databases", December 2002: www.academy.ac.il/bioethics/hebrew/report2/report2-h.html (in Hebrew).

[6] Prof. A. Reches, "Recommendations and conclusions concerning genetic research in large populations", the Israeli Medical Association' Ethics Board, January 2003 (in Hebrew).

recommendations suggested by these two bodies are identical, among which are the suggestion to establish a national statutory authority to supervise public and commercial DNA databases of Israeli populations while also founding a national DNA bank. The Bioethics Advisory Committee to name this body "The authority for collections of genetic samples and information of Israeli populations". Both reports further propose that this authority design ethical guidelines for research among ethnic groups of large populations. The Bioethics Advisory Committee specifically addresses the hazards of potential discrimination based on collective genetic information. The IMA suggest to handle ethical issues in genetic research of large populations through the patients' physicians who would be bound to secrecy concerning the individual results.

Recommendations

The following recommendations are suggested to improve regulation over clinical and genetic research:

- A law proposal, currently facing approval, may, according to biotech companies, potentially create new barriers in establishing Israel as an attractive center of clinical research. This incomplete proposal should be adjusted prior to its approval by addressing challenging issues.
- Efficiency of the process by which clinical trials are currently approved must be improved, at least by means of a predefined schedule. The current regulatory instruments result in an operational bottleneck and the law of genetic information does not regulate clinical trials. Prolonged approvals (9-12 months) by the authorized voluntary Helsinki Committees result in the rejection rate of 90%. Ambiguity and high costs are deterring factors for companies requesting approvals, particularly immature companies whose economic sustainability depends on the successful achievement of milestones.
- Regional Helsinki Committees must be founded and a national committee should be considered.
- Obligations of the originating parties of clinical trials must be defined properly as should instruments of enforcement.
- Due to the public support provided to academic institutions, it is advisable that ethics committees will evaluate not only the right of participants in trials but also the overall goals of research and ethical social repercussions.
- In addition to particular ethics committees, a national, inter-institutional, academic ethics committee should be founded, to help standardize research customs at large and genetic research in particular.
- A national authority, similar to the FDA, is required to orderly regulate clinical and genetic trials. This authority would serve as a professional and ethical advisory body to legislation and government while also acting as a licensing authority for genetic clinics.
- Public bioethics committees should be founded, representing commercial companies, practitioners, academics, philosophers, and legal experts.

Appendix II

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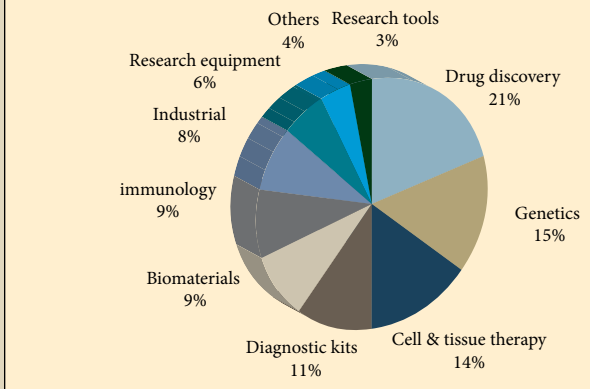
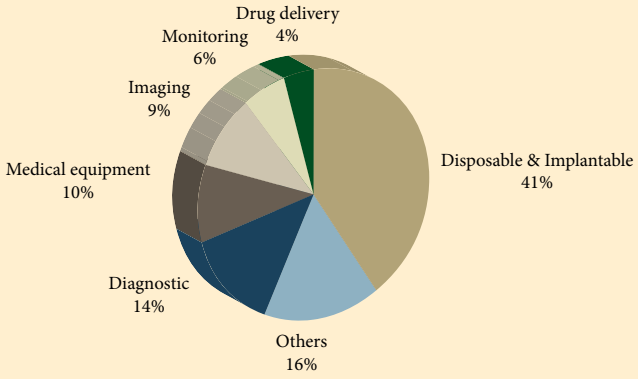
Appendix III

