Pharmaceutical Regulations Under Turkish Law

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This October, some important changes were made to The Turkish Customs Code with the 5911 numbered Code and also the new Customs Regulation within EU harmonization. Those regulations brought some revolutionary amendments, some of which are related to the protection of intellectual and industrial property rights within the scope of the Turkish Customs Law.

This article is designed to provide a brief introduction to the requirements for licensing, importing and introducing pharmaceutical products to the Turkish market. Some key issues to keep in mind are the documents necessary for registration and licensing, the timeline for accomplishing the regulatory work, the terms of data exclusivity that might apply to the products and pricing regulations and schemes that are also relevant to companies wishing to manufacture or distribute pharmaceuticals products in Turkey.

For the specific purpose of this article, references are made to Licensing Regulation on Human Medicinal Products ("**Licensing Regulation**").

Licensing

Pursuant to Article 5 of the Licensing Regulation, pharmaceutical products cannot be launched on the market before obtaining a license to be granted by the Ministry of Health. In order to obtain a license, real persons or legal entities resident in Turkey shall file an application to the Ministry of Health by submitting the documents listed under the Licensing Regulation published in the Official Gazette dated January 19, 2005 and numbered 25705.

The application documents include, without limitation, (i) description of control methods used by the manufacturer; (ii)toxicological and pharmacological tests and clinical trials; and (iii) where a pharmaceutical product is manufactured under a license (granted by a third party owner of intellectual property) or will be imported, a certificate (and a Turkish translation thereof) issued by the licensor or the supplier demonstrating that the manufacturer/importer is the sole representative which is authorized to manufacture and/or sell the product in Turkey, or if any, a certificate illustrating that a real person or legal entity other than the sole authorized representative in Turkey has also been authorized for co-marketing and the written consents of the real persons or legal entities that will be engaged in co-marketing activities.

Import

Apart from obtaining an import license in accordance with the Licensing Regulation as mentioned above, pursuant to the Communiqué on Import of Certain Products that are Audited by the Ministry of Health (*Communiqué No: 2012/20*), a certificate of control shall be obtained from the Ministry of Health for the import of pharmaceutical products (and active substances).

This certificate of control shall be obtained before the import of the relevant pharmaceutical product by submitting certain documents such as a pro forma invoice or standard invoice, certificate of analysis and approved health certificate issued by the competent authority in the country of origin. The certificates of control shall be valid for a period of 12 months except for the certificates of control issued for the pharmaceutical substances subject to the Communiqué on Standardization of Foreign Trade in Relation to Import of Certain Substances, which require a

special permit to be obtained from the Ministry of Health (Communiqué No: 2011/4), which shall be valid for a period of 6 months.

Specifications of Any Elementary Substances Used for Manufacturing Pharmaceutical Products

In addition to the above, pursuant to Article 5 of the Regulation on Pharmaceutical and Medicinal Products (*published in the Official Gazette dated October 23, 2003 and numbered 25268*); specifications of any elementary substances used for manufacturing pharmaceutical products shall be declared by the manufacturer during the license application to be registered by the Ministry of Health.

These specifications shall not be low quality when compared to Turkish Pharmacopeia, European Pharmacopeia, British Pharmacopeia or United States Pharmacopeia specifications. These specifications shall be attached to the petition or pro forma invoices to be submitted as per the decision of the relevant import regime.

Pursuant to Article 5 of the Pharmaceuticals Import Regulation, the specifications of the pharmaceutical products to be imported are specifications that are registered at the country of origin as the basis of the license thereof.

The Ministry of Health shall approve these specifications. For the import of elementary substances of pharmaceuticals, according to Article 6 of the Pharmaceuticals Import Regulation, a certificate indicating that the substances have been manufactured in compliance with the appropriate specifications to be issued by the importer country's health authority is required to be submitted. Once the import is conducted, the Ministry of Health may also require a certificate of analysis of the manufacturer for each batch. Upon evaluation of the foregoing, the Ministry of Health issues a quality control certificate.

Timeline for Registration

Licensing Regulation Article 15 regulates that, upon completion of the preliminary evaluation period which can be a maximum of 90 days (including the time period granted to the applicant to complete the missing documents/information in the application file); the applications shall be evaluated and concluded within 210 days.

However, the applications pertaining to pharmaceutical products which are original in treatment or diagnosis, which are innovative or are required from a public health perspective to reduce public healthcare expenditures and to ensure rapid public access to the drug, shall be completed within a maximum of 180 days.

