INNOVATIVE PHARMACEUTICAL INDUSTRY IN ISRAEL

AS A GROWTH ENGINE FOR HEALTHCARE, RESEARCH AND INNOVATION 2021





MESSAGE FROM PHARMA ISRAEL'S CHAIRMAN



Last year, the world began dealing with the outbreak of the Covid-19 virus, which created global challenges and affected every aspect of our lives. This battle, which is not yet over, made us all understand that public health is the base for living a normal life in our country and throughout the world.

Immediately upon the outbreak of the virus and its global impact, pharma companies began working tirelessly to develop dozens of technologies and solutions enabling the diagnosis, treatment and prevention of the spread of Covid-19. The pharma industry developed solutions at record speeds and invested enormous resources in order to provide the public with tools to fight the virus, while closely cooperating with the authorities and

with the various pharma companies.

Here in Israel, for the time being, we can say that our rapid adoption of new technologies enabled us to fully resume our normal lives, as well as commercial and social activities.

As we present in this booklet, the pharmaceutical industry's impact on the Israeli economy and society is enormous. Its ability to make innovative therapies available to the public has a direct impact on citizens' quality of life, life expectancy and enables the complete eradication of particular diseases.

Furthermore, multinational pharmaceutical companies make substantial investments in Israeli companies, conduct clinical research, support the healthcare system and provide compassionate use treatments to patients in Israel - all while creating thousands of diverse, high-quality jobs that, among other things, enable us to retain experts in Israel with advanced degrees in the life sciences.

The innovative drug industry is a world leader in innovation with the highest ratio of investment in research and development, ahead of the computer and software industries and other advanced industries. Integrating this industry's high capabilities in the innovation-based Israeli economy creates significant development opportunities for the local business environment, while integrating advanced technologies in the Israeli healthcare system.

As a rule, in order for pharmaceutical companies' abilities to receive optimal expression, frequent dialogues must be maintained between them and the government ministries and authorities. Dialogues such as these will enable mutual collaboration between the private and public sectors for the benefit of all citizens and for improving the quality of their lives.

I wish for all of us, as citizens of Israel, that we continue to enjoy a high-quality healthcare system that promotes and includes innovative therapies and that constantly strives to improve itself for the benefit of all of us.

Shlomo Mena

Chairman, Pharma Israel Association

MESSAGE FROM PHARMA ISRAEL'S DIRECTOR-GENERAL



This booklet is being published at a time when the State of Israel is striving to return to routine life after enduring a year-long grave health crisis caused by the global outbreak of Covid-19.

The Covid-19 crisis taught us that there is a strong correlation between health and economics. A stable and strong healthcare system is an imperative precondition without which there can be no national resilience. The State of Israel's willingness to adopt advanced medical technologies at record-breaking speed in order to eradicate the pandemic - primarily the Covid-19 vaccine - enabled it to succeed in extricating itself from the deep crisis while many other countries are still struggling.

We are living in the age of innovation and enormous progress in developing new medicines and technologies. The rapid development of vaccines that are effective against Covid-19 exemplifies the innovative pharmaceutical industry's considerable capabilities in providing pharmacotherapy solutions for contending with new or incurable diseases.

Today, there are more than 7,000 new medicines at various stages of research and development around the world, a large ratio of which are personalized medicines and targeted therapies designed to deal with complex medical conditions. Concurrently, we are witnessing enormous investments in startup companies engaging in the life sciences, some of which are led by high-tech industry executives who consider this field a primary generator of change in the modern world.

Developing a new medicine is a long, complex and highly expensive process. It requires the industry and the healthcare authorities to join forces from the earliest stages of research and development and until the medicine is registered and approved for use, in order to guarantee quality, efficacy and safety. Many countries around the world have succeeded in turning the life sciences into a major growth engine, by creating an advanced regulatory environment that encourages investments and supports innovation. The Covid-19 crisis and the way that the State of Israel contended against it have created an unprecedented opportunity to turn the life sciences into a major growth engine in Israel too.

The extensive presence of multinational innovative pharmaceutical companies in Israel, which are members of the Pharma Israel association, is the foundation for positioning Israel as a preferred location for advancing medical innovation. The challenge shared by the companies and the Israeli government is to invest the resources needed to jointly design a national plan for leveraging the unique advantages existing in Israel in order to advance clinical research activities, deepen the cooperative efforts between the public healthcare system and the pharmaceutical industry, and also with the hope of creating research, development and manufacturing centers.

Furthermore, adapting the local regulations to the accepted standards in developed countries will enable the State of Israel to take an active part in international initiatives designed to make innovative therapies available through rapid and efficient registration processes.

Finally, and most importantly: staying healthy is the key. As we show in this booklet, the life sciences industry, headed by the pharmaceutical companies, provides us with hope for healthier and better lives. If the private and public sectors - the business community and government ministries - join forces to expand this industry's activities in Israel, we will be able to advance Israel's society and economy for the benefit of us all.

Efrat Cohen

Director-General, Pharma Israel

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EXECUTIVE SUMMARY

The objective of the innovative pharmaceutical industry (ethical drugs), which is one of the largest and leading industries at a global scale, is to develop innovative, lifesaving medicines, vaccines and therapies that improve the quality of life of millions of patients worldwide.

Companies in this industry invest enormous resources in research and development, are at the vanguard of scientific discoveries in the field of medicine and play a major role in contending with the challenges of morbidity in countries throughout the world.

The innovative pharmaceutical industry also constitutes a global economic growth engine and a leading force in medical innovation and development in the life sciences.

The innovative pharmaceutical industry has a significant presence in Israel, which has been steadily expanding in recent decades upon the entry of new multinational innovative pharmaceutical companies into Israel and the expansion of the activities of existing companies. This presence enables Israel's citizens to benefit from better health thanks to rapid access to innovative and effective pharmacotherapies, contributes to improving the standards of the medical services being provided, of education and of advancing research infrastructures, and particularly, of widescale clinical trials.

Additionally, these companies make medicines available every year that save lives and improve quality of life within the framework of the national healthcare services basket and outside that framework through compassionate treatments and participation in clinical trials. In addition to contributing to the health of Israel's citizens, these companies also provide benefits to the economy, including: diverse, high-quality employment, positioning Israel as a major hub for medical innovation and advancing and supporting startups and other entities in the healthcare, medicine and life sciences ecosystem in Israel.

The purpose of this report is to present the impact of international innovative pharmaceutical companies' presence in Israel on the Israeli economy in a wide variety of aspects.

This report is based on a comprehensive and in-depth research study - the first of its kind in Israel - conducted by the Pharma Israel association, its member companies and TASC Consulting & Capital.

This study included a comprehensive review of a variety of public sources of international and local information, interviews with industry leaders and the collection of data from the multinational innovative pharmaceutical companies operating in Israel that have not yet been publicized.

In addition to the current impact of these companies and their activities in Israel, this report also includes a review of anticipated trends worldwide and in Israel, and recommendations to the various policy-setters for continuing to realize and leverage the inherent potential offered by multinational pharmaceutical companies' presence in Israel.



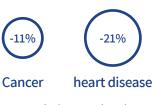
THE GLOBAL INNOVATIVE PHARMACEUTICAL INDUSTRY -KEY FIGURES

Research and development of a new medicine



The innovative pharmaceutical industry's contribution to public health on a global scale

% drop in global mortality rate



over the last two decades

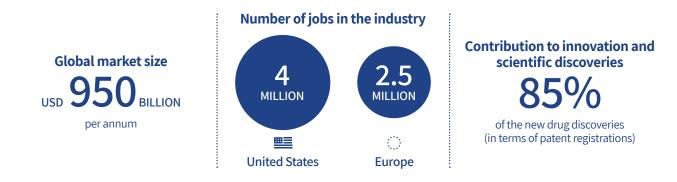


Vaccines for chicken pox, measles, whooping cough and other diseases, USA data

% improvement in work productivity

after taking original drugs in the USA, 2013-2015

The innovative pharmaceutical industry's contribution to the global economy



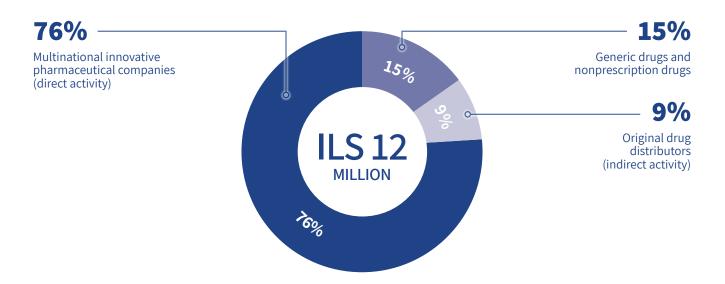
Source: TASC analysis based on sources 1-19; see bibliography.



MULTINATIONAL INNOVATIVE PHARMACEUTICAL COMPANIES: IMPACT ON HEALTH, THE ECONOMY AND INNOVATION IN ISRAEL

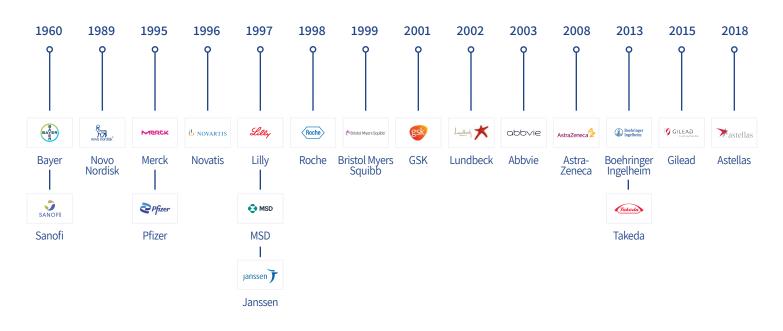
The industry in Israel and its volumes of activity

Size of the drug market in Israel in 2019, in ILS billions



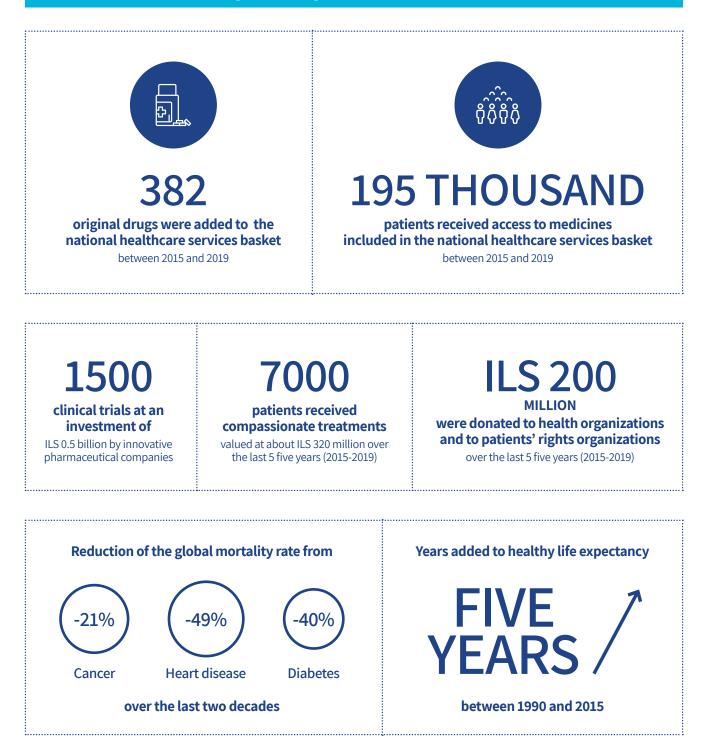
Source: TASC assessment, based on sales data (major healthcare players' expenditures on medicines in 2019) and their validation by the Ministry of Health and by industry leaders.

