CONTENTS

01 REGULATORY, PRICING, AND REIMBURSEMENT OVERVIEW

1. What are the regulatory authorities with jurisdiction over drugs, biologicals, and medical devices in your country?

Turkey's Ministry of Health ("Ministry") is the main regulatory and responsible authority for drugs, biologicals and medical devices.

Regulatory authorities with jurisdiction over drugs, biologicals and medical devices in Turkey are the:

- Ministry of Health,
- Turkish Medicines and Medical Devices Agency ("TİTCK" - *"Türkiye İlaç ve Tıbbi Cihaz Kurumu").*

2. What is the regulatory framework for the authorization, pricing, and reimbursement of drugs, biologicals, and medical devices?

There are various regulations on authorization, pricing and reimbursement of drugs, biologicals and medical devices in Turkey. In general, these are based on the Law on Pharmaceutical and Medical Preparations numbered 1262 published in the Turkish Official Gazette dated 26 May 1928 and numbered 898 *(İspençiyari ve Tıbbi Müstahzarlar Kanunu)*.

In addition to the main law, other regulations in this area include:

- Law on the Pharmacists and Pharmacies numbered 6197 published in the Turkish Official Gazette dated 24 December 1953 and numbered 8591 *(Eczacılar ve Eczaneler Hakkında Kanun)*,
- Main Law on Medical Services numbered 3359 published in the Official Gazette dated 15 May 1987 and numbered 19461 *(Sağlık Hizmetleri Temel Kanunu),*
- Regulation on the Safety of Medicinal Product published in the Turkish Official Gazette dated 15 April 2014 and numbered 28973 (*İlaçların Güvenliliği Hakkında Yönetmelik),*
- Regulation on Pharmacists and Pharmacies published in the Turkish Official Gazette dated 12 April 2014 and numbered 28970 *(Eczacılar ve Eczaneler Hakkında Yönetmelik),*
- Council of Ministers Decree on the Pricing of Human Medicinal Products published in the Turkish Official Gazette dated 24 February 2017 and numbered 29989 *(Beşeri Ürünlerin Fiyatlandırılmasına Dair Karar)*,
- Regulation on Manufacturing Plants for Human Medicinal Products published in the Turkish Official Gazette dated 21 October 2017 and numbered 30217 *(Beşeri Tıbbi Ürünler İmalathaneleri Yönetmeliği)*,
- Implementing Regulation for Labelling, Package Leaflet and Tracing of Human Medicinal Products published in the Turkish Official Gazette dated

25 April 2017 and numbered 30048 *(Beşeri Tıbbi Ürünlerin Ambalaj Bilgileri, Kullanma Talimatı ve Takibi Yönetmeliği)*,
• Regulation on the Licensing of Human Medicinal Products published in the Turkish Official Gazette dated 19 January 2005 and numbered 25705 *(Beşeri Tıbbi Ürünler Ruhsatlandırma Yönetmeliği)*,
• Regulation on the Surveillance and Examination of Human Medicinal Products published in the Turkish Official Gazette dated 22 March 2005 and numbered 25763 *(Beşeri Tıbbi Ürünlerin Güvenliğinin İzlenmesi ve Değerlendirilmesi Hakkında Yönetmelik)*,
• Communiqué on the Pricing of Human Medicinal Products published in the Turkish Official Gazette dated 29 September 2017 and numbered 30195 *(Beşeri Tıbbi Ürünlerin Fiyatlandırılması Hakkında Tebliğ)*,
• Regulation on Promotion of Medicinal Products for Human Use published in the Turkish Official Gazette dated 3 July 2015 and numbered 29405 *(Beşeri Tıbbi Ürünlerin Tanıtım Faaliyetleri Hakkında Yönetmelik)*,
• Guidelines for the Labelling, Instructions and Tracing of Human Medicinal Products issued by Ministry of Health *(Beşeri Tıbbi Ürünlerin Ambalaj Bilgileri ve Kullanma Talimatına İlişkin Kılavuzlar)*,
• Regulation on Clinical Research for Medication and Biological Products published in the Turkish Official Gazette dated 13 April 2013 and numbered 28617 *(İlaç ve Biyolojik Ürünlerin Klinik Araştırmaları Hakkında Yönetmelik)*,
• Regulation on Traditional Herbal Medical Products published in the Turkish Official Gazette dated 6 October 2010 and numbered 27721 *(Geleneksel Bitkisel Tıbbi Ürünler Yönetmeliği)*,
• Regulation on Clinical Research for Medical Devices published in the Turkish Official Gazette dated 6 September 2014 and numbered 29111 *(Tıbbi Cihaz Klinik Araştırmaları Yönetmeliği),*
• Regulation on Sales, Advertisement and Promotion of Medicinal Devices published in the Turkish Official Gazette dated 15 May 2014 and numbered 29001 *(Tıbbi Cihaz Satış, Reklam ve Tanıtım Yönetmeliği)*,
• Regulation on Medical Devices published in the Turkish Official Gazette dated 7 June 2011 and numbered 27957 *(Tıbbi Cihazlar Yönetmeliği)*,
• Regulation on Test, Control and Calibration of Medical Devices published in the Turkish Official Gazette dated 25 May 2015 and numbered 29397 *(Tıbbi Cihazların Test, Kontrol ve Kalibrasyonu Hakkında Yönetmelik).*