Distribution of Israeli companies according to subsectors

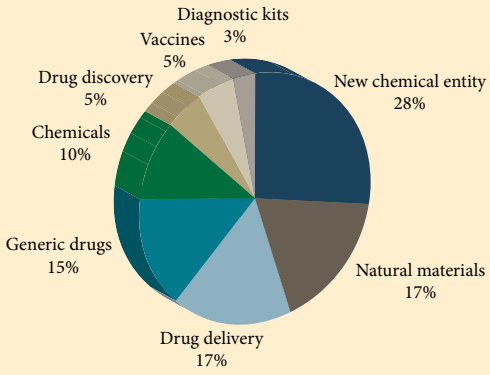
Israel's Biotech Companies



Israel's Pharma Companies



Israel's Medical Device Companies



Source: ILSI database, 2006-7

Appendix IV

Publicly traded Biomed companies – Financial profile

Name	Index	Annual Return 2007* (%)	Yield YTD 2008** (%)	Market Cap** (M NIS)	Company descirption
Given Imaging ***	TA75, TA100, Tel-Tech 15	12.6	-37	1668.3	Develops, manufactures, and markets imaging systems, including wireless capsule endoscopy, to diagnose gastrointestinal diseases
Clal Biotechnology Industries (CBI)	Tel-Tech	-34.4	-4.1	535.9	Invests in life science companies, including CompuGen and BioCancell
Shamir Optical Industry ***	Mid Cap-120, Tel-Tech	6.6	-36.2	392.5	Develops, manufactures, and markets multifocal lenses
Kamada	Mid-Cap 50, Mid Cap-120, Tel-Tech	58.9	-18.5	344.3	Develops, manufactures, and markets biopharmaceutical therapeutics
XTL Biopharmaceuticals ***	Mid Cap-120, Tel-Tech	-12.6	18.2	248.4	Develops, manufactures, and markets therapeutics for the treatment of diabetic neuropathic pain and HCV
Compugen ***	Tel-Tech	-34.9	19.6	211.0	Engages in research and discovery of therapeutics and diagnostic products as well collaborations through which these can be developed into FDA approved products
BioLineRx	Mid-Cap 50, Mid Cap-120, Tel-Tech	-34.7	-19.9	196.3	Develops therapeutics for the treatments a various diseases
InterCure	Tel-Tech	-22.8	-5.5	167.3	Develops and markets medical devices for home-use treatment of high blood pressure and mental stress

Appendix IV (continued)

Publicly traded Biomed companies – Financial profile

Name	Index	Annual Return 2007* (%)	Yield YTD 2008** (%)	Market Cap** (M NIS)	Company descirption
Brainsway	Tel-Tech	16.8	70	158.3	Engaged in research and development of medical devices for the treatment of neurological and psychopathological disorders
BioMedix	Mid Cap-120, Tel-Tech	-1.4	-35.4	144.3	Invests in life science companies through a technological incubator
Mazor Surgical Technologies	Tel-Tech	7.7	3.7	139.7	Develops, manufactures, and markets surgical devices
LifeWave	Mid-Cap 50, Mid Cap-120, Tel-Tech	101.4	-31.6	135.5	Develops, manufactures, and markets medical devices for the treatment of chronic wounds
Can-Fite BioPharma	Mid Cap-120, Tel-Tech	-32.8	-1.9	132.0	Develops drugs for autoimmune diseases and cancer
Medigus	Tel-Tech	-21.4	-6.8	103.1	Engages in research and development of endoscopic devices for the treatment of gastronomical disorders
Exalenz Bioscience (BreatID)	Mid Cap-120, Tel-Tech	45.5	-35.2	99.3	Develops and markets medical devices for the diagnosis and treatment of liver and gastronomical disorders
NasVax	Mid Cap-120, Tel-Tech	14.4	-36.8	97.7	Engages in research and development of intranasal vaccination technologies
D. Medical Industries	Tel-Tech	111.2	-26.2	90.1	Engages in the development of products used to treat diabetes
Itamar Medical	Tel-Tech	-14.3	-9.9	83.1	Develops and markets non-invasive medical devices and software for treatment of sleep and cardiology related disorders

Name	Index	Annual Return 2007* (%)	Yield YTD 2008** (%)	Market Cap** (M NIS)	Company descirption
Evogene	Tel-Tech	-12	0.8	82.3	Engages in research and development of biotechnologically improved plant traits
Biocell	Mid Cap-120 Index, Tel-Tech	-48.1	-35.1	80.4	Owner of Protalix, developer of pharmaceuticals based on plant cell culture technology
Hadasit Bio-Holdings	Tel-Tech	-21.9	-43.9	49.3	Invests in medicinal and biotechnological research and development companies
Applisonix		-14.7	12.5	48.2	Develops long term hair removal devices
Bio-Light Life Sciences Investments	Tel-Tech	-61.1	-22.9	47.6	Invests in pharmaceutical and medical device companies
TopSpin Medical	Tel-Tech	-52.5	-29.4	44.7	developed cardiology imagining
Capital Point	Tel-Tech	-24.2	-33.3	44.5	Owner of technological incubators investing in biotechnology and medical device companies
BioCancell Therapeutics		-3.7	-23.2	37.4	Foreign company engaged in the development of pharmaceutical treatment for cancer
Medical Compression Systems (DBN)		-44.4	-6.7	36.6	Develops, manufactures, and markets a medical device aimed to improve blood flow
Micro Medic		147.9	-41.2	33.7	Invests in diagnostic and therapeutic research companies
Sialo Technology		-17.9	-42	29.6	Engages in research and development of endoscopic pulverization of human salivary gland stones

