

ISRAEL - A SOLID TRACK RECORD IN CLINICAL RESEARCH



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In January 1994, President Bill Clinton and Prime Minister Yitzhak Rabin announced the creation of the US-Israel Science and Technology Commission. One of the objectives of the commission was to promote cooperation between the two countries in the field of science and technology, with emphasis on harmonisation of regulatory standards for drug development and approval. As part of the programme, FDA officials provided training in GCP, GLP and GMP to both Israeli Ministry of Health officials and industry professionals.

Clinical research, on behalf of international drug companies, mainly European, has been conducted in Israel since the mid 1970's, however, as a result of the harmonisation process, numerous multinational drug companies established R&D centres in Israel and placed an increasing portion of their clinical research in Israeli institutions. In addition, many global contract research organisations (CROs) have followed suit and have been enjoying impressive growth rates ever since.

Life Science Credentials

Israel has emerged as one of the world's most prominent centres of R&D in biotechnology and life sciences, has the largest per capita number of scientists in the world and is currently ranked third place in the world with regard to the number of new life science patents registered.

Through its special biotech initiative, the government has made it a top priority to assist biotech companies to accelerate the development of early-stage drug candidates. In addition to providing research grants,

government-sponsored technology incubators offer operational, regulatory and commercial expertise to get companies ready to attract private investment. In the past five years, several private incubators have been established based on collaboration between academic institutions, venture capital firms and the drug industry.

Several prominent drugs, such as Copaxone®, Rebif®, Exelon®, Doxil® and Rasagaline/Azilect® originated in Israeli academic research at the Weizmann Institute of Science, the Hebrew University of Jerusalem and the Hadassah Medical Center (see Table 1). Currently, 18 Israeli drugs are in advanced stages of clinical development, encompassing small molecules, biologics and cell therapeutics. Dozens more are in preclinical development.

Table 1: Marketed Drugs of Israeli Origin

PRODUCT	INDICATION	ORIGINATOR	DEVELOPER
Copaxone®	Multiple Sclerosis	Weizmann Institute of Science	TEVA
Relif®	Multiple Sclerosis	Weizmann Institute of Science	Serono
Gonal-F®	Infertility	Weizmann Institute of Science	Serono
Exelon®	Alzheimer's Disease	Hebrew University of Jerusalem	Novartis
Doxil®	Ovarian Cancer	Hadassah Medical Center	Johnson & Johnson
Rasagaline® Azilect®	Parkinson's Disease	Technion Institute of Technology	TEVA

Recognising the high potential in Israel, numerous international drug companies have set up special task forces actively seeking opportunities to purchase early-stage drugs or the rights to develop and market them.

The Healthcare System

Israel has a population of over 7.3 million people and its healthcare system, governed by the National Health Insurance Law, operates 47 general hospitals and over 2,000 community-oriented primary care clinics which employ about 32,000 physicians. Medical centres affiliated with one of the country's four medical schools are heavily involved in basic and clinical research, and many of their staff members have had fellowship training abroad in specialised fields. The hospitals have a modern infrastructure, are generally well equipped and provide medical care comparable to Western standards.

The country allocates 8.3% of its GNP to health (2004) and enjoys a relatively low infant mortality rate (4.5 per 1000 live births) and an average life expectancy of 81.8 years for females and 77.6 years for males.

The Clinical Trial Landscape

Over the past three decades Israel has been involved in the conduct of clinical trials. European drug companies, among them Bayer AG, Boehringer Mannheim, Hoechst AG (that merged with Rohne-Poulenc to become Aventis), Hoffman-La Roche and many others, were the first to place their late-stage development projects in Israel, followed by American and Japanese drug companies. Israeli hospitals have since participated in numerous global academic (TIMI Study Group, EORTC and others) and industry trials and have consistently demonstrated not only exemplary enrolment rates, but a high level of data quality and compliance with applicable guidelines and regulations. In the past 15 years, the number of foreign registration studies has grown substantially with a shift towards more complex, early-stage clinical trials.

In 2007, 276 clinical drug trials were initiated at 1,067 study sites, and their contribution to Israel's gross domestic income, from investigator grants only, was about 400 million US dollars. In addition, about 80 medical device trials were conducted in that year at 545 study sites.

The Ministry of Health, the Israeli Medical Association and the academia appreciate the importance of clinical research to society, improved patient care, medical education and international scientific collaboration. It is therefore important that they all work in tandem to further expand the capacity and competence of clinical trial personnel. To ensure high quality, ICH-compliant clinical trials, most hospitals have made GCP training mandatory for investigators and their study personnel, while periodic inspections and audits are conducted by the Directors of Hospital and the Ministry of Health. Furthermore, an increasing number of clinical research professionals have gained Association of Clinical Research Professionals (ACRP) certification, attesting to their drive for professionalism and excellence in that field.

Clinical Trial Authorisation

In Israel, a sequential review process is in place, where study protocols are first reviewed by the Institutional Ethics Committee (EC) of each participating hospital, and subsequently by the MOH. However, so called "special trials", i.e. Phase 3 trials or trials with compounds with which the MOH is familiar based on prior review of earlier stage protocols, require only local EC and Director of Hospital approval. The average timeline for

approval of study protocols in that category is about six to seven weeks. Though all other trials require MOH approval, only about 30% of those "non-special trials" are reviewed by the MOH Central Committee's panel of experts. These are mainly first-in-man and paediatric clinical trials. The average timelines are 12 and 18 weeks for the non-special, not first-in-man trials and those requiring Central Committee review, respectively.

Eager to further streamline the clinical trial review process, the current draft legislation for clinical trials in humans proposes the adoption of a parallel review process that should significantly reduce approval times.

Key Success Factors

What are the key success factors that drive Israel's continued growth and attractiveness for clinical research, despite the emergence of lower cost countries with several-fold larger populations?

The scientific and medical expertise in many therapeutic areas is probably one of the most important assets Israel has to offer. Clinicians have a genuine interest and passion in pioneering novel therapeutic approaches, and when specialised expertise is required, there are many leading names to choose from. Secondly, disease-specific, nationwide clinical research networks have been established that operate under the leadership of experienced professionals providing administrative and logistic support to participating study centres. Similarly, nearly all major medical centres have built an effective research support infrastructure accessible to clinicians that conduct clinical trials. Furthermore, by virtue of the public healthcare system, community and hospital physicians collaborate closely in the management of their patients, which facilitates the referral of patients who wish to participate in therapeutic trials to a study site for a specific research programme.

Since most hospitals and community clinics maintain patient records electronically, information regarding the prevalence of specific disorders and the suitability of patients for a specific programme is easily retrievable, which expedites the feasibility assessment prior to committing to a clinical trial.

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that they talk to veteran companies who will unequivocally confirm that, in contrast to common perceptions, these circumstances have had minimal impact, if any, on their programmes.

Summary

Although Israel is no longer the cheapest country for conducting clinical trials, multinational drug companies acknowledge the quality of research and the "can-do" attitude of Israeli investigators. Israeli sites have consistently lived up to their enrolment targets, and frequently exceeded them. ■



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