Chapter 17

ISRAEL

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I INTRODUCTION

The life sciences industry in Israel is a dynamic and ever-growing industry that evolves in tandem with developments in the respective fields of science and technology. The Israeli life sciences industry consists of various disciplines, such as medicinal preparations, medical devices, biotechnology, etc. and includes, inter alia, leading international companies (e.g., the world’s largest generic pharmaceutical company and one of the ten largest pharmaceutical companies in the world).

The life sciences industry in Israel is highly regulated. Medicinal preparations (‘preparations’) are mainly regulated by the Pharmacists Ordinance,\(^2\) corresponding regulations,\(^3\) procedures and guidelines issued by the Ministry of Health (MOH).

The Israeli regulatory regime of medical devices (‘devices’) is currently under development. The Medical Devices Law was enacted in 2012, and the MOH is currently in the process of drafting various regulations and guidelines.\(^4\)

The regulatory authorities for preparations and devices are the Pharmacy Department and the Medical Devices Department, within the MOH.

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1 Dovev Apel is a partner at S. Horowitz & Co.
2 The Pharmacists Ordinance (New Version) 1981.
3 The Pharmacists Regulations (Preparations) 1986; the Pharmacists Regulations (Good Manufacturing Practice) 2008.
4 The Medical Devices Law 2012. The Law will enter into force only after the relevant regulations are enacted. At this stage, only a portion of the regulations has been enacted (viz., the Medical Device Regulations (Registration of a Medical Device and the Renewal Thereof), 2013). Nonetheless, in February 2014 the MOH published a Circular advising on the implementation of the principles of the Medical Devices Law as of April 2014.
II THE REGULATORY REGIME

i Classification

Generally, the distinction between preparations, devices and other products (e.g., biological preparations and food supplements) is based on their respective definitions, as outlined in the applicable legislation.

For products constituting combinations of preparations and devices, or whose classification is unclear or disputed, the MOH’s guideline provides that classification would be based on the product’s primary mode of action. If a product is registered in more than one ‘recognised country’,\(^5\) including the United States, the preference will generally be the classification of the US Food and Drug Administration.

For preparations, the guidelines also distinguish between generic and innovative products. The registration of a generic preparation is an abbreviated procedure, mainly involving proof of bioequivalence to the reference innovative preparation.

Israel is a ‘second-line’ country (i.e., the registration and marketing authorisation as granted by a recognised country\(^6\) would be a condition for the registration and marketing in Israel).

Additional categories of preparations include ‘biological preparations’ and their follow-on versions called ‘biosimilars’. Biosimilars are distinguished from standard generic preparations, mainly owing to the complexity of the biological active substances that render their follow-on versions as similar, albeit not identical. The registration of biosimilars thus requires experimental data (clinical and non-clinical) proving their similarity to reference preparations, from the perspective of quality, safety and efficacy. Furthermore, biosimilars and their reference preparations are not interchangeable, unless decided otherwise, \textit{ad hoc}, by the MOH.

ii Non-clinical studies

The regulation of non-clinical studies in Israel focuses on experimental testing carried out on animals.\(^7\)

In general, animal testing is approved, provided that the goals of the experiment cannot be met by reasonable alternatives. Additionally, experiments may not be performed for cosmetic testing purposes. Experiments on animals must be conducted by a qualified investigator, approved by the Council for Animal Experiments. The Council

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5 The recognised countries under the Medical Devices Law are: Austria; Belgium; Britain; Canada; Denmark; Finland; France; Germany; Greece; Iceland; Ireland; Italy; The Netherlands; Norway; Portugal; Spain; Sweden; Switzerland; and the USA.

6 A ‘recognised country’ is defined in the Pharmacists Regulations as any one of the following: Australia; Canada; each member of the EU; Iceland; Israel; Japan; New Zealand; Norway; Switzerland; and the USA.

also issues permits to institutes performing studies. Institutes carrying out studies are required to report to the Council annually, and upon discovery of failures or problems with the experiment.

The Council is further required to appoint an audit committee to investigate claimed violations of the original experiment permit. Punitive sanctions may be imposed, for example, where an experiment is performed without the proper permits.

Furthermore, non-clinical studies must be carried out in an authorised accredited laboratory in compliance with the OECD’s Principles of GLP.8

### iii Clinical trials

Clinical trials are largely regulated by regulations and guidelines,9 which outline the procedure for filing applications for the conduct of clinical trials and their approval process.

Generally, an application must be approved by the managers of the Institute, the Helsinki committee of the institute (the Israeli term for the Institutional Review Board, the IRB) and the MOH, prior to the clinical trial. ‘Special clinical trials’, in which the level of risk to the subjects is limited and which give rise to no exceptional ethical issues concerning the risks-benefits balance, generally do not require the MOH’s approval. The classification of a clinical trial as special or non-special should be determined by the IRB within 48 hours from the receipt of the full application. Applications of non-special trials are transferred immediately to the MOH.