Multinational innovative pharmaceutical companies that established direct operations in Israel, by year



MULTINATIONAL INNOVATIVE PHARMACEUTICAL COMPANIES: IMPACT ON HEALTH, THE ECONOMY AND INNOVATION IN ISRAEL

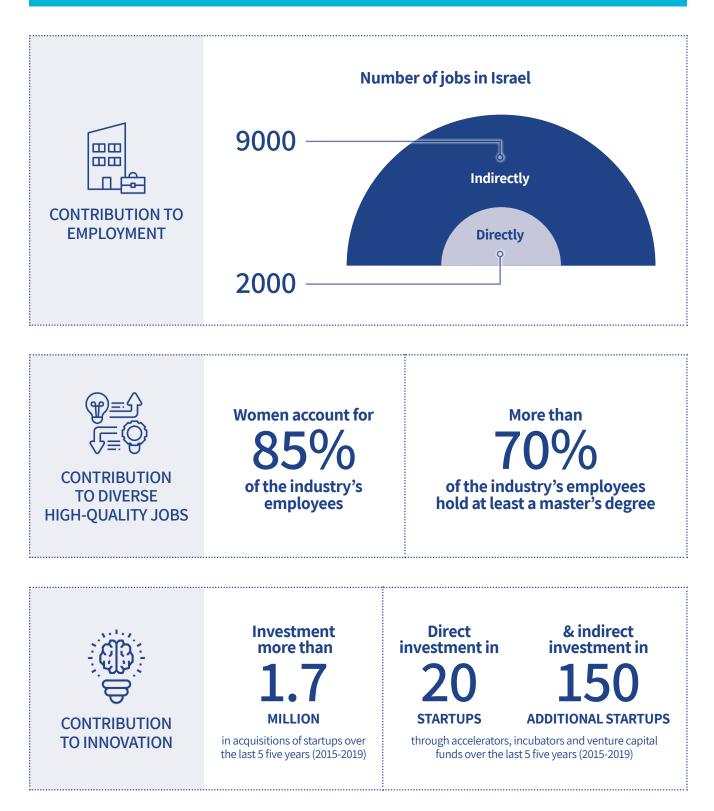
The contribution of original drugs to public health

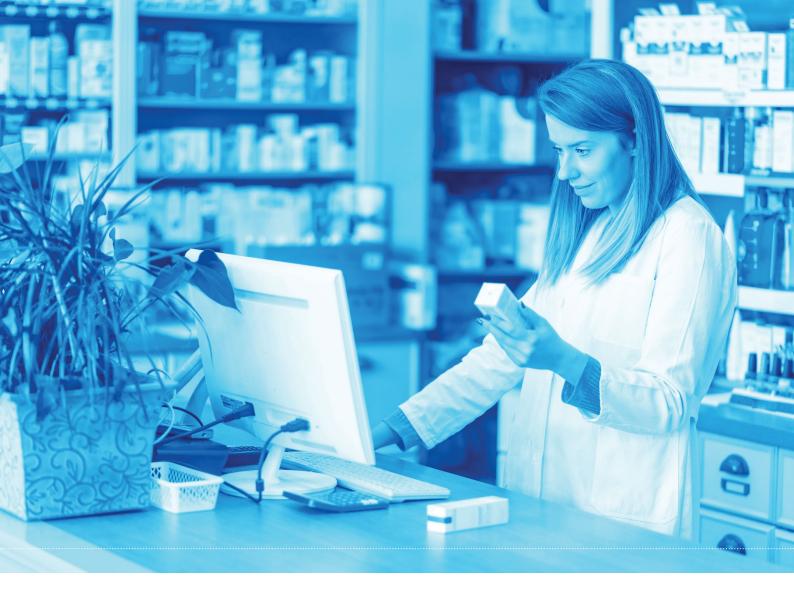


Source: TASC and Pharma Israel analysis, based on sources 20-51; see bibliography.

MULTINATIONAL INNOVATIVE PHARMACEUTICAL COMPANIES: IMPACT ON HEALTH, THE ECONOMY AND INNOVATION IN ISRAEL

The contribution of original drugs to the economy and innovation





THE GLOBAL INNOVATIVE PHARMACEUTICAL INDUSTRY

The innovative pharmaceutical industry is one of the largest and most meaningful industries in the world - it's an innovation leader that has a direct impact on the lives of millions of patients worldwide. The industry's goal is to develop medicines, vaccines and technologies to cure and prevent diseases by investing enormous resources in research and development, while closely collaborating with the scientific and medical communities and with the leading healthcare authorities. Furthermore, considering the volume of activity and the focus on innovation and on research and development processes, this industry serves as an economic growth engine in many countries and provides high-quality employment opportunities to millions of people in direct and indirect employment spheres.

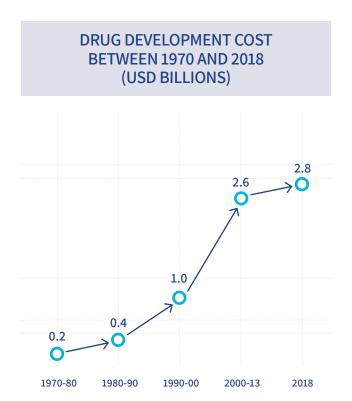
COMPLEXITY OF THE R&D PROCESS FOR A NEW DRUG -FROM THE LABORATORY TO THE PATIENT

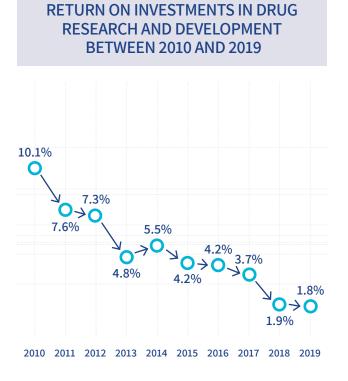
RESEARCH AND DEVELOPMENT OF AN ORIGINAL DRUG IS A MULTI-YEAR PROCESS COMPRISED OF SEVERAL KEY STAGES. BILLIONS OF DOLLARS ARE INVESTED IN EVERY NEW DRUG

An original drug is a new drug developed after a long and complex research and development process. An original drug is patent-protected for 20 years, usually as of the application submission date, but effectively, for the most part, at issue is market exclusivity for only 5 to 12 years.¹ When the patent expires, any pharmaceutical company may manufacture a competing generic drug containing the same active ingredient as that of the original drug.

During the research and development of a new drug, the innovative pharmaceutical companies take action to ensure that every drug approved for use by the health authorities and marketed will comply with the highest and most stringent standards of efficacy, safety and quality. Due to the increasing complexities involved in developing new drugs, which include, inter alia, the tightening of the regulatory requirements and of meticulous quality control, the overall cost of developing a new drug has nearly tripled within only about two decades - from about USD 1 billion in the early 2000s² to about USD 2.8 billion in 2018.³

At the same time, the ROI (return on the investment) in R&D has been dropping steadily over the last decade - from an average 10% in 2010 to only about 2% in 2019.⁴



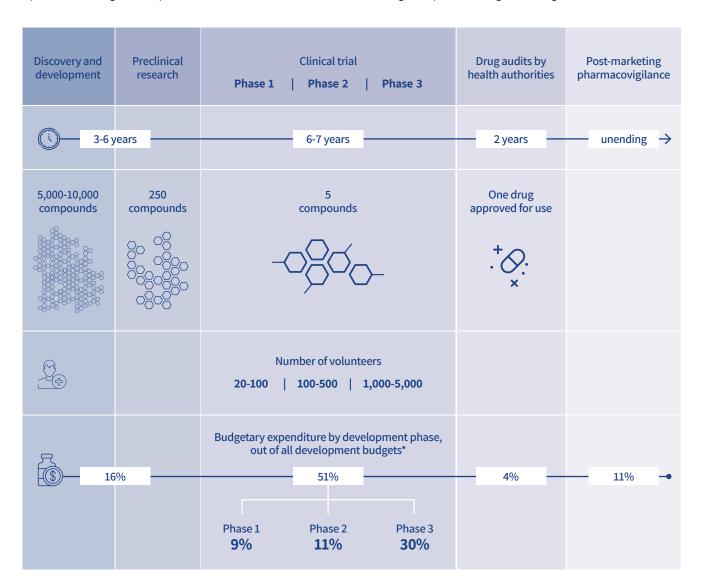


Source: Neil Lesser & Sonal Shah, 2019

Source: DiMasi et al., 2016; Wouters et al., 2020

The various stages in the research and development process

The original drug research and development process is comprised of five key stages: from discovering the drug from among a huge number of molecules, the initial development and the preclinical stages, through the clinical trial stage (which largely include three phases, phases 1, 2 and 3), through the regulatory stage of registration of the drug and approving it for marketing, up to the last stage subsequent to the launch and distribution of the drug - the pharmacovigilance stage.



* About 18% of the total budgetary expenditures during the development stages do not fall under one of the stages.

STAGE 1 - DISCOVERY AND INITIAL DEVELOPMENT

During the initial stage, thousands of molecules are identified and examined that may serve as a foundation for developing the new drug.

During this stage, an average of 5,000 different molecules will be analyzed and only about 250 molecules will proceed to a preclinical stage.⁵

STAGE 2 - PRECLINICAL STAGE

The purpose of this stage is to perform a preliminary analysis of the drug's safety and efficacy, before any clinical trials begin. This stage accounts for about 16% of the overall cost of developing a new drug.⁶

STAGE 3 - CLINICAL TRIALS STAGE

This is the longest and most expensive stage in the research and development process, which also entails considerable uncertainties - this stage continues on average for about six to seven years,⁷ the cost of this stage accounts for about 50% of the overall cost⁶ and the success rates during this stage are very low and reach only about 7%.⁷

Clinical trials are conducted at different medical centers throughout the world with volunteers with differing characteristics participating in them in order to ascertain the drug's efficacy, safety and quality in a wide variety of populations.

Clinical trials are largely comprised of three phases:

Phase 1: During this phase, the drug's safety and optimal dosage regimens are analyzed. This analysis is performed by administering the drug to dozens of usually healthy volunteers.

Phase 2: During this phase, the drug's efficacy and side effects are analyzed. The drug is administered to hundreds of volunteers who have the disease that the drug is intended to treat.

Phase 3: During this phase, the drug's efficacy, quality and safety are extensively analyzed on a diverse population sampling.

STAGE 4 - REGULATORY STAGE

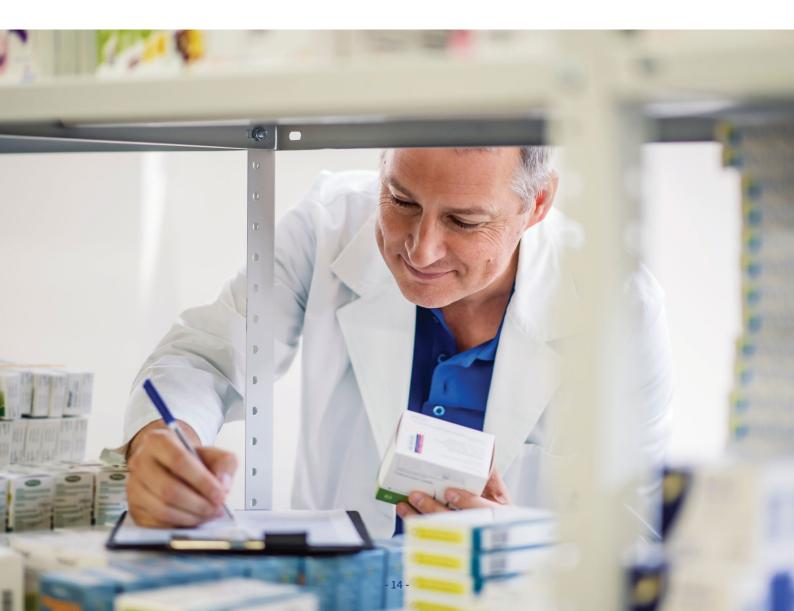
Upon completing the clinical trials, the drug is submitted for regulatory approval by the health authorities (such as the FDA in the United States, the EMA in Europe, etc.) for registration of the drug and for approving the drug for marketing.