Turkish texts and unofficial translations for some of these can be found at TİTCK's official website: **https://www.titck.gov.tr/Mevzuat**

3. What are the steps to obtaining authorization to develop, test, and market a product?

Developing a medicinal product takes considerable time in Turkey. The Ministry requires strict criteria for each step during this process (testing, licensing or marketing).

The authorization process generally involves:
• Preliminary examination,

- Evaluation of application,
- Approval or denial of application,
- Receiving the authorization of sale.

Pharmaceutical products cannot be launched on the market before obtaining a license, which is granted by the Ministry. To obtain a license, an application must be made to the Ministry by submitting the documents listed under the Licensing Regulation on Medicinal Products.

Before submitting a license application, the applicant must conduct toxicological and pharmacological tests, as well as clinical trials. The Regulation on Clinical Research outlines the procedure for conducting clinical trials. The application procedure begins with submitting a clinical trial dossier simultaneously to both TİTCK and the Ethics Committee (appointed by the Ministry). The Ethics Committee submits its review and assessments to TİTCK. The approval process takes approximately 7 to 15 days. Following the Ethics Committee's assessment, TİTCK delivers a report to the Ministry within 30 days for administrative evaluation and approval.

Subsequently, to distribute the drug, the applicant must obtain marketing authorization, which is regulated under the Licensing Regulation on Medicinal Products. TİTCK is the responsible administrative body. To obtain marketing authorization, real persons or legal entities who are resident in Turkey must file an application to the Ministry, including the documents listed under the Licensing Regulation on Medicinal Products. When granting marketing authorizations, the Ministry considers whether *(Article 16, Licensing Regulation on Medicinal Products)*:

- Efficacy of the envisaged usage conditions have been proved,
- The pharmaceutical's reliability has been proved,
- Adequate technical and pharmaceutical properties exist.

The Ministry has discretion to waive some of these criteria on the basis of public health. Such a decision can be given with regard to pharmaco-economic data.

Real person(s) applying for marketing authorization must be graduates from pharmacy, medicine, or chemistry faculties, and be entitled to operate in these disciplines in Turkey. Legal person(s) applying for marketing authorization must employ a person who meets these criteria *(Article 7, Licensing Regulation on Medicinal Products).*

If a medicinal product will be imported into Turkey, the following certificates (issued by the license owner of the medicinal product) must be obtained from the local marketing authorities abroad and submitted to TİTCK with Turkish translations *(Article 8, Licensing Regulation on Medicinal Products):*

- Certificate showing that the importer is the sole representative authorized to manufacture and/or sell the medicinal product in Turkey.
- If co-marketing occurs:
    - o A certificate showing that a real person or legal entity other than the sole authorized representative in Turkey is also authorized for the purpose of co-marketing,

o Written consent from real persons or legal entities who will be engaged in co-marketing activities.