An application can be submitted only by a licensed physician. Additionally, the application requires the submission of the sponsor’s undertaking form.

Furthermore, the engagement between the sponsor and the lead investigator requires the approval of a committee established and operated under the supervision of the MOH.10

The investigator is required to obtain the participant’s informed consent in writing, following a clear, verbal, non-pressuring explanation. The Investigator is further required to inform the participants of any new information that could affect their decision to participate.

The lead investigator and the sponsor are required to report to the MOH of the clinical trial’s progress and conclusion, including serious adverse events.

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8 Under the Laboratory Accreditation Authority Law 1997, laboratories in Israel are accredited in accordance with the OECD’s Principles of Good Laboratory Practice (GLP), including non-clinical in vitro experiments.

9 The Public Health Regulations (Medical Trials in Human Beings) 1980; the MOH Guidelines for Medical Trials in Humans, as updated in 2014.

10 Circular No. 4/10, ‘Rules for the engagement of MOH Institutes with commercial companies’ (‘Circular 4/10’).
iv  Named-patient and compassionate use procedures

Preparations

Generally, a preparation may be marketed in Israel only if it is registered in the registry of preparations, by the MOH. Nonetheless, the MOH is authorised, under corresponding regulations and guidelines, to approve the marketing of a preparation even if it is not registered, or not in accordance with its registration, provided that the preparation falls within the specified exemptions, and provided further that it does not harm public health. These exemptions include, *inter alia*, preparations imported by a pharmacy or sick fund or manufactured in Israel in small quantities.\(^\text{11}\)

Said exemption may be applied for the importation of a preparation for the personal use of a specific patient (‘a named patient’). It further applies to ‘essential medical treatment’ and ‘compassionate use’.\(^\text{12}\)

Devices

A device may also be marketed in Israel only if it is registered with the MOH, unless it falls within the products listed in the Second Addendum to the Law.

Furthermore, the MOH is authorised, under corresponding regulations, to approve the manufacturing and marketing of devices that are unregistered or not in accordance with their registration, *inter alia*, for ‘essential medical treatment’ and ‘compassionate use’.

v  Pre-market clearance

Preparations

As previously noted, a preparation may be marketed in Israel only if it is registered with the MOH, unless it falls within the specified exceptions and provided that it will not harm public health.

An application to register a preparation may only be filed by an Israeli resident or a company registered in Israel.

A preparation will be accepted for registration upon the following principle conditions:

- the preparation satisfies the quality requirements, and is found to be appropriate for medical use;
- the preparation is found to be safe and efficient for its intended use and its name is not misleading;
- the preparation is manufactured in accordance with good manufacturing practices (GMP); and
- the registration holder maintains a pharmacovigilance (PV) system.

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11  Section 29(a)(3) of the Pharmacists Regulations.
12  Circular No. 19/07, ‘Approval of medicinal preparation according to Section 29 of the Pharmacists Regulations (Preparations), 1986, and the attached Notice concerning the Manager Consent according to the Pharmacists Regulations (Preparations), 1986’ (‘MOH Circular No. 19/07’).
For imported preparations, a Certificate of Pharmaceutical Product (CPP), indicating the approval and marketing of the preparation in a recognised country, is further required.13

The MOH may further register the preparation subject to certain conditions, for post-registration control purposes.

A manufacturer or an importer of preparations is required to obtain GMP approval from the MOH, in order to ensure the quality and safety of such preparations.

According to the GMP Regulations, the manufacturer of a preparation will verify manufacture of the active pharmaceutical ingredients (API) in accordance with GMP, by carrying out audits at their manufacturing sites. Where such audits cannot be carried out, other means of verification may apply.

For generics, the Registration Guideline provides an abbreviated registration procedure.

For biological preparations and biosimilars, the MOH guideline generally adopts the policy of the European Medicines Agency (EMA).14

Under the MOH’s policy,15 homeopathic products are not registered as preparations, since their therapeutic efficiency has neither been proven to, nor considered by, the MOH. Homeopathic products are approved for importation and marketing, provided their safety is proven.

Attribution of medical indications or therapeutic characteristics on packaging and on any advertising material is prohibited, unless approved by the MOH in advance, based on clinical data.16 Homeopathic products are stored in pharmacies behind the counter, separated from preparations and sold by a pharmacist. The holder of the marketing authorisation is required to report any complaint or suspected adverse event to the MOH.

Devices

As noted above, a device may be marketed in Israel only if it has been registered with the MOH, unless listed in the Second Addendum to the Devices Law, and save for the exemptions mentioned in Section II.iv, supra.