This process may take between six months and two years depending upon the regulatory requirements and the authorities' workload.

At the end of this stage, the drug may be marketed in countries where the drug was approved for use.⁷

STAGE 5 - PHARMACOVIGILANCE STAGE

For years after the drug is marketed, the companies continue monitoring the drug's safety and efficacy for patients being treated with it, inter alia, by monitoring these patients and through side effects reports from the medical community.



ORIGINAL DRUGS' CONTRIBUTION TO BETTER PUBLIC HEALTH

THE DEVELOPMENT OF THE INNOVATIVE PHARMACEUTICAL INDUSTRY OVER DECADES HAS LED TO BREAKTHROUGHS IN GLOBAL MEDICINE AND TO THE ERADICATION OF PREVIOUSLY INCURABLE DISEASES. ORIGINAL DRUGS PROVIDE THERAPEUTIC SOLUTIONS FOR SEVERE DISEASES AND ALLEVIATE THE SUFFERING OF MILLIONS OF PATIENTS AND HAVE LED TO A STEADY RISE IN QUALITY OF LIFE AND LIFE EXPECTANCY

Original drugs have helped to significantly lower the global mortality rate from deadly diseases over recent decades.

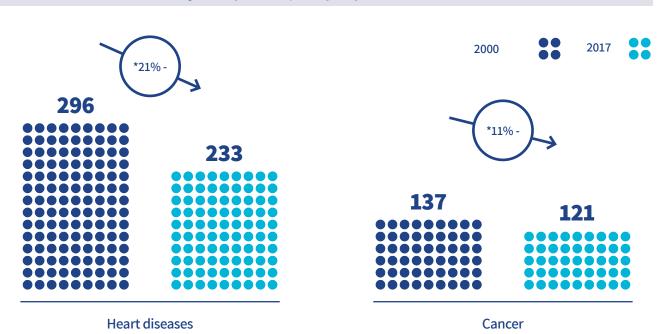
For example, the mortality rates from cancer and heart diseases - two of the deadliest causes of morbidity - have significantly dropped over recent decades. The global mortality rate from cancer decreased by about 11% since the early 2000s,⁸ and innovative therapies, including with original drugs, contributed to about 73% of the total decrease in the mortality rate.⁹

Similarly, original drugs have helped to significantly reduce the mortality rate from heart diseases, which has dropped by about 21% since the early 2000s.

Coupled with the dramatic drop in the mortality rates from severe diseases, original drugs have helped extend life and improve the quality of life of millions of patients over the years. Innovative drugs launched over recent decades enable patients with previously incurable severe and complex diseases to receive regular treatments that significantly improve their conditions and extend their life expectancy. Accordingly, deadly diseases have gradually become chronic diseases that people can continue living with over many years.

For example, the pharmacotherapy developed for AIDS (HIV) enables many patients - for whom contracting this disease used to be a death sentence - to live for many years with the virus as a chronic illness. Accordingly, the number of people who died from AIDS in Europe has dropped by 66% between 2009 and 2018.

Another example is the development of drugs for Hepatitis C, which resulted in a significant increase in patients' cure rate, from 40% to about 95% over the last two decades. Additionally, a patient's average duration of treatment has been significantly shortened from about 48 weeks to only about 12 weeks.⁹



Decrease in the mortality rate per 100,000 people from 2000 to 2017

* Average annual percentile change

Source: Our World in Data, 2019

Innovative pharmaceutical companies are also at the vanguard of the research and development of vaccines enabling the full eradication of severe diseases and lower mortality, as well as significant savings in costs to healthcare systems.¹⁰ In developed countries, such as the United States, pediatric immunizations have enabled the nearly complete eradication of diseases that had affected extensive populations and had overloaded the healthcare system, such as chicken pox, measles, whooping cough and polio.

Additionally, the development of a vaccine against the papilloma virus has prevented the deaths of young women from cervical cancer, which develops after contracting the virus. For example, the UK began immunizing young women against the papilloma virus in 2008 and succeeded in reducing the spread of the disease among young women from a ratio of about 15% to nearly complete eradication of the virus in 2020.¹¹

Decrease in morbidity in the United States as a result of the development of vaccines against various diseases

Disease	Reported incidents of morbidity during the year prior to the development of the vaccine	Reported incidents of morbidity in the US after the vaccine was developed (in 2017)	Decrease
Chicken pox	4,085,120	102,128	- 98%
Measles	530,217	120	- >99%
Whooping cough	200,752	18,975	- 91%
Mumps	162,344	6,109	- 96%
Hepatitis A	117,333	4,000	- 97%
Smallpox	29,005	0	- 100%
Polio	16,316	0	- 100%

Source: Centers for Disease Control and Prevention, 2019



ORIGINAL DRUGS SIGNIFICANTLY IMPROVE PATIENTS' MEDICAL CONDITION FOR A WIDE VARIETY OF DISEASES, WHICH RESULTS IN HIGHER WORK PRODUCTIVITY IN THE ECONOMY

Original drugs currently provide solutions for patients with complex diseases and can extend life expectancy and improve quality of life, inter alia, by alleviating the symptoms of the diseases. As a result, many patients are able to return to the workforce and resume normative independent lifestyles.

A study performed in 2016,¹² quantified the improvement in various functional characteristics having a major impact on the quality of life of patients with complex diseases, such as cancer, AIDS, multiple sclerosis and other diseases. The study found that innovative medical therapies, including with original drugs, contributed to improving the quality of life of millions of patients in the United States between 2000 and 2012.

For example, up until a decade ago, patients with arthritis received medical treatment only during the late stages of the disease, after irreversible damage had already been caused to joints. As a result, arthritis patients endured years of impaired daily functioning, pain and suffering and challenges in social functioning - even after receiving the optimal treatment.

The development of new original drugs has enabled a solution to be provided to these patients already at the early stages of the disease while preventing damage to joints and consequential secondary injuries, which results in dramatic improvement in their quality of life.

Concurrently, original drugs have contributed to increasing the work productivity of patients with chronic diseases as a result of significant improvement in their medical condition. **Original drugs have contributed to an average 30% increase in work productivity,** in terms of number of workdays and work output.¹

THE MEDICAL BENEFITS THAT ORIGINAL DRUGS PROVIDE ARE REDUCING THE EXPENDITURE ON HEALTHCARE AND ARE EASING THE BURDEN ON HEALTHCARE SYSTEMS THANKS TO THE DOWNTREND IN THE HOSPITALIZATION AND TREATMENT RATES

Patients with severe and chronic diseases who adhere to their treatment regimen with original drugs contributes to their requiring fewer healthcare services, because these original drugs prevent their conditions from deteriorating to the point of hospitalization, mitigate the life-threatening symptoms and reduce the complexities of hospitalizations.¹⁴

Original drugs contribute to easing the burden on the healthcare systems, which are suffering from shortages of resources coupled with a significant rise in their volumes of expenses over the years. Within this context, it should be noted that although original drugs account for only about 16%¹⁵ of the national expenditure on healthcare in OECD member states, they provide major benefits and potential cutbacks in expenses on consumption of healthcare services.



THE INNOVATIVE PHARMACEUTICAL INDUSTRY AS A GLOBAL ECONOMIC GROWTH ENGINE

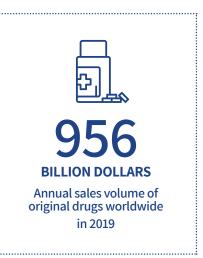
THE INNOVATIVE PHARMACEUTICAL INDUSTRY CONTRIBUTES TO ECONOMIC GROWTH IN MANY COUNTRIES WORLDWIDE AND LEADS IN THE LEVEL OF INNOVATION, IN SCIENTIFIC DISCOVERIES AND IN THE VOLUME OF INVESTMENTS IN RESEARCH AND DEVELOPMENT COMPARED TO COMPARABLE MEGA INDUSTRIES

The innovative pharmaceutical industry is one of the world's largest industries with an annual sales volume totalling about USD 950 billion (2019 data).¹⁶

The innovative pharmaceutical industry's volume of investments in research and development constitute about 15% of its total revenues - i.e., about USD 150 billion per annum. These investments have increased over the last two decades by an average of 5% per annum.⁶

The ratio of investment in research and development out of the total revenues in the innovative pharmaceutical industry is unprecedently higher than that of other advanced industries that are considered innovation leaders - 15% in the innovative pharmaceutical industry compared to only about 11% in the software and computer industries.⁶

Pharmaceutical companies' investments in research and development are demonstrated by the multitude of scientific discoveries and by the fact that innovative pharmaceutical companies are responsible for about 85% of the patents for drug discoveries.¹⁷



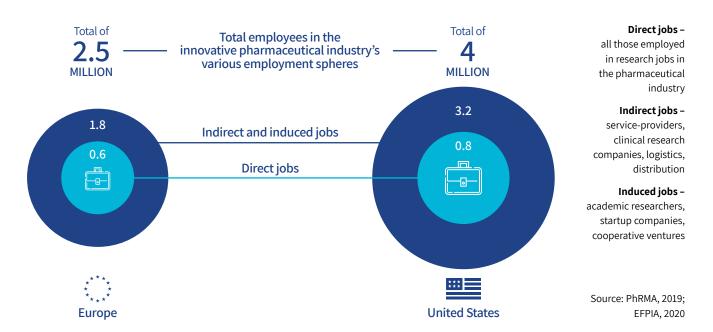
Ratio of R&D investments to total sales in 2019, by sector

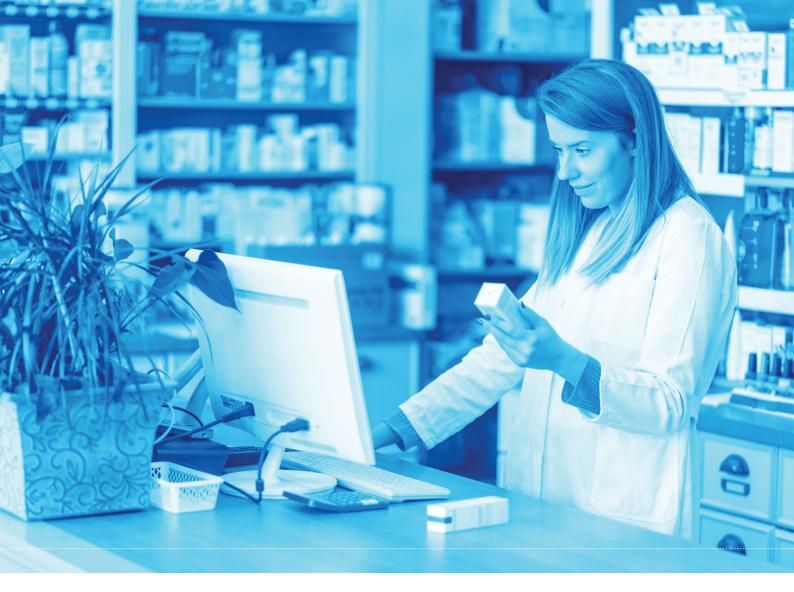
15.4%		Pharma and biotechnology
1	10.8%	Software and computer services
	8.4%	Computer hardware
	5.6%	Consumer goods
	4.9%	Electronic equipment
	4.5%	Automobiles and parts
	4%	Aerospace and defense
	4% 8888888	888 Average of all sectors
Source: EFPIA, 2020	3.7%	Healthcare equipment and services

THE INNOVATIVE PHARMACEUTICAL INDUSTRY PROVIDES EMPLOYMENT OPPORTUNITIES TO MILLIONS OF PEOPLE WORLDWIDE, PARTICULARLY HIGH-QUALITY JOBS FOR GRADUATES WITH ADVANCED DEGREES

The innovative pharmaceutical industry directly employs about 1.5 million people in Europe and in the United States and, in total, indirectly employs more than 6 million people.¹⁸⁶¹⁹ These data reflect a partial picture of the global volume of employment, since these companies also have a major presence in Asian countries (particularly in Japan), in Australia and in other countries in the Americas. Since the innovative pharmaceutical industry is based on research and development, it needs highly skilled employees with special qualifications. The industry provides hundreds of thousands of relatively high-paying jobs to people with advanced college degrees and enables the continued establishment and development of the scientific community and of global knowledge assets.