4. What are the approximate fees for each authorization?

The costs for obtaining authorization vary depending on the type of the medicine or the medical product. These are updated annually. Some of the 2018 fees include:

- License Registration Fee (Medicines produced abroad): TRY 45,788
- License Registration Fee (Medicines produced in Turkey): TRY 22,894
- License Application Fee (Medicines produced abroad): TRY 3,565
- License Application Fee (Medicines produced in Turkey): TRY 2,377
- Scientific Review Cost: TRY 50,000
- License Renewal Fee: TRY 1,366
- Pharmaceutical Warehouse License Fee: TRY 3,013
- Pricing Commission Application Fee: TRY 1,000

For further fees and costs please see this link: **https://www.titck.gov.tr/FiyatTarifesi**

5. For how long are marketing authorizations/registrations valid? How are marketing authorizations/registrations renewed?

Marketing authorizations are valid for five years *(Article 21, Regulation on the Licensing of Human Medicinal Products)*. To renew a marketing authorization, it should be presented to the Ministry with necessary pharmacovigilance data, along with data on quality, safety and efficacy which outlines all changes which have occurred since the authorization was issued. The renewal application must be made no later than three months before the five-year authorization period expires.

6. How does the authorization process differ between brand-name products and generic products? Are there differences for local manufacturers versus foreign-owned manufacturers?

The toxicological, pharmacological tests and pre-clinical, clinical trials contained in the original medicinal product's dossier do not necessarily have to be provided to evaluate the generic product's application. Article 9 of the *Regulation on the Licensing of Human Medicinal Products* regulates the abridged application for numerus clauses and some exceptional cases related to the generic products.

Pharmaceutical products owned by both local and foreign manufacturers cannot be launched on the market in Turkey before obtaining a license from the Ministry *(Article 5, Regulation on the Licensing of Human Medicinal Products; Article 3, Pharmaceutical and Medical Preparations Law)*. To obtain a manufacturing site permit from the Authority, applicants must:

- Employ a responsible manager meeting the requirements under the Regulation on Manufacturing of Medicinal Products,
- Employ a quality assurance and quality control manager,

- Establish a quality control unit,
- Ensure the manufacturing facility complies with the guidelines of good manufacturing for the medicinal products,
- Submit an original or certified copy of a non-sanitary enterprise certificate,
- Present an environmental impact assessment report (if required).

Importers of pharmaceutical products must also obtain a certificate of control from the Ministry that is Audited by the Ministry *(Communiqué on Import of Certain Products; Communiqué No: 2012/20).*

7. How are combination products (drug + drug, drug + biologic, drug + device, biologic + device, drug + biologic + device) regulated

Biological medicinal products are defined as products where the active substance is a biological substance *(First Annex, Article 3.2.1.1(b), Licensing Regulation on Medicinal Products)*. Biological products are regulated in detail under the Biosimilar Medicinal Products Guidelines (Product Guidelines).

Accordingly, a biological medicinal product is a product made from a biological source (or extracted), where a combination of physicochemical biological tests together with the production process, and review are required to determine the quality of its active substance *(Article 1.3, Product Guidelines)*.

Applications for marketing authorization for combination products are regulated under Article 9(a)(3) of the Licensing Regulation on Medicinal Products.

8. How is compliance with regulation monitored and evaluated? Is the regulatory regime comparable with the U.S. Food and Drug Administration or the European Medicines Agency expectations and requirements?

The European Medicines Agency's compliance system has three stages:

- Research and development – Including:
  - o Good Laboratory Practice (GLP),
  - o Good Clinical Practice (GCP),
  - o Good Manufacturing Practice (GMP).
- Marketing authorization application – Focused on pharmacovigilance inspections and sampling and testing.
- Post-authorization -Including monitoring via Good Distribution Practice (GDP) and product defects

The U.S. Food and Drug Administration (FDA) follows a similar route for monitoring compliance to the European system. The FDA observes pre-manufacturing, manufacturing and post-manufacturing phases with distinguished bodies and procedures.

TİTCK conducts checks on the development, manufacturing, storage and distribution phases until the drugs reach the end user. All processes related to compliance are carried out by the Drug Control Department. Under TİTCK's review system, GLP, GCP, GMP and GDP mechanisms are accompanied by complaints. A mechanism called Good Pharmacovigilance Practices (GPvP) also exists, whereby license holders and contracted pharmacovigilance service organizations are audited.