An application to register a device with the MOH may only be filed by an Israeli resident or by a company registered in Israel.

The basic requirements for the registration of devices are: (1) the benefit outweighs the risks; (2) the device has been found to be efficient and of appropriate quality for its intended use; (3) the device has been manufactured according to GMP; and (4) the device’s name is not misleading.

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13 Guideline REG 08_2012, ‘Procedure for Filing Applications for the Registration of Medicinal Preparations (including Amendments and Renewals)’ (‘the Registration Guideline’).
14 Guideline No. 127, ‘Registration Conditions and Use Policy for Biosimilar Preparations’ (‘Guideline No. 127’).
15 Guideline No. 10, ‘Homeopathic Products’.
16 Additional restrictions concerning the advertisement and labelling of homeopathic product are detailed in the said MOH guideline.
However, if the device is registered or approved for marketing in one of the countries listed as a recognised country and is being marketed in said country, the MOH will register the device for the same period as approved in such recognised country.

vi Regulatory incentives

**Patent term extension**

The Israeli Patents Law\(^\text{17}\) empowers the Registrar of Patents to extend the term of certain patents for an additional term not exceeding five years beyond the 20-year period of protection. Such extension order may be granted only with respect to ‘basic patents’, protecting a preparation, a substance (an API), a process for the manufacture of such substance or preparation or the use thereof, or a device for which licensing is required.

An extension order will be granted only if the following conditions are met:

a the substance, the process for its manufacture or use or a preparation that contains the substance or the process for its manufacture, or the device, has been claimed in the basic patent that is in force;

b a preparation containing the substance is registered in the Registry of Pharmaceutical Preparations;

c the registration according to paragraph (2) is the first registration allowing for use of the substance in Israel for medicinal purposes;

d no prior extension order has been granted in respect of the basic patent or the substance;

e the application for the extension order has been filed in good faith;

f the scope of protection to be granted under the extension order will not exceed the protection granted under the basic patent;

g an extension of the patent term protecting such preparation or device (‘the reference patent’) has been granted in the US; and

h an extension to the reference patent has been granted and has not yet expired in one or more of the following EU Member States: France, Germany, Italy, Spain and the UK (‘the EU five’).

In the event that marketing authorisation has not been obtained in the countries designated in points (g) and (h) above (commonly known as the ‘two states requirement’), the conditions set out in those paragraphs shall not apply.

Subject to the following, an extension order shall remain valid for a period equal to the shortest extension afforded to the reference patent in a recognised country.\(^\text{18}\) In any event, the extension term will not exceed five years. The extension order further provides that the overall period of the Basic Patent and the extension order shall terminate no later than 14 years from the date the first marketing authorisation in a recognised country. Moreover, the extension order shall expire no later than the first date of expiry of the extension period granted in a recognised country, in which marketing authorisation has been obtained, or revocation of any reference patent.

\(^{17}\) The Patents Law 1967 (the Patents Law).

\(^{18}\) A ‘recognised country’ is defined, for this purpose only, to mean the EU five and the US.
The extension term will also expire, *inter alia*, if: (1) the registration of the preparation containing the substance is cancelled; or (2) the basic patent is revoked or amended in such a way that the substance, the process for its manufacture, the use of the substance, the preparation incorporating the substance or the process for its preparation, or the device, is no longer protected under the patent.

An application for an extension order should be filed 90 days following the grant by the MOH of marketing authorisation. This period is not extendable.

**Market exclusivity for originator products**

Israeli law provides, under certain circumstances, protection to confidential data submitted as part of a marketing authorisation application, provided that its origination entailed considerable effort. New chemical entities (NCE) registered in Israel are therefore entitled to a period of market exclusivity, during which the MOH will not issue a marketing authorisation for a new medicinal product containing said NCE. No regulatory exclusivity period is granted for a new indication.

The market exclusivity period will be capped by the earlier of the following:

a. six years from the registration date of the preparation that contains NCE in Israel; or
b. six years and six months from the registration date of the preparation that contains NCE in a recognised country.¹⁹

Other provisions aimed to encourage the furtherance and development of products for rare diseases, diseases that are prevalent in developing countries and pediatric use, are not available in Israel.

**vii Post-approval controls**

**Preparations**

The registration holder of a preparation is required to manufacture²⁰ or import preparations only in accordance with the registration conditions, including validated infrastructure and facilities. In addition, the MOH is authorised to conduct periodic inspections of the plant, in accordance with the EMA Guidelines.²¹

A registration holder may engage subcontractors to carry out the manufacturing and importation activities. However, the parties’ respective responsibilities should be clearly defined in the contract.