Number of employees directly and indirectly employed in the pharma industry in the United States and in Europe (in millions)







MULTINATIONAL INNOVATIVE PHARMACEUTICAL COMPANIES' ACTIVITIES IN ISRAEL AND THEIR CONTRIBUTION TO PUBLIC HEALTH

The innovative pharmaceutical industry has a major presence in Israel, which is reflected in the direct operations of 19 multinational innovative pharmaceutical companies in Israel. Just like in the global arena, the companies' presence in Israel also has a major impact on the advancement of medicine and public health. Furthermore, the innovative pharmaceutical companies in Israel are acting as an important growth engine for Israel's economy by encouraging innovation and investments, by adopting international standards, by creating opportunities for people to enjoy high-quality employment and by collaborating with local technology companies.

THE INNOVATIVE PHARMACEUTICAL INDUSTRY IN ISRAEL AND ITS VOLUME OF ACTIVITIES

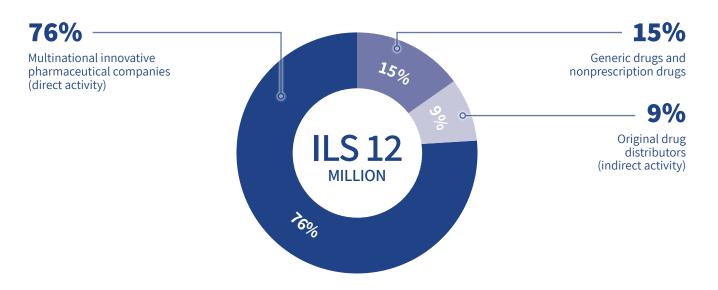
The innovative pharmaceutical industry is part of the life sciences sector, which has become one of the most important sectors in the Israeli economy in recent years and a center of attraction for foreign and local investments, with more than 1,600 active companies and more than 80,000 employees.³⁶

The pharmaceutical industry is contributing substantially to the development of this sector, alongside the medical device, information technologies, diagnostics and biological development sectors.

The pharmaceuticals market in Israel is estimated at about ILS 12 billion per annum,³⁷ with the volume of sales of original drugs accounting for about 85% of the market.

The majority of the innovative pharmaceutical industry's activities in Israel is carried out directly through the multinational companies' local subsidiaries, and indirectly through other companies via distributors. The direct activities are estimated as accounting for about 90% of the market, while the indirect activities account for the remaining 10%. Accordingly, the market size of the multinational innovative pharmaceutical companies operating directly in Israel is assessed at about ILS 9 billion.³⁷

Size of the drug market in Israel in 2019, in ILS billions



Source: TASC assessment, based on sales data (major healthcare players' expenditures on medicines in 2019) and their validation by the Ministry of Health and by industry leaders.

The multinational innovative pharmaceutical companies' direct activities in Israel have been steadily expanding over recent decades. Currently, 19 multinational pharma companies are directly operating in Israel, which have established local companies and have united under "Pharma Israel" - the association of R&D-based pharmaceutical companies.

As elaborated later on in this section, the companies' direct activities create major advantages for public health.

The very presence of a multinational company's representative office in Israel reflects the international headquarters' deep commitment to the local market, facilitates rapid, ongoing information flows and decision-making flexibility and uses various mechanisms to make innovative medicines rapidly and extensively available to the public in Israel. Their local presence also creates close relations between the multinational companies and the medical and scientific communities in Israel, with the joint objective of improving the quality of medicine and advancing research activities.

Upon establishing their local activities, the multinational companies have expanded and deepened their activities in Israel over the years.

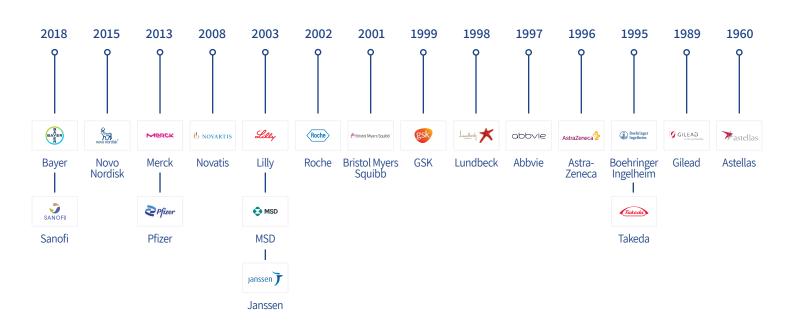
The companies currently hold comprehensive clinical research systems, are partners in technology incubators and sign research and collaboration agreements with HMOs and with research institutions.

They also support fledgling local companies and create collaborative ventures with well-established companies for the purposes of advancing research studies and breakthrough products, such as integrating artificial intelligence in the development efforts based on Israel's extensive capabilities in the digital healthcare arena.

In this way, they are generating considerable contributions to economic development and to leadership in research and innovation.

Notwithstanding the innovative pharmaceutical companies' major contribution to the advancement of healthcare in Israel, the ratio of expenditures on medicines in Israel is relatively low and accounts for about 13% of the total expenditure on healthcare, compared to 16% on average in OECD member states.

It should be noted that the national expenditure on healthcare in Israel is also relatively low (8.8% of the GDP in Israel compared to the average in OECD member states), such that the real expenditure on medicines in Israel is significantly lower than in OECD member states.³⁸



INNOVATIVE PHARMACEUTICAL COMPANIES ENABLE PATIENTS IN ISRAEL TO GAIN ACCESS TO INNOVATIVE MEDICINES

THE PRESENCE OF INNOVATIVE PHARMACEUTICAL COMPANIES IN ISRAEL INCREASES THE SUPPLY OF INNOVATIVE THERAPIES THAT ARE AVAILABLE TO THE PUBLIC THROUGH THE NATIONAL HEALTHCARE BASKET

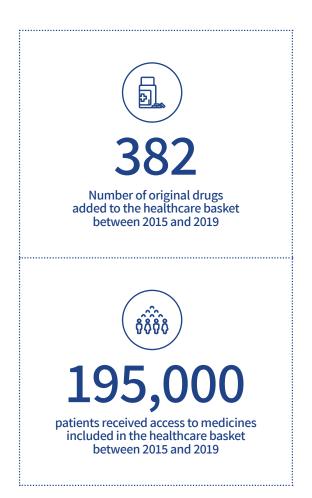
The public health system in Israel operates by virtue of the National Health Insurance Law of 1994. According to this law, all residents of Israel are entitled to a national healthcare services basket, which is updated annually based on the recommendations of a public committee to expand the basket of healthcare services, which is called the National Healthcare Basket Committee.

This committee issues its recommendations to the government about which medicines and technologies out of the variety of available medical technologies should be included in the national healthcare services basket, within the budgetary constraints. This basket mechanism gives Israeli citizens early access to advanced medical technologies with public funding.

The innovative pharmaceutical companies' direct presence in Israel accelerates the inclusion of innovative technologies into the national healthcare services basket.

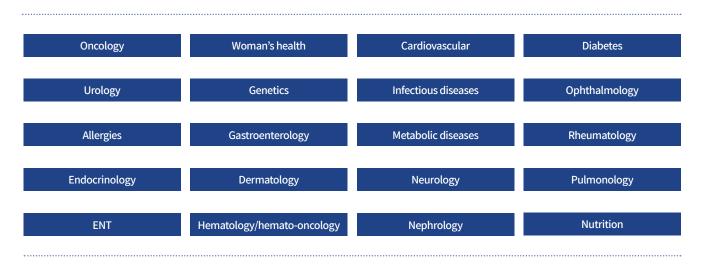
The introduction of new drugs in Israel shortly after they are registered and approved for marketing in the United States and in Europe enables the Israeli public to gain access to innovative therapies months and even years before they are available to patients in other countries.

Over the years, there have been significant increases in the number of patients entitled to medicines within the framework of the national healthcare services basket, in the number of new original drugs and in the variety of therapies for chronic and acute diseases that have been added to the basket. From 2015 to 2019, 382 new original drugs were added, which provided solutions for 195 thousand new patients.⁴⁰





Original drugs currently being provided to the public in Israel through the national healthcare services basket offer innovative solutions for a wide variety of diseases in various spheres of medicine, including:



The variety of therapies available in the national healthcare services basket for severe diseases has also increased over the years, such as the significant increase in the number of oncological therapies and in the number of medicines for rare diseases.⁴⁰

INNOVATIVE PHARMACEUTICAL COMPANIES PROVIDE COMPASSIONATE, LIFE-SAVING TREATMENTS FOR PATIENTS FOR WHOM NO OTHER SOLUTION IS AVAILABLE

Compassionate treatments are provided to patients for whom no treatment exists that is suitable for their illness and when the treating physician believes that it is warranted to try and help them using a new drug that has not yet been registered in Israel or that is registered for a different indication.

The pharmaceutical companies provide these treatments with the authorization of the Ministry of Health and at the request of the medical institution, provided that the drug will be available for the entire course of treatment and that the treating physician performs medical follow-ups. Compassionate treatments are provided only in instances when the treating physician believes that the benefit gained from providing the treatment outweighs the risk involved. The treatment is provided at no cost to the patient and involves the patient signing an informed consent form.

The pharmaceutical companies are not obligated to provide these treatments, and their value has been estimated at from hundreds to thousands of shekels per patient. In this way, life-saving treatments were provided to Covid-19 patients, to cancer patients, to patients with ALS (amyotrophic lateral sclerosis) and more.

From 2015 to 2019, innovative pharmaceutical companies provided compassionate treatments in Israel that helped save the lives of about 7,000 patients, and at the inclusive value of about ILS 320 million.⁴¹



INNOVATIVE PHARMACEUTICAL COMPANIES CONTRIBUTE TO THE ADVANCEMENT OF PUBLIC HEALTH AND TO THE EXPANSION OF RESEARCH ACTIVITIES AND MEDICAL INNOVATION BY CONDUCTING CLINICAL TRIALS

Participating in clinical trials is another way in which patients can receive an innovative medical solution in the absence of any other treatment alternative. Patients participate in clinical trials at no cost to them, provided that they sign an informed consent form. Clinical trials provide many significant advantages to patients:

LAST RESORT TREATMENT

Treatments for medical problems for which no adequate solution exists in the market and that may save patients' lives and significantly extend their lives relative to the existing alternatives.

EARLY ACCESS TO INNOVATIVE EFFECTIVE THERAPIES

Clinical trials are also conducted in relation to diseases for which a solution exists in order to develop more effective medical therapies with fewer side effects than the existing therapies.

For example: cancer patients who participate in clinical trials testing innovative drugs having fewer side effects than the severe side effects accompanying most chemotherapy treatments.

MEDICAL TREATMENT BY LEADING PHYSICIANS

As part of the clinical trials, patients receive access to the top physicians and medical teams, who are globally recognized as experts in their fields, who provide close supervision, optimal treatment and advice to patients about their medical condition, as part of the clinical trial.

MEDICAL TREATMENT AT NO COST

The medical treatments during clinical trials are provided to patients at no cost to them, thereby enabling patients to gain access to life-saving treatments that they could not otherwise afford.



In addition to contributing to public health, the conducting of clinical trials in Israel provides considerable benefits by developing medical knowledge in Israel and boosts the international standing of Israeli medical institutions and physicians.





* The Ministry of Health's report includes only public hospitals and Clalit Healthcare Services. According to conversations with sources in the industry, the volume of clinical trials being conducted in other institutions is assessed at about 30% of the total market. Furthermore, the innovative pharmaceutical companies' ratio of clinical trials out of all clinical trials is 57%.