Appendix IV (continued)

Publicly traded Biomed companies – Financial profile

Name	Index	Annual Return 2007* (%)	Yield YTD 2008** (%)	Market Cap** (M NIS)	Company descirption
ITGI Medical		-24	-38.7	27.2	Develops stents and products for vascular applications
BSP Biological Signal Processing		1	-21.6	23.6	Engages in research and development of cardiac diagnostic devices
Procognia		-63.1	-46.2	16.6	Engages in research, development, manufacture, and marketing of technological products to biological and life science pharmaceuticals
BioView		-15.8	-36.6	16.3	Develops, manufactures, and markets computerized imaging systems
Elutex		-50.3	-23.2	16.2	Engages in research and development of medicinal coatings for implantable medical devices
BiondVax Pharmaceuticals		-78.7	3.5	14.1	Develops vaccines for multi-season flu and Avian influenza
WideMed		-60.7	-33.9	12.2	Develops signal processing algorithms for computerized biomedical signal analysis applied in clinical information systems
T.R.D Instrum.		-45.7	-4.1	5.5	Develops, manufactures, and markets dental medical devices
			Total Market Cap:	**5613.3**	

*** True to 12/23/2007;**

**** True to 03/27/2008;**

***** Dual listed company**

Index	2007*	2008**
TA100	24.80%	-17.64%
Mid-Cap 50	0.40%	-19.22%
Mid Cap-120	2.10%	-19.40%
Tel-Tech	-1.90%	-27.57%

Appendix V

Post IPO returns of biomed companies in TASE

Company	IPO date/ first trading day	Post IPO returns* (%)	Capital listed for trading in IPO (M NIS)	Capital listed for trading** (M NIS)	Market cap** (M NIS)	Market maker
Kamada	8/31/2005	115.31%	6.41	11.27	332.8	Excellence
Can-Fite BioPharma	10/6/2005	-40.70%	128.87	192.11	146.39	Prisma
TopSpin Medical	9/6/2005	-60.70%	158.84	186.23	50.28	Prisma
NasVax	12/26/2005	-4.49%	26.71	30.9	123.58	Harel
Bio-Light Life Sciences Investments	12/27/2005	-40.41%	28.9	50.1	58.82	Prisma
BioView	3/7/2006	-65.16%	8.67	8.78	21.47	Prisma
Medigus	3/12/2006	-35.85%	56.64	57.1	124.54	*
T.R.D Instrum.	4/17/2006	-90.56%	12.91	12.91	5.42	*
Medical Compression Systems (DBN)	5/16/2006	-56.33%	8.61	12.78	45.79	*
BSP Biological Signal Processing	5/18/2006	-60.09%	9.91	10.4	58.64	Excellence
Capital Point	6/4/2006	-64.54%	7.17	7.58	45.48	Excellence
BioCancell Therapeutics	8/17/2006	-32.04%	11.17	12.4	43.28	Prisma
WideMed	12/7/2006	-77.57%	10.9	11.03	12.62	Prisma
LifeWave	12/13/2006	6.48%	11.37	12.01	151.94	Clal betucha
Hadasit Bio-Holdings	9/1/2006	-42.52%	15	19.41	60.16	Excellence
Brainsway	1/4/2007	64.65%	35.13	35.13	157.71	Clal betucha
Applisonix	1/29/2007	-2.68%	13.47	13.53	51.04	Prisma
BioLineRx	2/11/2007	-57.31%	61.37	62.5	177.45	Prisma
Elutex	2/13/2007	-54.79%	18.49	18.8	21.38	Clal betucha
Clal Biotechnology Industries (CBI)	3/6/2007	-37.31%	86.01	86.01	565.09	Prisma
				Total market cap:	**2,253.9**	

* Calculated from closing price at fist trading day to 3/9/08

** True to 3/9/08

Works Consulted

This report is based on the Financial Innovations Lab and workgroups that have assembled over the past six months as well as previous reports.

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