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¹⁹ Including Australia, Canada, members of the EU, Iceland, Japan, New Zealand, Norway, Switzerland and the USA.
²⁰ Under the Pharmacists Ordinance, the term ‘manufacturing’ is defined broadly as including ‘mergence, blending, assembly, refining, processing, transformation and activation of any chemical or physical process for the preparation of a product or the packaging of a product’.
²¹ EMA/572454/2014 ‘Compilation of Community Procedures on Inspection and Exchange’.
The manufacturing department of the registration holder is required to control the manufacturing process, in accordance with written and approved standard operating procedures, perform validation of new processes or major changes, and periodic revalidation of key stages of the manufacturing processes.

Furthermore, the manufacturer or importer must maintain an independent quality assurance department (QA). The QA is required, inter alia, to deal with complaints concerning the quality of the preparation and to investigate recalls from the market.

The first batch of a registered preparation must be approved by the MOH prior to being marketed in Israel for the first time.

The registration holder is also required to establish and maintain a PV system and to appoint a qualified person for pharmacovigilance.22

The registration holder is required to inform the MOH of any relevant change to the registration conditions. The manufacturer may not make material changes unless approved in advance by the MOH.23

Unauthorised changes could constitute grounds for the revocation of a registration. The MOH might also revoke a registration if the product may cause harm or is found to be inefficient, or if its registration requirements are not met. The MOH is required to allow the registration holder to submit arguments prior to rendering its final decision in this regard.

Under certain circumstances, the MOH is authorised to order a recall for the removal of preparations from the market.24

Following notification by the manufacturer, the MOH will delete an agent’s status as registration holder. The MOH may, in accordance with the manufacturer’s notification, approve a new agent as the registration holder. The previous registration holder may continue marketing his or her inventory for a period of one year.

As noted in Section II.v, the MOH may subject the registration of preparations to certain conditions for post-approval control purposes. One such condition – the existence of a regular and ongoing supply – was recently addressed by the MOH, by directing the registration holders to hold, at any point in time, an inventory sufficient for at least 30 days of consumption (beyond the ongoing inventory available in pharmacies and clinics). In exceptional cases (e.g., preparations with a short shelf life), an exemption must be approved in advance.

Furthermore, a registration holder is required to inform the MOH of temporary marketing cessation or the expected shortage of a preparation in Israel, six months in advance. Accordingly, it is mandatory that the registration holder maintain an inventory of preparations intended to be marketed in Israel for a minimum period of six months.

22 Guideline No. 6, ‘Reporting on Adverse Events and New Safety Information’.
23 Guideline No. EX-009/01, ‘Guideline for Filing an Application for Change in a Medicinal Preparation from the Quality Aspect’.
24 Guideline No. 3, ‘Prohibition of Use of a Medicinal Preparation and/or its Recall from the Market’.
Biosimilars require strict monitoring and proactive reporting of adverse reactions as well as the submission of a risk management plan, risk evaluation and mitigation strategy.\textsuperscript{25}

**Devices**
The registration holder is required to inform the MOH of any change in the data submitted at the time of registration of the device.

The Minister of Health is authorised to enact regulations pursuant to which the registration holder will be required to perform follow-up operations and inspect the registered device. Regulations of this nature have not yet been drafted.

The Minister of Health is also authorised to enact regulations regarding post-marketing surveillance, including a duty to report to the MOH of any known ‘special event’ arising in connection with registered devices. Such special events include:

\begin{itemize}
\item[a] a serious malfunction in the device that may endanger the patient’s health;
\item[b] use of the device that caused or was suspected of causing unexpected damage to the patient’s physical or mental health, or that caused significant damage or death; and
\item[c] action taken by any health authority or an announcement published by the manufacturer, the registration holder or any health authority concerning the device, its marketing and use, or any new safety data published in the main scientific literature in the field.
\end{itemize}

Regulations of this nature have not yet been drafted. However, a MOH guideline is currently being drafted based on the corresponding American and European guidelines.

The Minister of Health is authorised to enact regulations for the recycling of disposable devices. At this stage, said regulations have not yet been drafted.

\textit{viii Manufacturing controls}

**Preparations**
As noted in Section II.vii, the GMP Regulations largely include conditions under which a manufacturer or an importer can obtain GMP approval from the MOH, and the basic requirements for manufacturing and testing preparations, in order to ensure their quality and safety.

The responsible pharmacist is required to notify the MOH of any transfer of ownership of the relevant manufacturing facilities.

**Devices**
One of the basic requirements for the registration of a device is that it is manufactured in compliance with the GMP requirements.

\textsuperscript{25} Guideline No. 127.
Marketing a device in Israel requires a certificate from the health authority or equivalent regulatory body of the country in which the device was manufactured, certifying that the manufacturer's GMP standards accord with the requirements of ISO 13485.