Source: TASC's assessment, based on the Ministry of Health report (summary of the committee's activities for engagements with commercial companies for 2014-2018), 2020.

As stated above, innovative pharmaceutical companies conduct research every year in collaboration with a variety of public hospitals, HMOs, private medical centers, medical research institutions and with providers of community medical services. In recent years, multinational innovative pharmaceutical companies have entered into about 1,500 engagements for clinical trials per annum⁴² at a total investment exceeding ILS 500 million per annum.⁴³

It should be noted that the total annual investment specified above encompasses only medical institutions' receipts in respect of hospitalization and tests, but does not include additional expenses, such as the medicine costs during the research activities, medicine storage or financing of the costs of additional medical service-providers, such as pharmacists and teams of various healthcare professions. Therefore, the companies' volume of investment in clinical trials in Israel is far larger than the sum specified above.

Clinical trials are exceedingly important for improving the quality of medicine and for medical institutions and teams to develop treatment and research knowledge and capabilities. Through clinical trials, physicians are exposed to the leading therapies in the world, to knowledge and to the leading standards of supervision and control over medical treatments.

Most clinical trials are RCTs (randomized control trials) and are considered "sterile" since they do not include a representative sampling of all patient populations.

Additionally, the companies cooperate with HMOs that collect real world evidence of the effects of marketed medicines, which is analyzed by the companies and used to create a knowledge base about their modes of action and their effects in order to improve future medicines.

Besides improving the quality of medicine, clinical trials enable R&D infrastructures to be built at public hospitals. Today, the State of Israel constitutes one of the world's preferred locations for conducting clinical trials,⁴⁴ and is ranked in 5th place in the world in the index of the number of international clinical trials per capita over the last two decades.* This, despite the fact that the volume of public investments in research infrastructures in medical institutions in Israel is limited compared to the investments in comparable developed countries. Therefore, the funding of clinical trials that comes from pharmaceutical companies enables the various medical institutions to engage in research at today's significant volumes.

In addition to their investments in clinical trials in Israel for the development of medicines, the companies also invest in independent research by investigators and physicians at medical institutions to develop medical knowledge and highquality treatments and to help outstanding investigators engage in long-term research.

^{*} The index ranks countries with a population exceeding 2 million.

INNOVATIVE PHARMACEUTICAL COMPANIES INVEST IN DEVELOPING KNOWLEDGE AND EXPERTISE IN THE HEALTHCARE SYSTEM, IN PROVIDING TRAINING TO MEDICAL TEAMS AND IN SUPPORTING PATIENT **ORGANIZATIONS**

Innovative pharmaceutical companies' presence constantly affects the healthcare system in a variety of additional ways:

BY PROVIDING THE HEALTHCARE SYSTEM, TREATMENT-PROVIDERS AND PATIENTS WITH DIRECT ACCESS TO INFORMATION

Multinational companies' direct presence in Israel enables the healthcare system and the various treatment-providers to receive up-to-date relevant information, professional support and assistance making swift and efficient decisions, without having to work indirectly with multinational headquarters.

BY MONITORING AND CONTROLLING STANDARDS ALONG THE ENTIRE SUPPLY CHAIN

The companies manage the process of importing medicines to Israel until they reach patients, and they verify that this value chain complies with strict international standards. The companies also collect information about the use of the medicines and monitor side effects, report them to the Ministry of Health and build plans to mitigate future risks and to support patients.

BY PROVIDING TRAINING AND SUPPORT TO **MEDICAL TEAMS**

Innovative pharmaceutical companies support and cooperate with the medical community in Israel in augmenting their knowledge and the quality of their research. In addition to the joint activities relating to clinical trials, medical standards are improved through educational seminars and conferences in Israel and abroad, which enable investigators to interact with the extensive scientific community in their fields.

BY SUPPORTING PATIENTS' ORGANIZATIONS

Patients' organizations are one of the support pillars for patients and their families during difficult times. These organizations take action to ensure that patients can fully exercise their rights, represent patients before health authorities and provide emotional and economic guidance and support. The companies help these organizations by providing information, help raise public awareness of diseases and by expanding the access to critical treatments.

Innovative pharmaceutical companies' direct contribution to healthcare organizations, to patients' organizations and to the training of medical teams is estimated at about ILS 200 million between 2015 and 2019, coupled with a wide variety of additional unquantifiable benefits of

significant economic value.⁴



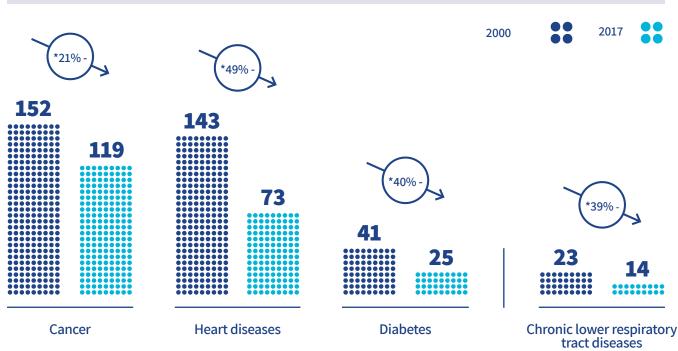
CONSTANT IMPROVEMENT IN HEALTH OUTCOMES HAVE BEEN SEEN IN ISRAEL OVER THE YEARS, THANKS TO THE USE OF ORIGINAL DRUGS, SIMILARLY TO THE GLOBAL TREND

ORIGINAL DRUGS HAVE SIGNIFICANTLY HELPED LOWER MORTALITY RATES AMONG PATIENTS SUFFERING FROM DEADLY DISEASES AND EXTEND THE LIVES OF PATIENTS WITH CHRONIC ILLNESSES IN ISRAEL OVER RECENT DECADES

The mortality rates from two of the deadliest causes of morbidity in Israel - cancer and heart diseases - have dropped dramatically over the years thanks to medical advancements and innovation, combined with the use of original drugs. The mortality rate from heart diseases in Israel has dropped steeply by about 49%, while the comparable rate internationally decreased by about 21% since the early 2000s.⁴⁶ Similarly, the mortality rate from cancer in Israel has dropped by about 21%, while the rate internationally dropped by about 21% since the early 2009, 46 Similarly, the mortality rate from cancer in Israel has dropped by about 21%, while the rate internationally dropped by about 11% during the same years.

Concurrently, original drugs helped lower the mortality rate from chronic lower respiratory tract diseases by about 39% and from diabetes by about 40% since 2000.⁴⁶

In addition to significantly lowering mortality rates, original drugs helped extend and improve the quality of life of patients with chronic diseases. For example, the pharmacotherapy developed for AIDS has enabled many patients in Israel to live with the disease and has lowered the mortality rate among patients by about 70% since the mid-1990s.⁴⁷



Mortality rate per 100,000 in Israel between 2000 and 2017, by cause of death

* Average annual change

Source: Ministry of Health report: Leading causes of death between 2000 and 2017.

ORIGINAL DRUGS SIGNIFICANTLY IMPROVE THE QUALITY OF LIFE OF PATIENTS WITH CHRONIC DISEASES, THEREBY ENABLING THEM TO PERFORM DAILY ACTIVITIES AND INTEGRATE IN THE JOB MARKET AT SIGNIFICANTLY HIGHER RATES OVER THE YEARS

The population of chronically ill patients in Israel reaches more than half a million people - 470 thousand diabetes patients,⁴⁸ 180 thousand patients with heart failure⁴⁹ and 70 thousand patients with chronic hepatitis C.⁵⁰ Similar to the situation in other developed countries, original drugs currently provide a solution for these patients in Israel too, enable the extension of life expectancy and improve quality of life, inter alia, by alleviating the symptoms of these diseases.

Accordingly, a study conducted in Israel in 2017 quantified the rise in lifespan according to a healthy life expectancy index (disability-adjusted life years), which takes into account death and disability. The study⁵¹ found that the years of healthy life rose from 67 to 71.7 (i.e., addition of 4.7 years of healthy life) between 1990 and 2015, mainly as a result of improvements in the medical conditions for which original drugs provide a solution, such as heart diseases, skin diseases, stroke, congenital defects and kidney diseases.

During those same years, there was about a 65% drop in the morbidity burden of heart diseases and about a 45% drop in the morbidity burden of cerebrovascular events. About half of this drop is a result of the availability of improved medical treatments, including original drugs.







MULTINATIONAL INNOVATIVE PHARMACEUTICAL COMPANIES' IMPACT ON INNOVATION AND THE ECONOMY IN ISRAEL

Multinational innovative pharmaceutical companies have expanded their presence in Israel over the last two decades and will continue expanding their activities in Israel in the coming years, thereby providing major benefits towards advancing healthcare, employment and innovation in Israel. These companies' presence and their activities generate thousands of high-quality jobs, both directly and indirectly, contribute considerably to the development of the life sciences industry and of medicine in Israel and encourage innovation through their promotion and support of hundreds of startup companies.

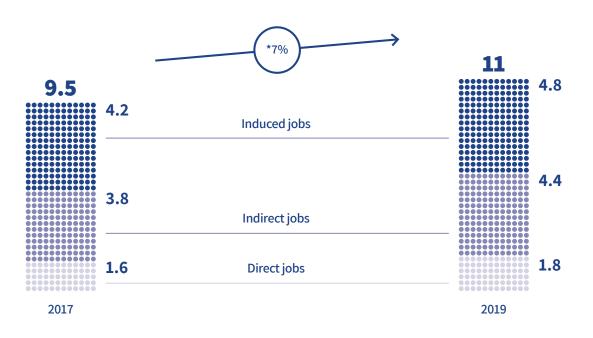
THE INNOVATIVE PHARMACEUTICAL INDUSTRY PROVIDES HIGH-QUALITY EMPLOYMENT OPPORTUNITIES TO MORE THAN 10,000 PEOPLE IN ISRAEL

A survey conducted by TASC among multinational innovative pharmaceutical companies operating in Israel found that the companies directly employed about 1,800 people in 2019. Subsequent to this survey, an assessment was made of the multinational companies' impact on creating indirect jobs (indirect and induced jobs). The assessment was based on a study conducted in the United States by the PhRMA Association (the Association of Pharmaceutical Research and Manufacturers of America), which provided estimates as to the ratio between direct jobs and indirect jobs, according to the direct, indirect and induced jobs that innovative pharmaceutical companies are generating.⁵² It should be noted that, when adapting the proposed methodology to the Israeli market, estimates were used that are compatible with the structure of the market in Israel, such as the absence of manufacturing functions in Israel.

We divide the volume of jobs created by the companies in Israel into three main categories:⁴¹

- 1. **Direct jobs (industry employees):** encompasses all people directly employed by the innovative pharmaceutical companies, including company executives, investigators, regulatory personnel, medical directors, marketing and sales personnel, medical representatives, IT, administrative and support personnel. The industry provides about 1,800 direct jobs.
- 2. Indirect jobs (industry support employees): encompasses raw materials suppliers and subcontractors providing services to the industry (such as research, pharmacy, distribution, storage, cleaning, food services, etc.). The industry provides about 4,000 indirect jobs.
- 3. Induced jobs (jobs induced by the industry): jobs that are indirectly affected by the industry's activities, including physicians, investigators and startup companies. The industry provides about 4,800 induced jobs.

Impact of the presence of innovative pharmaceutical companies in Israel on the volumes of employment (2017-2019), in direct and indirect jobs (thousands of employees)



* Average annual change

Source: TASC analysis of Pharma Israel's survey of innovative pharmaceutical companies and an estimate of the impact on indirect employment spheres (indirect and induced jobs), 2020.

THE INNOVATIVE PHARMACEUTICAL INDUSTRY IN ISRAEL OFFERS A WIDE VARIETY OF EMPLOYMENT OPPORTUNITIES

The innovative pharmaceutical industry requires expertise in medicine, in the life sciences, in the exact sciences, in technology and in other disciplines. Accordingly, the industry employs a high ratio of college graduates in all departments operating in Israel.