9. What is the potential range of penalties for noncompliance?

Administrative fines can range up to TRY 1,000,000 and five years of imprisonment *(Article 18, 19 and 20, Pharmaceutical and Medical Preparations Law)*. The range of penalties is quite wide, including different administrative penalties and prison sentences. For instance, the minimum penalty limit for making promotions and sales contrary to the Law is TRY 100,000 *(Article 18(2))*, whereas to import a product without permission is deemed to be smuggling and imposed to a penalty of 1 to 5 years of imprisonment and judicial fine of up to 10,000 days, which is regulated by Anti-Smuggling Law numbered 5607 published in the Official Gazette numbered 26479 and dated 31 March 2007 *("Kaçakçılıkla Mücadele Kanunu")*.

10. Is there a national healthcare system? If so, how is it administered and funded?

The state is responsible for organising and regulating the healthcare system, as well as for procurement of public healthcare services, taking into account Article 60 of the Constitution. The Ministry is responsible for operating protective and remedial healthcare services. However, healthcare services are also carried out by other ministries, universities, and private institutions, as permitted by legislation.

The national healthcare service is primarily financed by the state budget, revolving funds, fund incomes, and taxes. Social security premiums (public and private health insurance). Other private payments (for example, donations) support the public healthcare system's funding.

11. How does the government (or public) healthcare system function with private sector healthcare?

The Code on Fundamental Health Services numbered 3359 published in the Official Gazette numbered 19461 and dated 15 May 1987 *("Sağlık Hizmetleri Temel Kanunu")* aims for every person living in Turkey to have access to an equal healthcare system.

The Ministry is responsible for establishing hospitals and public health institutions to provide medical services to the public. Both public and foundation universities with medical faculties in their incorporation may also establish hospitals as per the Higher Education Code numbered 2547 published in the Official Gazette numbered 17506 and dated 6 November 1981 *("Yükseköğretim Kanunu")*.

Private hospitals have become very common in Turkey in recent years. The establishment and operational principles for private hospitals are regulated under Regulation on Private Hospitals published in the Official Gazette numbered 24708 and dated 27 March 2002 *("Özel Hastaneler Yönetmeliği")*.

Health services provided by both public, institutional and private sector corporations are supervised by the Ministry.

Most health services provided by public health institutions are covered under General Health Insurance (Article 63 and 64, Law on Social Insurance and General Health Insurance published in Official Gazette numbered 5510 and dated 31 May 2006; *"Sosyal Sigortalar ve Genel Sağlık Sigortası Kanunu"*).

Health services provided by private health institutions might be covered by General Health Insurance according to the contracts between the Social Security Institution and provider.

12. Are prices of drugs and devices regulated and, if so, how?

The Ministry of Health sets the maximum prices and invokes pricing measures to ensure that medical products are made available to consumers on proper terms, to ensure a more efficient and sustainable healthcare system.

Turkey adopts a reference pricing system whereby pharmaceutical prices are determined based on the reference prices from five reference countries (among European Union countries) determined by the Ministry of Health.

The reference price refers to the lowest warehouse sales price for original and licensed products (exclusive of discount) in the reference countries. However, if a country where the product is produced or imported from is not one of the reference countries, but the warehouse sales price of the relevant product is lower than the reference prices in the reference countries, the lower price will be considered as the reference price.

The Ministry of Health has discretion to change reference countries, provided it makes an announcement at least two months before. In this pricing method, equivalent of 1 (one) Euro in TRY is used, upon multiplying with the adaptation co-efficient designated as 70 percent of the average annual Euro value to be calculated upon taking into basis the daily indicative Euro foreign exchange sales rate realizations of the Central Bank of the Republic of Turkey declared in the Turkish Official Gazette of the previous year.

The pricing procedure timeline is as follows:

- The Price Evaluation Commission (consisting of representatives of the Ministry of Finance, Ministry of Development, Undersecreteriat of Treasury and Directorate of Social Security Organization) sets a meeting within the first six months of each year to evaluate drug prices.
- A license holder applies to the Ministry of Health, including the price declaration form and supporting documents indicating the determination process of the price.
- Applications for receiving an initial price are concluded within 60 days, although this can be extended by up to 30 days depending on work load.
- Price-related applications other than the initial pricing must be finalized within ten days.