Here too, the registration holder must notify the MOH of any transfer of ownership of the relevant manufacturing facilities.

ix Advertising and promotion

Preparations

The term ‘advertising’ is defined in the Pharmacists Regulations as an act of disseminating information, in writing, through the media or by any other means.

The Pharmacists Regulations distinguish between advertisements directed at health-care professionals and those directed at the general public and advertisement of prescription and non-prescription preparations. As a general rule, advertising a preparation cannot contradict its registration, nor can it attribute indications which were not specifically approved.

Advertisements for health-care professionals, of prescription and non-prescription preparations, are permitted, provided they emphasise the approved indications.

Online advertising for health-care professionals is permitted, subject to certain limitations, such as applying mandatory means to identify users prior to them gaining access to said information.

In contrast, advertising of prescription preparations directed at the general public is prohibited. However, under special approval, explanatory information may be handed personally to a patient by the attending physician.26

MOH guidelines concerning the improvement of compliance in patients who were prescribed preparations and raising the public awareness of various diseases27, may also allow registration holders to provide patients with a broader range of information. However, such information cannot include advertising content or encourage the consumption of preparations.

Advertising of non-prescription preparations is permitted, subject to its preliminary approval by the MOH. Such advertising must be accurate, clear and consistent with the registered indications. The regulation sets forth mandatory data that must be included in such advertising, as well as data that must be excluded. Restrictions are also imposed on

26 Guideline No. 24, ‘Advertising of Medicinal Preparations in accordance with Regulation 28’ (‘Guideline No. 24’).

27 Guideline No. 137, ‘Rules for the Improvement of Educated Use and Medicinal Treatment Compliance in Patients who were Prescribed with Prescription Medicinal Preparations, via Noncommercial Information’; Guideline No. 134, ‘Raising Diseases Awareness - Rules for the Accessibility of Information to the General Public, Funded or Conducted under the Auspices of a Registration Owner or a Third Party’.
advertisements including a comparison between products. An unapproved advertisement may result in a clarification notice, cancellation or prohibition of the advertisement and cessation of future marketing or cancellation of the product’s registration certificate.  

Promotion of preparations is also prohibited, specifically, raffles, handing out sample products or promising an additional preparation.

The rules of the Broadcasting Authority and the Second Authority for Television and Radio further regulate broadcasted commercials and the concession owner’s liability with regard to misleading health-related advertisements or the unauthorised advertisement of medicines. While the former prohibits almost all forms of advertisement of preparations, the latter allows commercials for non-prescription preparations, under various circumstances.

**Devices**
The MOH is authorised to supervise the advertising of devices but, currently, no regulation to this effect has been drafted.

x Distributors and wholesalers

**Preparations**
The Pharmacists Ordinance distinguishes between wholesale and retail marketing. While wholesale marketing may only be carried out by a wholesale pharmaceutical business or a health institution, retail marketing may only be carried out by a pharmacy.

Under the GMP Regulations, preparations and APIs must be distributed under Good Distribution Practices (GDP). In this context, Israeli law adopted the principles of the EU regulatory regime.

Furthermore, a wholesale pharmaceutical business used for the storage or transportation of APIs must comply with the GDP requirements. The MOH is authorised to conduct periodic audits of such businesses, in accordance with risk management and a list of priorities, at least every three years, following which a GDP certificate may be granted.

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28 Guideline No. 24, Section 3.7; a letter from the MOH to Responsible Pharmacists, manufacturers, importers, and owners of registered preparations.


31 A ‘wholesale pharmaceutical business’ is defined in the Pharmacists Ordinance as a business run by a Responsible Pharmacist, used for the storage, wholesale or wholesale distribution of medicinal preparations or pharmaceutical raw materials.
**Devices**
Transportation and storage of devices can be performed only by a licensed business that possesses a certificate from an entity recognised by the MOH, certifying its compliance with the requirements of ISO 9001.

**xi Classification of products**

**Preparations**
The Israeli legislation distinguishes between distribution of prescription (Rx) and over-the-counter (OTC) preparations, which can only be performed by a pharmacist, and distribution of general sales list (GSL) preparations, which may not necessarily be carried out in a pharmacy or by a pharmacist.

The classification of the relevant preparations is determined by the MOH, at the time of registration. The registration holder may apply to reclassify an Rx preparation as OTC.

**Devices**
The MOH is authorised to register a device, subject to certain conditions and restrictions, including restricting its use to professionally qualified personnel and/or only in accordance with a physician’s order.