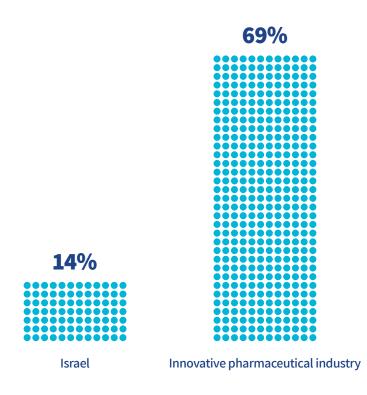
An uptrend in the volumes of employment and in the variety of jobs has been evident over the last decade resulting from the companies' expansion of their activities in Israel to new fields and the closer relations with the local life sciences industry, which is reflected by the about 15% increase in the volume of direct employment in the innovative pharmaceutical industry in Israel over the last two years. The table below shows the innovative pharmaceutical companies' principal spheres of activity in Israel, and the types of employees needed for each department. We also note that the majority of the companies' growth is in the volumes of jobs in research, development and training.

Innovative pharmaceutical companies' main activities in Israel and types of employees needed

MEDICAL	The medical departments provide scientific support to physicians and employ employees holding PhDs in medicine, in veterinary science and in the life sciences, including biology, chemistry, etc.
MARKET ACCESS	Market access and drug pricing departments are responsible for the commercial interfaces with health organizations.
	These departments hire experienced employees holding advanced degrees in economics and accounting, as well as analysts who are proficient working with business intelligence tools and big data.
SALES AND MARKETING	The sales and marketing departments are responsible for designing and assimilating the marketing strategy and for maintaining ongoing scientific dialogues with physicians, nurses and pharmacists. These departments hire employees who understand the medicines' medical and scientific contribution to disease treatment and, in most cases, they hold degrees in the life sciences or in paramedical disciplines, and some also hold an MBA.
	Considering the intensifying uptrend in the use of technological tools for marketing and for making information accessible to the industry's customers, digital-based marketing jobs are also on the rise.
REGULATION AND QUALITY	The regulation and quality departments are responsible for the registration of medicines in Israel, for training employees, for providing information to patients, and have overall responsibility for the supply chain of medicines being imported to Israel, with a special focus on safety and quality.
	For the most part, regulation departments hire experienced employees holding advanced degrees in pharmacy.
CLINICAL TRIALS	Employees in the clinical trials departments must have suitable training in conducting research and therefore, for the most part, they hold degrees in life sciences and are certified CRAs (Clinical Research Associates).
	In addition to clinical trials, a need has developed for data-based researchers; consequently, the companies have begun hiring data scientists in recent years.
INNOVATION	Considering the expansion of activities in Israel, the international companies' deeper relations with Israel's life sciences industry and the recognition of the existing potential for innovative collaborative efforts, in recent years many companies have been offering jobs in the fields of business development, innovation (from finding startups to invest in, to venture capital funds, incubators, etc.) and also initial stages of R&D.

As stated, considering the innovative pharmaceutical industry's focus on professionals with advanced degrees, the ratio of people employed in this industry in Israel⁴¹ who hold a master's degree is five times higher than the national average.⁵³

Ratio of people hired who hold at least a master's degree, 2019



Source: TASC analysis of Pharma Israel's survey of innovative pharmaceutical companies, 2020; OECD, 2020.

The TASC survey of multinational companies also found that, compared to comparable industries54 and Israeli companies engaging in similar fields,55 the multinational innovative pharmaceutical companies offer better and more attractive terms to employees. In this way, they directly contribute to reducing the "brain drain" from Israel and to preventing people from taking jobs not related to their college majors (such as graduates with degrees in chemistry, biology, clinical pharmacy, etc.).



The survey also found that the ratio of women employed in this industry is particularly high, compared to the general pharmaceutical industry⁵⁶ and comparable industries.⁵⁷ They account for about 85% of the human capital in the innovative pharmaceutical industry, particularly at senior management echelons. Accordingly, the number of female CEOs in the industry has ranged between

30% and 50% in recent years.⁴¹

INNOVATIVE PHARMACEUTICAL COMPANIES PROMOTE LOCAL INNOVATION THROUGH COLLABORATIONS, INVESTMENTS AND ACQUISITIONS OF STARTUP COMPANIES

In addition to pharmaceutical companies' core activities as described above, innovative pharmaceutical companies substantially contribute to the advancement of all segments of the life sciences industry in Israel by acquiring companies, by investing in incubators, in accelerators and in venture capital funds, and by active participation in the forwarding of know-how to these companies.

They also constitute major distribution channels for new technologies and for introducing them to broad international markets: $^{\!\!\!\!^{41}}$

ACQUISITIONS OF STARTUP COMPANIES

Between 2015 and 2019, innovative pharmaceutical companies invested ILS 1.7 billion in the acquisition of 20 Israeli biotechnology companies. The companies acquired focus on innovative technologies, including the use of artificial intelligence tools to develop advanced personalized medical treatments (precision medicine).⁴¹

ACTIVE PARTICIPATION IN INCUBATORS AND ACCELERATORS

Over the last five years (2015-2019), innovative pharmaceutical companies have contributed to the development of about 150 startup companies through collaborative activities in incubators, accelerators and venture capital funds from the seed stages to business maturity stages.

INTRODUCTIONS TO INTERNATIONAL MARKETS

In addition to providing financial support, innovative pharmaceutical companies are helping startup companies create knowledge assets and connections with sources in international markets, from the markets in the United States and Europe to markets in China and Japan, which have traditionally been less accessible by Israeli entrepreneurs. These efforts helped startups grow to significant operating volumes in diverse fields, such as the development of medicines for chronic diseases, first-in-class medicines and other medicines.⁴¹

VENTURE CAPITAL FUNDS

Innovative pharmaceutical companies are major investors in venture capital funds, which later invest in medical and biological startups with the goal of encouraging innovation and initiatives in the local industry. The venture capital funds provide seed money to startup companies to enable them to develop and realize their inherent potential. Pharmaceutical companies also provide startup companies with access to extensive knowledge bases, with physical and economic resources, as well as connections to international experts.



Investment of ILS 1.7 billion in acquisitions of Israeli biotechnology companies Direct investment in about 20 startups, and contribution to the development of about 150 additional startups through accelerators, incubators and venture capital funds over the last 5 years (2015-2019) Sharing of knowledge and connections and introductions to international markets





FUTURE TRENDS AND DEVELOPMENTS

Innovative pharmaceutical companies will continue constituting a key factor in contending with the challenges of morbidity worldwide and in Israel, including the aging of the population, the rise in the morbidity burden of chronic diseases and of diseases of the 21st century (neurological, psychological, etc.). Within this framework, the companies will continue developing breakthrough technological solutions, such as biological therapies and cell therapies, treatments for orphan diseases and advancing precision medicine, which enables the pharmacotherapy to be customized for the patient's unique characteristics. Concurrently, the companies will continue developing and assimilating practices in healthcare systems that support the patient-centered care approach, which espouses the provision of information, sharing in decision-making, and improving the doctor-patient journey. Finally, the companies are leveraging the digital healthcare revolution and intend to continue investing in digital technologies and integrating them in their operations, including the use of applications, sensors and remote medicine, big data and artificial intelligence.

The current Covid-19 crisis triggered unprecedented acceleration of the vaccine research and development processes and led to close cooperative efforts with the health authorities, without compromising the quality of the development. It is reasonable to assume that, looking ahead, the Covid-19 crisis will lead to the defining of new standards for the global development of medicines and vaccines.

KEY TRENDS AFFECTING THE GLOBAL INNOVATIVE PHARMACEUTICAL INDUSTRY

GLOBAL DEMOGRAPHIC AND EPIDEMIOLOGICAL CHANGES ARE CREATING DIFFERENT MORBIDITY PATTERNS AND PHARMACEUTICAL COMPANIES ARE PROVIDING CUSTOMIZED SOLUTIONS

The global population mix is expected to change dramatically in the coming years. Global forecasts are that the number of people above the age of 65 can be expected to increase by about 40% within the coming decade from 700 million people in 2019 to about 960 million people by 2029,²⁰ while the elderly population in Israel is expected to double itself by 2035.

Population aging constitutes one of the major challenges facing healthcare systems worldwide, due to the fact that this population is characterized by a high morbidity rate and heightened consumption of medical services and medicines. Furthermore, the comorbidity rate (when a person suffers from multiple active diseases at the same time) is expected to rise significantly.

More elderly patients will begin reporting that they are suffering from four and more diseases simultaneously.²¹ This trend is not expected to skip over young patients suffering from rare diseases for which no medical solution previously existed.

Another dominant trend is the rise in the number of people contending with mental health illnesses, which are also called "21st-century pandemics" due to their high incidence. This uptrend is also explained by the heightened awareness of these illnesses and by better diagnostic capabilities.

Accordingly, many countries are indicating that psychological illnesses, such as depression and anxiety, are imposing a heavier burden on the healthcare system than deadly diseases, such as cancer and diabetes.²²

The pharmaceutical industry constitutes a key factor in contending with the challenges deriving from the changes in demographics and morbidity.

The industry is developing innovative solutions for improving the quality of life of patients with chronic and complex diseases, is customizing the medical treatment to patients' characteristics (as is presented below), and is increasing the focus on diseases for which treatment solutions are lagging significantly behind, such as psychological illnesses and rare diseases.

AGAINST THE BACKDROP OF MAJOR TECHNOLOGICAL ADVANCES, THE INNOVATIVE PHARMACEUTICAL INDUSTRY IS DRIVING INNOVATIVE MEDICAL DEVELOPMENTS

In light of the material progress achieved over the last two decades in mapping the human genome sequence and developing advanced computer capabilities, the field of precision medicine is enjoying significant growth and development.

This field enables medical treatments - especially pharmacotherapies - to be customized to the patient's unique characteristics, based on medical history, genetics, and differences in environment and lifestyle. In this way, precision medicine enables a reduction in side effects and significant improvement in the clinical outcomes.

The use of precision medicine has developed and expanded considerably in recent years. Between 2014 and 2018, the ratio of personalized medicines approved annually by the US FDA rose from 21% to 42%.²³

Another significant trend is the pharmaceutical industry's shift from basing itself on simple chemical molecules to reliance on proteins in complex biological medicines that work on the cell's biological mechanisms.

In 2019, the market share of biological medicines exceeded 40% of the total medicine sales in the United States.²⁴ These medicines are highly capable of targeted disease treatment.