During the determination process, the Ministry of Health considers information provided by the license holder which is liable for the accuracy of the information provided to the Ministry of Health.

The licence holder must inform the Ministry of Health about price fluctuations. Its liability in this respect will continue beyond completing the application.

The Ministry of Health has discretion to check the accuracy of information and documentation through national or international data bases, as well as via official inquiries.

Drug prices cannot be determined in foreign currency. Price determination is solely made in TRY.

The limits on profit rates vis-à-vis the drug's retail price are as follows:

WAREHOUSE SALE PRICE	WAREHOUSE PROFIT	PHARMACY PROFIT
UP TO TRY 10 (INCLUSIVE)	9%	25%
BETWEEN TRY 10 AND 50 (TRY 50 INCLUDED)	8%	25%
BETWEEN TRY 50 AND 100 (TRY 100 INCLUDED)	7%	25%
BETWEEN TRY 100 AND 200 (TRY 200 INCLUDED)	4%	16%
MORE THAN TRY 200	2%	12%

13. How are drugs and devices used by patients paid for? What roles do public and private payers play?

The Social Security Institution is a public organization for private sector and blue-collar public-sector workers in Turkey. It allocates a global budget to reimburse healthcare services offered in public hospitals, subject to conditions determined annually. It finances several drugs and devices.

The Social Security Institution has two commissions for financing drugs and devices:

- The Drug Reimbursement Commission,
- The Medical and Economic Evaluation Commission.

These commissions determine which drugs and devices will be covered by and paid from General Health Insurance.

Retired persons receive a 90% deduction from the purchase price for drugs, while active insured members receive an 80% deduction

If a device or drug is not covered by the General Health Insurance, patients must pay for it themselves.

Some Private Health Insurers may also pay for drugs and devices which are not financed by the Social Security Institution, according to the agreement between insurance company and consumer.

14. Who dispenses drugs and devices to patients and how are those dispensers compensated?

Drugs can only be sold in licensed drugstores or drug trade houses (*Article 1, Law on Pharmaceuticals and Medicinal Preparations*). Title of pharmacists is a debatable issue in Turkey, as per the Turkish Commercial Code and Supreme Court's decisions, pharmacists are deemed to conduct their business operations as "merchants".

Regardless of whether a pharmaceutical is prescription or nonprescription, it can only be sold at pharmacies and pharma-organizations (such as pharmaceutical warehouses) (*Article 1, Law on Pharmaceuticals and Medical Preparations)*. Turkish legislation prohibits the sale of pharmaceuticals via the internet or any other electronic medium *(Article 24, Law on Pharmacists and Pharmacies)*.

15. What are the professional and legal responsibilities of those who dispense drugs and devices? What role do they play in providing patient care, information, and safety?

Pharmacists are the sole entities authorized to dispense drugs. A valid degree from the pharmacy faculty of a foundation university or a public university is required. Pharmacists' duties, obligations and liabilities are regulated in detail by the Code on Pharmacists and Pharmacies.

Pharmacists are prohibited from carrying out wholesale drug transactions or taking part in biddings. Additionally, pharmacists cannot enter agreements with institutions, physicians or organizations or any other third parties about promoting prescriptions, promising benefits, nor offer prizes or bonuses. Pharmacists will be held personally liable for breaches and administrative fines of between TRY 5,000 and 50,000 will apply. Penalties can be doubled for repeat offences.

Any person who produces, stores or sells products containing toxic substances which are subject to license without obtaining necessary permissions is liable for imprisonment ranging from two months to one year *(Article 193, Turkish Criminal Code)*.

Within the scope of patient care and safety, pharmacists have the obligation to duly and accurately inform consumers under the Consumer Protection Law. Instructions, directions and adverse effects must be provided to the consumers, accordingly necessary steps should also be taken about the feedbacks from the consumers with regards to a drug's adverse effects and symptoms.

Under the Data Protection Law, pharmacists must take necessary measurements to protect consumers' personal data.