Furthermore, the MOH is authorised to prescribe technical specifications for devices on the basis of which regulations were enacted for the licensing of special devices used by medical institutions, such as MRIs and CT scanners.\(^{32}\)

**xii Imports and exports**

**Preparations**
Under the Pharmacists Ordinance, the term ‘marketing’ is broadly defined to include ‘importing’. The following are required in order to obtain an approval to import a preparation into Israel:\(^{33}\)

\(a\)
- a CPP indicating the approval and marketing of the preparation in a recognised country;

\(b\)
- importation may only be performed by a pharmaceutical company, a wholesale pharmaceutical business or a storage facility of a health institute;

\(c\)
- an application for an import certificate may be filed only by a pharmacist appointed by the applicant and approved by the MOH; and

\(d\)
- the preparation must be registered in the Registry of Preparations, or fall within the specified exemptions of preparations that may be manufactured, marketed and used even if unregistered, or not in accordance with its registration.\(^{34}\)

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\(^{32}\) The Public Health Ordinance, 1940; the Public Health Regulations (Special Medical Devices) 1994.

\(^{33}\) The Pharmacists Regulations; the GMP Regulations; the Registration Guideline; MOH Guideline No. 33, ‘Importation and Marketing of Medicinal Preparations and Pharmaceutical Materials’; and MOH Circular 19/07.

\(^{34}\) Section 29 of the Pharmacists Regulations.
The MOH will not issue an import certificate, unless the following conditions are met: (1) the preparation was transported into Israel by licensed dealers in recognised countries; and (2) en-route to Israel, the preparation was stored only in recognised countries.

Special permits are required for importation and exportation of narcotics. Importation permits are valid for one year, while exportation permits are valid for only three months, with the possibility of three months’ extension. Special permits are also required for importation of psychotropics and dangerous drugs.

**Devices**
The term ‘marketing’ in the Devices Law is similarly defined broadly to include ‘importation’ of devices. Therefore, identical principal requirements applicable to the importation of preparations, apply to devices.

The registration holder is required to identify the importer in the registration application, and the MOH will include the importer’s details in the registration certificate, on the basis of which the importer can then apply for an import permit.

Marketing an imported device requires a certificate from the health authority or any other regulatory body of the country in which the device was manufactured, certifying that the manufacturer’s GMP standards satisfy the requirements of ISO 13485. Furthermore, carriers of devices must possess a certificate from an entity recognised by the MOH, certifying that their storage and transportation conditions meet the requirements of ISO 9001.

**Controlled substances**
Narcotics may be supplied in Israel only by a licensed pharmacist to hospitals, doctors, licensed pharmacists, a person who has been prescribed a narcotic or a person who holds a permit to buy narcotics. A permit for the manufacturing, possession or use of narcotics may be granted by the MOH, subject to specific disclosure requirements.35

A manufacturer or a wholesaler of psychotropics may only sell drugs listed in the First Addendum to the Pharmacists Ordinance to doctors, licensed pharmacists, dentists, veterinarians or permit holders. In addition, a manufacturer or a wholesaler may not engage in the retail of psychotropic drugs, unless it is separate from the wholesale business.

**Enforcement**

**Preparations**
The MOH has a general authorisation to inspect and enforce regulations relating to the registration, manufacturing and marketing of preparations.

The MOH is authorised to impose administrative sanctions if a business is conducting itself in a way that harms or could harm public health, contrary to the Pharmacists Ordinance, the GMP Regulations or the preparation’s registration.

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35 The Dangerous Drugs Ordinance (New Version) 1973; and the Dangerous Drugs Regulations 1979.
conditions. Such sanctions include, *inter alia*, prohibition of the manufacture or sale of preparations or APIs and, if required, the seizure and destruction of preparations. The MOH may further deny its approval of the business, delay its issue, or not renew it.

The Pharmacists Ordinance generally authorises the imposition of criminal sanctions following breach of its provisions. However, in practice, such sanctions are imposed mainly in cases of pharmaceutical crime (for importation and distribution of counterfeit preparation). Criminal sanctions may also be imposed following non-compliance with the Dangerous Drugs Regulations. Where the offender is a company, the CEO, director or any person who manages the company may be found liable as well.

The MOH may appoint inspectors to supervise the implementation of the provisions of the GMP Regulations. Said inspectors may enter a place where preparations or APIs are manufactured, stored or offered for sale, in order to check them and their manufacturing processes, demand relevant data and documents, etc. Furthermore, the Department for Fighting Pharmaceutical Crime within the MOH is actively involved in the struggle against pharmaceutical crime.

As detailed in Section VIII *infra*, a proposed bill for the amendment of the Pharmacists Ordinance includes provisions relating, *inter alia*, to the imposition of criminal sanctions and administrative enforcement measures, including monetary sanctions, in the event of breach of the respective provisions of the Pharmacists Ordinance or the relevant regulations.

**Devices**

The Minister of Health is authorised to appoint inspectors to supervise the implementation of the provisions of the Devices Law.