Additional breakthrough technologies have also been developed, such as cell therapy, which changes the mode of action of particular cells so that they fight the disease, and gene therapy, which treats disease by changing, improving or replacing genes inside cells in order to change the genetic code. These therapies enable diseases to be completely cured. Furthermore, these therapies are administered for a short period, unlike other medicines and therapies that are administered over long periods. The use of these therapies is beginning to gain momentum: by July 2020, the US FDA had approved 18 such technologies²⁵ and the FDA commissioner expects that between 10 and 20 additional technologies will be approved annually as of 2025.²⁶

IN LIGHT OF THE NEW MEDICAL DEVELOPMENTS, THE FOCUS ON AND CAPABILITY OF PROVIDING IMPROVED SOLUTIONS FOR RARE DISEASES ARE INCREASING, AND ORPHAN DRUGS ARE BEING LAUNCHED TO TREAT A LIMITED NUMBER OF PATIENTS

Pharmaceutical companies are continuing to discover new molecules, a significant percentage of which are developed into first-in-class medicines; i.e., medicines that use a new and unique mechanism of action for treating a disease or medical condition. Attesting to this, first-in-class technologies accounted for about 42% of all medicines approved by the US FDA in 2019.²⁷

Additionally, new molecules are also being used to develop orphan drugs - medicines that provide a solution for diseases affecting a very limited number of patients, and therefore, their development is far more complex. The US FDA defines an orphan drug as a medicine to treat a disease that affects fewer than 200,000 people in the United States. Pharmaceutical companies have been significantly increasing their focus on these unique solutions and are offering new hope to patients throughout the world. Just like with first-in-class medicines, the development of orphan drugs is also gaining momentum: while the ratio of orphan drugs out of all medicines approved by the FDA during the 2000s was about 20%, their ratio in 2019 rose to about 45% of all approved medicines.²⁸

IN RECENT YEARS, THE MEDICAL COMMUNITY HAS BEEN DRIVING A SIGNIFICANT CHANGE AND SHIFTING TO A POLICY OF PATIENT-CENTERED CARE. INNOVATIVE PHARMACEUTICAL COMPANIES ARE INTEGRATING THIS APPROACH IN THEIR ACTIVITIES AND ARE HELPING TO ADVANCE IT IN HEALTHCARE SYSTEMS

The patient-centered care approach is based on a deep understanding of and a focus on the patients' journey, on patients' involvement in their care and on the involvement of their care-givers, on the importance of providing information, the needed support and tools so that patients will optimally adhere to their pharmacotherapy regimens. The pharmaceutical companies serve as a pioneering force in patient-centered care, enabling the advancement of research, the assimilation of tools and ongoing discourse that focuses on patients and their needs, as well as the development of advanced economic models enabling access to advanced therapies while dividing up the risks among the insurers and the healthcare systems around the world.

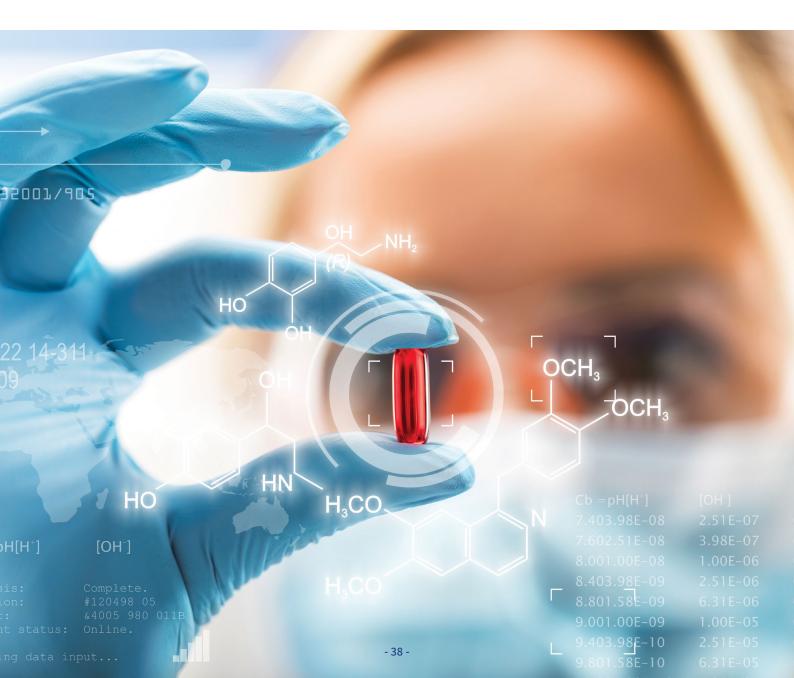
PHARMACEUTICAL COMPANIES ARE DEVELOPING MEANS TO IMPROVE THE PATIENT JOURNEY AND THE APPROACH TOWARDS TREATMENT, FROM THE DEVELOPMENT STAGES TO THE STAGE OF OPTIMAL PATIENT ADHERENCE:

- Connecting patients and their representatives to medicine development processes through patient advisory councils that become involved already at the clinical trial stage.
- Building economic mechanisms and risk-distribution agreements that enable insurers and healthcare systems to finance new medicines (patient access schemes).
- Developing professional content, knowledge and training on the subject of patient engagement, for both employees in the pharma industry and for medical teams.
- Developing tools for patient medication adherence, such as digital tools that help patients keep track of their treatment, special applications for taking medicines, etc.
- Developing patient support programs that: provide information about diseases and medicines; help patients schedule appointments and obtain refunds; deliver medicines to patients' homes; and forward updates to the treating physicians.
- Offering disease management programs to help patients with chronic illnesses manage their illnesses better and improve their quality of life.

PHARMACEUTICAL COMPANIES ARE EXPANDING THEIR ACTIVITIES RELATING TO DIGITAL HEALTHCARE AND ARE LEVERAGING THE INFORMATION, BIG DATA AND ANALYTICS REVOLUTION

Pharmaceutical companies are increasing their volumes of investment in technological developments by acquiring startup companies and creating collaborations with established technology companies. Since 2014, there has been a significant uptrend in the annual volume of investments in the field of digital healthcare by the ten largest innovative pharmaceutical companies in the world and, between 2014 and 2019, the volumes of investment in this field exceeded USD 4 billion.²⁹

As part of this uptrend, innovative pharmaceutical companies are investing in and developing technologies based on big data and artificial intelligence technologies. These technologies help companies identify various morbidity trends, identify disease characteristics, perform early diagnoses, monitor patients' responses to pharmacotherapy, and offer considerable potential for streamlining research and development processes (accelerating processes for discovering new molecules) and for identifying additional indications for existing medicines. These technologies are also used to increase the value and assistance to patients with managing their diseases, with medication adherence/ compliance, as well as to monitor side effects after a medicine is launched on the market.



THE INNOVATIVE PHARMACEUTICAL INDUSTRY'S EFFORTS TO HELP FIGHT THE COVID-19 PANDEMIC TRIGGERED AN UNPRECEDENTED ACCELERATION OF THE R&D PROCESSES AND CREATED OPPORTUNITIES FOR CLOSER COLLABORATIONS WITH HEALTH AUTHORITIES

The outbreak of Covid-19 at the end of 2019 and its global spread at the beginning of 2020 prompted the innovative pharmaceutical industry to position itself at the front line and to take unprecedentedly swift action to find a solution for contending with the virus.

The considerable knowledge amassed by the industry over decades has enabled pharmaceutical companies to offer a variety of solutions for eradicating the pandemic. Inter alia, the companies developed and provided tests to detect Covid-19 in record times, considerably accelerated the R&D processes for vaccines and therapies based on technologies developed over the years and found to be safe and effective for use, and took action to expand the use of existing medicines to also treat Covid-19 patients. For the first time, fruitful collaborations developed between competing companies to jointly advance R&D processes and to expand production lines in order to guarantee the regular, continuous and proper supply of medicines and vaccines against Covid-19.

Within less than a year of the outbreak of the virus, the pharmaceutical industry had succeeded in developing a safe and effective vaccine against the virus that had shut down the entire world and threatened to paralyze the global economy. The vaccine is a cornerstone in the process of resuming routine life alongside Covid-19.

The rapid development of the Covid-19 vaccine was possible thanks to a combination of several factors:

- The pharmaceutical companies, governments and research institutions prefunded the entire R&D process, which provided economic security and enabled progress to be made quickly without needing to raise money according to milestones and successes during the process.
- Some of the vaccines are based on advanced technologies and on laboratory-developed substances, thereby eliminating the need to cultivate a weakened version of the virus, which takes time.
- Due to the considerable urgency, the three clinical trial phases were conducted concurrently under the supervision of the authorities and under stringent controls.

- Due to the rapid spread of the virus worldwide and the public's high awareness, volunteers for the clinical trials were recruited immediately and at unprecedentedly high volumes.
- Digital means were used extensively during the processes of recruiting volunteers and of tracking infected patients, alongside other measures.

As stated, one of the greatest achievements en route to a vaccine was the extraordinary cooperation between the pharmaceutical companies and the leading health authorities around the world. The collaboration between both parties and the complete transparency throughout all of the R&D stages enabled: existing technologies to be used in order to develop a new vaccine rapidly; the recruitment of tens of thousands of volunteers for clinical trials; real-time control and supervision of the research and manufacturing processes; and, finally, the issuance of emergency authorizations to immediately use several vaccines of various companies. The health authorities' close accompaniment of the pharmaceutical companies and the support provided to the industry by governments all over the world also helped dispel some of the public's concerns about the accelerated R&D processes en route to the Covid-19 vaccine.

Additionally, one of the greatest challenges for countries that import medicines extensively, such as Israel, was to ensure the availability of medicines throughout the supply chain for all patients during a global crisis. The innovative pharmaceutical companies operating in Israel took action to increase their inventories of medicines in order to avoid any shortages and to ensure treatment continuity for patients.

The companies also provided compassionate treatments and experimental treatments to Covid-19 patients, supported medical associations in heightening patients' awareness of the importance of adhering to treatment regimens for various diseases during the Covid-19 period, continued their clinical research activities through remote monitoring and supplying investigational products to trial participants' homes, provided remote medical services and donated to organizations and NPOs that helped patients in various contexts.

MORE THAN 1,750 GLOBAL CLINICAL TRIALS

investigating treatments and vaccines against Covid-19 (correct to February 2021)

Timeframe required to sequence viruses for various diseases

197_{YEARS} to isolate the characteristics of **measles**









INNOVATIVE PHARMACEUTICAL COMPANIES' ACTIVITIES IN ISRAEL DURING THE COVID-19 CRISIS

The Covid-19 crisis had a widespread impact on the public's health and on the stability of the local economy and imposed a heavy burden on the healthcare system. A concern also arose about diminished medical care for patients who are other than Covid-19 patients. Consequently, the pharmaceutical companies joined the national battle and provided assistance in several channels during this challenging period:

- Medicine inventories in Israel were increased significantly in order to prevent any possible shortage as the global situation worsened.
- Experimental treatments of Covid-19 were provided in severe cases as part of the companies' clinical development channel.
- Financial support was provided to the various medical associations to raise awareness of Covid-19 and of ways to contend with it.
- Employees of the companies holding degrees in the life sciences were made available to provide explanations about Covid-19 at no charge.
- Shuttle services to medical centers were provided at times when public transportation was shut down.
- Medicines were delivered to patients' homes at no change in order to prevent exposure to Covid-19.
- Digital software was developed that helps patients independently maintain medication adherence.

- Remote nurse services were provided through the development and use of digital tools.
- Financial donations were given to various entities in the healthcare system for purchases of medical equipment.
- Financial donations were given for the development of telemedicine services.



5

SUMMARY AND RECOMMENDATIONS TO POLICY-SETTERS

The innovative pharmaceutical industry established itself in Israel over the last two decades. As this report shows, the industry's favorable impact on public health and on the Israeli economy and society is quite significant and its contribution to the advancement of innovation is considerable.

In the era of medical innovation and scientific breakthroughs and particularly after the crisis of the outbreak of the Covid-19 pandemic and the industry's efforts to rapidly develop vaccines and medicines against the virus, a substantive opportunity has arisen to position Israel at the vanguard of countries supporting the research and development of innovative medicines, and to promote fruitful collaborations between multinational companies and local companies.

POLICY MEASURES NEEDED TO PROMOTE AND LEVERAGE THE INNOVATIVE PHARMACEUTICAL INDUSTRY'S PRESENCE IN ISRAEL AND TO POSITION THE STATE OF ISRAEL AS A PREFERRED LOCATION FOR MEDICAL INNOVATION

Multinational innovative pharmaceutical companies have expanded their presence in Israel over the last two decades and will continue expanding their operations in Israel in the coming years, thereby providing major benefits towards advancing health, employment and innovation in Israel.

The companies are working vigorously to make innovative medicines and therapies available rapidly to prevent diseases, extend life expectancy and to alleviate the suffering of millions of patients.

Furthermore, the expansion of their operations in Israel and the deepening of their relations with the local life sciences industry lead to high-quality employment opportunities and better standards of quality control and work procedures throughout the value chain. In addition to these activities, it appears that the local market offers opportunities for the companies to leverage their technological capabilities.