If a device ceases to comply with its registration conditions or any of the restrictions prescribed by the MOH, its registration in a recognised country has been revoked, or the MOH suspects that it may harm public health, the MOH is authorised to impose administrative sanctions including discontinuation or restriction of manufacture or marketing of a device or deletion of its registration, restriction on the advertisement and recall from the market.

Furthermore, breach of the following provisions of the Devices Law is considered a criminal offence: (1) manufacturing or marketing unregistered devices, not for personal use, or not in accordance with their registration conditions; (2) instructing the use of, or using, unregistered devices; and (3) instructing the use of, or using, devices not in accordance with the MOH’s instructions or restrictions. It will also be deemed a criminal offence if a registration holder fails to carry out follow-up activities, inspect registered devices, or fails to report special incidents.

In such events, the court has the authority to impose criminal sanctions, including imprisonment and fines. Where the breach is committed by a company, the fines are doubled. Furthermore, office holders may be found liable for offences committed by the company or any of its employees.
III PRICING AND REIMBURSEMENT

The Israeli sick funds are required to provide to all Israeli citizens and residents a basic basket of medications and medical services (the Health Basket),\(^36\) for which the patient pays the deductible price only.\(^37\) The Health Basket is updated annually by the MOH’s general manager, based on the recommendations of the Public Committee.

The Ministers of Health and Finance are authorised to regulate the prices of services and products by issuing a relevant order.\(^38\)

Three means of price regulation are applied in the field of preparations: \(^39\)

\(a\) price-fixing by the regulator is applied with regard to Rx preparations.\(^40\) Under this regulation, the price list is periodically updated. However, owing to continued erosion in preparations’ prices in Israel, a price freeze was recently imposed with respect to low-cost preparations (under 16 shekels);

\(b\) submission of an application prior to increasing prices above the fixed price is applied with regard to OTC preparations;\(^41\) and

\(c\) report of prices and profits is applied with regard to GSL preparations.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

MOH policy, procedures and guidelines are subject to judicial review, within the framework of a petition filed with the Israeli Supreme Court.

Concrete decisions, relating to specific preparations or technologies, are initially dealt with by appeal procedures within the MOH.\(^42\) According to the MOH guidelines, a decision given by the MOH in the appeal process will be considered final. However, in practice, such decision is subject to judicial review, through a petition filed with the Israeli Supreme Court.

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36 The National Insurance Law 1994 (the NIH Law).
37 The deductible price is currently set at 16 shekels. If the price exceeds 118 shekels or 126 shekels, depending on the sick fund, the deductible price will be 15 per cent of the consumer price (if a generic alternative exists, the deductible price will be 10 per cent of the consumer price or 16 shekels, whichever is lower).
38 The Supervision of Prices on Services and Products Law 1996.
40 The Order for the Supervision on Prices of Products and Services (Maximum Prices for Rx Preparations) 2001, outlines the pricing method by referencing prices from several European countries.
41 Guideline for handling a request for the approval of an OTC preparation.
42 Guideline No. 73, ‘Objection to the manager’s decision to reject a request for the registration of a preparation in the register, or to a decision to reject a request for an additional indication, or to a decision to restrict a preparation within its registration’.
V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

Financial relationships between companies that market preparations and devices, and health-care professionals and health institutions and personnel, are subject to general restrictions set out in the Israeli Penal Law, 1977 and the Civil Service Rules, to which civil servants are subject, with regard to, *inter alia*, private practice and employment as well as the acceptance of benefits.

Said relationship is further subject to the restrictions in Circular 4/10,\textsuperscript{43} which requires engagements funded by commercial companies to be approved in advance by the MOH committee.\textsuperscript{44}

Donations made by certain entities to health institutions should be reported annually to the MOH.\textsuperscript{45} A donor who made a donation to an entity in the health field must report annually to the MOH. Furthermore, donations to physicians, pharmacists and investigators, in an amount exceeding the aggregate of 2,500 shekels per year, must also be reported.

The Physicians Association in Israel and representatives of the pharmaceutical companies in Israel published in 2004 a Joint Ethical Convention as a self-regulatory act. The Convention allows for the existence of a professional relationship between the two parties for the purpose of advancing medicine and science, while ensuring the physicians’ independence and professional integrity.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

No specific compensation regulations have been enacted with respect to preparations or devices in Israel. The Damaged Products Liability Law 1980 (the DPL Law) defines a ‘damaged product’ as a product that may cause bodily injury because of a flaw or as a result of disregarding the warnings included in the patients’ leaflet or use instructions. The DPL Law sets out the manufacturer’s liability for compensating a person who suffered bodily injury as a result of a damaged product, regardless of whether the manufacturer was guilty for the damaged product; this compensation is subject to a cap. Alternatively, said person can claim negligence on the part of the manufacturer.\textsuperscript{46} In such event, the manufacturer’s guilt must be established; however, the damage is not limited to bodily injury or to a compensation cap.