To this end, a series of measures should be taken that will position Israel as a preferred location for the innovative pharmaceutical industry and that will ensure the continued advancement of public health. The emphases should be on improving regulations, standardization and digitization, on making more medicines available, on strengthening the intellectual property protection and on supporting innovation.

1. SHORTENING DRUG REGISTRATION TIMETABLES AND INCREASING TRANSPARENCY AND FLEXIBILITY

We are in an era of medical innovation and of accelerated development of medicines, vaccines and therapies enabling full recovery, the extension of life expectancy or significant improvement in the quality of life of many patients. The Covid-19 crisis highlighted the possibility of reducing morbidity through the use of medicines and vaccines that are based on breakthrough technologies.

The Covid-19 crisis created an opportunity to improve regulations, to shorten timetables and to increase healthcare authorities' transparency, availability and flexibility. Their willingness to adopt new technologies and to enable them to be rapidly available to the public dictates that the Ministry of Health should accelerate the medicinal product registration and approval processes so that they are on par with its counterparts abroad, while maintaining its meticulousness about quality, safety and efficacy.

This is how the State of Israel succeeded in being the first country in the world to launch a rapid, wide-scale vaccination campaign of its population against Covid-19. It makes sense to also apply this approach to additional innovative technologies that can bring relief to patients.

In the State of Israel today, a new imported medicine may be registered and marketed only if it is registered in a recognized country (according to the list of countries specified in the Pharmacists Regulations (Preparations) of 1986). In recent years, the number of new medicines being submitted for registration each year has been increasing and, accordingly, the registration period lengthened significantly. This resulted in new original drugs becoming available in Israel at a lag compared to their launch in the United States and in Europe.

It is indisputable that the State of Israel must verify the quality, efficacy and safety of medicines, but it is warranted to streamline the registration process in various ways. For example:

- Adapting the local requirements to accepted international standards.
- Allowing registration applications to be submitted in Israel parallel to their submission to leading authorities, such as the EMA, the FDA or SwissMedic, or creating a fast registration track, based on the submission of the complete registration dossier that was submitted to an authority abroad.
- Expanding the Ministry of Health's cooperation with counterpart authorities around the world in order to enable joint examination of registration applications (alliances and cooperation agreements already exist between various healthcare authorities throughout the world).
- Increasing the reliance on companies' declarations regarding information revisions in leaflets and on packaging so that the registration inputs may be invested in examining and quickly approving new medicinal products.

2. DIGITIZATION OF MEDICINE REGISTRATION PROCESSES

A significant portion of the Israeli Ministry of Health's systems is not computerized and does not enable the performance of digital submissions. For example: medicinal product registration applications are still being submitted in physical hard copies, even though at issue are large complex documents. As a result, the registration processes are slow and cumbersome and may result in delays in making medicines and therapies available to citizens. In addition to delaying registration proceedings, the lack of computer systems precludes the use of digital information leaflets (patient leaflets and physician's leaflets) and therefore, leaflets cannot be revised immediately if there are safety updates, a change in dosage regimen, side effects and more.

Over the years, the health authorities in many countries have established computerized systems with uniform formats for submitting registration dossiers (such as eCTD). The fact that many health authorities are using similar systems enables them to join international alliances aiming to accelerate the registration processes of new medicinal products and to make innovative medicines and therapies available to citizens faster than in the past.

In conformity with Israeli Government Resolution 260 of 26.7.2020 to accelerate the digital services to the public, it would be advisable to establish computer systems that will enable full online submissions of electronically signed medicine registration applications. This will enable streamlining of processes, shortening of timetables and full transparency.

3. ADVANCEMENT OF CLINICAL RESEARCH STUDIES

As described in this booklet, clinical research activities have been expanding over the years in Israel. The expansion of these activities offers advantages to all stakeholders patients, physicians and hospitals. Patients receive earlystage innovative treatments by top experts, when for some patients, at issue is a last-resort treatment because no effective alternative exists. Physicians are able to participate in pioneering research studies, gain experience using stateof-the-art technologies and improve their professional skills. Hospitals are able to receive research budgets, additional staff and advanced medical instruments, to increase their revenues and boost their reputation and standing as leading institutions complying with international standards. Besides all of these advantages, clinical research activities contribute significantly to the Israeli economy, which is seeking new investments, and to the public health system, which is in need of additional resources.

The advantages mentioned above have triggered stiff competition over wide-scale clinical research studies between medical institutions and health systems throughout the world.

Israel is a magnet for clinical research studies and many multinational companies select it as a leading trial center. Nevertheless, in order for Israel to continue serving as such a magnet and to expand the volumes of research activities, it must promote changes in its regulatory policy, improve and streamline the processes for submitting and approving research applications and its monitoring and control mechanisms. This trend also characterizes the field of clinical trials, and many countries currently allow digital submissions of clinical trial applications. Sometimes, a central committee or leading medical institution may approve an application for several institutions concurrently in order to enable a multi-center clinical trial.

Computerized systems should also be established that will enable online electronic submissions of clinical trial applications. It is also advisable to encourage clinical trials at several Israeli healthcare institutions at the same time (multicenter clinical trials), inter alia, through mutual recognition among healthcare institutions, sweeping approvals by a central committee, the reduction of bureaucratic procedures and paperwork and the creation of uniform standards among the various institutions in Israel.

The need to make changes in the clinical trial system in Israel is magnified as a result of the trend advancing the new European regulation regarding the establishment of a central portal for submitting clinical trial applications that will operate throughout Europe and significantly facilitate collaborations among several countries. This regulation will make European countries attractive and competitive with Israel, and will affect Israel's ability to attract high-quality clinical trials.

4. EXPANDING THE ACCESS TO MEDICINES BY DEFINING AN ANNUAL TECHNOLOGICAL UPDATE RATIO OF THE NATIONAL HEALTHCARE SERVICES BASKET

One of the major challenges for any country's healthcare system is ensuring that patients receive optimal care through the most advanced and effective medicines, vaccines and therapies.

In Israel, the main channel for making new technologies available is the national healthcare services basket, which was established by virtue of the National Health Insurance Law of 1994. The national healthcare services basket enables medicines to be available to all patients in Israel. A public committee convenes annually to add services to the basket, particularly new medical technologies. This basket has been eroding over the years and its budget has not been revised according to the pace of the technological developments, according to the population growth and aging.

Over the last decade, the annual technological update of the basket has been less than 1% of the total value of the basket and, as a result, most of the technologies ranked by the committee as being the most critical (ranks of A8 and A9) have remained outside of the basket and therefore, adequate solutions are not being provided for patients' needs. To date, no annual mechanism has been defined for updating the basket's budget to enable the addition of innovative medicines and therefore, the basket's budget is subject to annual negotiations between the Ministry of Finance and the Ministry of Health. The existing uncertainty about the volume of the annual budget available to the basket committee seriously impedes the healthcare system's longrange planning.

In order to ensure that Israeli citizens can receive optimal access to innovative medicines, vaccines and therapies in the coming years as well, a permanent annual update ratio of the basket should be defined at a minimum of 1.65% of the overall cost of the basket -or about ILS 750 million per annum. The chairmen of the basket committee have vigorously supported this position over the years. This has also been the Ministry of Health's professional recommendation as submitted to the Prime Minister in 2019.

5. INCREASING INTELLECTUAL PROPERTY PROTECTION

R&D-based pharmaceutical companies are completely dependent upon the adequate protection of their intellectual property rights in general and their patents in particular. The exclusivity that intellectual property rights grant for a defined period constitutes the main incentive for the industry to continue advancing research and development activities and taking action to launch innovative medicines. Improving the protection of intellectual property rights will accelerate the pace of new medicine registrations in Israel.

The more that the intellectual property protection being provided in Israel will be similar to the extent of protection being provided to the innovative pharmaceutical industry in the United States and in Europe, the more it will be possible to ensure that innovative medicines will be launched in Israel shortly after they are launched in leading markets abroad, and to create enormous value to the State of Israel's economy and to the healthcare of its citizens.

The State of Israel has come a long way in improving the intellectual property environment. Nevertheless, the protection of intellectual property rights in Israel should be further strengthened by adapting the local law to the accepted standards in other countries, and explicit regulatory protection should be provided for confidential information contained in the registration dossiers of biological medicines.

6. PROMOTING INNOVATION AND DEVELOPMENT IN ISRAEL

As stated in this report, the innovative pharmaceutical industry is the industry that invests the highest ratio of its business turnover in research and development. In order to attract multinational companies to open research and development centers in Israel, action must be taken to create an attractive business and professional environment and to provide incentives to the field of drug research and development.

Several government life science and healthcare programs are already underway today that serve to attract companies to Israel, including the national digital healthcare program, which provides incentives for pilots and studies that integrate academia and industry in the digital healthcare arenas and improves the access to medical information (2017); the IPMP program (Israel Precision Medicine Program) to promote precision medicine initiatives for innovative and breakthrough research in Israel (2019); and the Bioconvergence Program, which is designed to integrate the fields of biotechnology and software and engineering (2020).

As part of the latter program, four multinational innovative pharmaceutical companies, in collaboration with Amazon, are planning to establish a computational laboratory and a biological research laboratory during 2021. The laboratories' objective is to integrate artificial intelligence into biology and medicine during the development of new medicines and therapies.

Experts in the industry argue that the success of these laboratories could facilitate an increase in AI-based research

and development and in other advanced technologies that may lead to the establishment of drug development centers in Israel. Such centers could constitute major growth engines for the local economy, as is already evident in comparable international markets.

In addition to these programs, it is critically important to increase investments in infrastructures and research incentives in healthcare organizations, which are critical components of the ability to engage in practical research and development in the field of healthcare towards new discoveries and applications.

Israel's investments in these infrastructures are currently lower than in other advanced countries and, as stated, a significant share of the infrastructure is being funded and operated by the innovative pharmaceutical companies. These conditions limit capabilities of developing and positioning Israel at the vanguard of international medical research.

Concurrent with the development of infrastructures in the various health organizations, the government should strive to develop national infrastructures and collaborations with the entire life sciences industry and should harness innovative pharmaceutical companies and their vast knowledge in order to advance practical and marketable scientific developments and applications.

To summarize: innovative pharmaceutical companies strive to continue advancing public health, improving current standards, expanding employment opportunities, being partners in the healthcare community, in research and innovation in Israel and expanding their research and development activities while leveraging the capabilities in the local economy.

They welcome the recent life science and healthcare programs that have been advanced and are pleased to be partners in them, and they encourage the advancement of measures to improve and streamline drug registration regulations, including the link with counterpart international health authorities, the advancement of the digitization of pharmacotherapy recordkeeping and management, and increasing investments in research and innovation infrastructures in Israel.

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PHARMA ISRAEL – ASSOCIATION OF R&D-BASED PHARMACEUTICAL COMPANIES OPERATING IN ISRAEL

Pharma Israel represents multinational innovative pharmaceutical companies that are world leaders in the development of medicines, vaccines and innovative medical technologies.

Pharma Israel's main goal is to improve the regulatory environment of the innovative pharmaceutical industry with the objectives of improving public health, providing patients in Israel with greater access to medicines and to the world's most advanced technological developments, as well as to promote research and development activities in Israel.

Pharma Israel strives to be an active partner in policy-setting processes in the healthcare sector. It maintains frequent and fruitful dialogues with government ministries, public entities and organizations in Israel and abroad that engage in the healthcare sector in general and in medicines in particular.

Since its founding in 1999, Pharma Israel has taken an active part in: increasing patients' access to innovative original drugs in Israel; improving and streamlining the drug registration process in Israel; strengthening the intellectual property environment; increasing the volume of clinical research in Israel; and promoting suitable conditions for expanding investments. All of these activities have contributed significantly to strengthening the State of Israel's standing as a hub for medical research and the early adoption of breakthrough medicines and medical technologies.



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