\textsuperscript{43} Originally, Circular 4/10 applied to the MOH (including its various units) and the Clalit Sick Fund employees; in practice, it is implemented by additional health institutions.

\textsuperscript{44} For example, trials; holding conferences, seminars and advanced training; publication of a trial’s results; donation of medicinal products and equipment; financing of staff salary; and travels abroad, including the participation in conventions.

\textsuperscript{45} The NIH Law.

\textsuperscript{46} The Civil Wrongs Ordinance (New Version).
VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Patent disputes and, in particular, pharmaceutical patents, are of special relevance to the life sciences sector in Israel.

The Restrictive Trade Practices Law 1988 (the RTP Law) excludes arrangements in which the owner of a patent registered in Israel dictates restrictions relating to the use of its patent. Notwithstanding this, the Restrictive Trade Practices Tribunal has held that this exclusion does not apply to actions of a patent owner who abuses his or her position as a monopoly. Therefore, ownership of a patent does not necessarily establish immunity from supervision under the Law, if the patent owner has a dominant position in the market.

The settlement of patent disputes may also be subject to the RTP Law. Nonetheless, thus far, the Restrictive Trade Practices Authority’s involvement in the pharmaceutical market has been very limited.

Furthermore, under the Patents Law, the Registrar may grant a compulsory licence if the patent owner abuses his or her position as a dominant firm (i.e., a monopoly). However, in practice, very few applications for a compulsory licence have been filed.

ii Transactional issues

Transactions are subject to the provisions of the RTP Law. Restrictive arrangements are prohibited, unless approved in advance or deemed exempt under the RTP Law. Furthermore, mergers that meet any of the thresholds prescribed in the RTP Law may be carried out only if approved in advance by the Controller of Restrictive Trade Practices, provided there is no reasonable suspicion that competition in the relevant market will be significantly harmed, or that the public will be harmed as a result. Granting exclusive licences for long-term periods (or for indefinite periods) may be considered as a merger, and, thus, subject to approval by the Controller of Restrictive Trade Practices.

Furthermore, as noted above, transfer of a marketing authorisation is subject to the MOH’s prior approval.

Transactional issues in Israel relevant to preparations and devices alike also involve patent transactions, such as patent assignment and licensing. The assignment of an invention and patent rights requires a written agreement, and must also be recorded in the Registry of Patents in order to be valid against third parties. A patent owner may grant exclusive or non-exclusive licences to use the patented invention. A licence so granted must similarly be recorded in the Registry of Patents to ensure its validity against third parties. Only an exclusive licence entitles the licensee to initiate infringement proceedings or apply for patent term extension.

VIII CURRENT DEVELOPMENTS

There is a proposed bill for the amendment of the Pharmacists Ordinance (Punitive Measures, Administrative Enforcement and Supervisory Authorities) 2015 (the Bill).

Originally, the object of the Bill was to confront the phenomenon of pharmaceutical crime and, particularly, counterfeit, theft and use of defective preparations. In time,
provisions and requirements previously included in regulations or MOH guidelines were also incorporated into the Bill. During the legislative process, emphasis was also placed on administrative punitive measures.

Among others, the Bill subjects the manufacturing, storage and distribution of preparations to compliance with GMP and GDP.

The Bill lays down a requirement to report a defect in a preparation and authorises the MOH to take action in order to safeguard public health.

The Bill further subjects the manufacturing, marketing and possession of a preparation (or raw material) that is contrary to the registration requirements, and that may mislead customers with regard to an ‘essential detail’ of the preparation, to criminal and civil liability. In this context, an ‘essential detail’ is restricted to the preparation’s name, dosage form, labelling, indication, its classification as a preparation, composition, strength, batch number, expiry date, origin and marketing or release documentation.

The Bill imposes punitive measures, in the form of imprisonment or a fine, based on the type and nature of the offence. In general, six months’ imprisonment would be imposed for misdemeanours committed at the level of retail marketing, while one to three years’ imprisonment would be imposed for serious offences committed at the level of manufacturing and wholesale distribution.

The Bill suggests monetary sanctions of 12,000 shekels to 400,000 shekels, for breach of the respective provisions of the Pharmacists Ordinance and the relevant regulations. Alternative administrative measures of advance warnings and binding undertakings have also been suggested.

The Bill authorises the Minister of Health to determine the circumstances and considerations under which the scope of monetary sanctions detailed above may be reduced.

The Bill also suggests the appointment of inspectors by the Minister of Health, who will have the authority to:

- enter a place where there exists a reasonable basis to assume that supervised preparations are being manufactured, stored or marketed;
- demand information or documents;
- take samples;
- prohibit the continuation of manufacture or marketing of preparations; and
- to the extent required, seize and destroy preparations.