Applicant

Where a pharmaceutical product will be imported, a certificate (and a Turkish translation thereof) issued by the licensor or the supplier demonstrating that the importer is the sole representative authorized to manufacture and/or sell the product in Turkey, or if any, a certificate illustrating that a real person or legal entity other than the sole authorized representative in Turkey has also been authorized for co-marketing and the written consents of the real persons or legal entities that will be engaged in co-marketing activities.

Special Protection for NCEs and Innovative Products

Although Turkey is not a member of the European Union, legislation in Turkey (and particularly the legislation regulating the Turkish pharmaceutical sector) follows the developments in European legislation. Therefore, following the EC Directive (2004/27/EC) ("**EC Directive**"), the Licensing Regulation was also amended by a regulation dated June 11, 2005.

The Turkish legislation did not establish a data exclusivity period in the same duration as regulated by the European legislation. According to this sub-paragraph of the Regulation the original pharmaceutical products, which have been licensed in a Customs Union Member State, are subject to a data exclusivity period of six years. This term of six years starts from the "first" licensing of such original product in any of the member States to the Customs Union. Please note that the Licensing Regulation does not provide any further term of exclusivity in the event of new therapeutic indications, a case that is covered by the EC Directive.

On the other hand, communications with the legal department of the Ministry of Health reveals that the Turkish regulator is in fact aware of the amendment to Article 10 of the EC Directive as follows: "The 10-year period referred to in the second subparagraph shall be extended to a maximum of 11 years if, during the first eight years of those 10 years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies." and is actually tending towards allowing one year of additional protection for data exclusivity in the case of new therapeutic indications.

Data Exclusivity Issues

Turkey implemented patent protection to its regulatory system in 1995 and subscribed to apply the data exclusivity with TRIPS and Customs Union agreements. The legal ground of the data exclusivity provisions in Turkish Law is European Union Regulations.

On the other hand, there is no particular provision in Turkish Law that exposes the scope of the data exclusivity protection. Data exclusivity protection is only mentioned within Article 9(a) of the Licensing Regulation. Article 9 of the Regulation promulgates the procedure for an "Abbreviated Application."

As per Article 9(a), if the applicant is conducting his application through an abbreviated application, he shall not be required to provide the results of pre-clinical tests or clinical trials if it meets the following conditions set below:

1. The medicinal product subject to the application is similar in principle to a medicinal product that has been licensed in Turkey previously and the permission is taken from the marketing authorization holder of the original medicinal product.

2. The components of the medicinal product have reasonable activity and admissible reliability settled in medical utilization.

3. The medicinal product is licensed as per the legislation in force and has elapsed from the data exclusivity period of the medicinal product. In order to apply this sub-provision, the original products should fall into one of the below product categories:

a) Products shall be original products that have been granted a license for the first time after January 1, 2001 in one of the countries of the Customs Union Area and for which no generic registration application had been filed in Turkey until January 1, 2005.

b) Original products that have been granted license for the first time after January 1, 2005 in one of the countries of the Customs Union Area.

Market Exclusivity and Generic Pharmaceuticals

In the European Union Regulations, market exclusivity is regulated as a different and separate protection period for two years during which a new drug is protected from direct competition from generics in a market. Please be informed that in Turkish Law there is no explicit provision for market exclusivity.

On the other hand it would not be false to state that the Ministry of Health's interpretation of the data exclusivity protection equals market exclusivity. In fact, we have experienced that Ministry of Health's practice of data exclusivity is to allow abbreviated license applications referring to an original product which is within the data exclusivity protection period and then to withhold the sales permission until the end of the data exclusivity period of the original product.

Evaluation of Pricing and Reimbursement for an NCE or an Innovative Product in Turkey

The pharmaceutical pricing system in Turkey is under the control of the Ministry of Health. Pursuant to the Communiqué amending the Communiqué concerning the Tariff to be Applied to Pricing of Pharmaceuticals ("**Tariff Communiqué**" dated April 14, 2012 and numbered 28264) the Ministry of Health exerts strict control over the pricing in the pharmaceutical sector by determining the innovator's base price on the first product to enter the market (i.e. original product). Subsequent generic entrants to the market must price their product at a predetermined percentage of the original product (i.e. generic product). In that respect, the Ministry of Health applies a reference pricing system to determine the prices of original and generic products.

Please note that a Price Evaluation Commission is formed with the participation of the representatives from the Ministry of Health, Ministry of Finance, State Planning Organization, Undersecretariat of Treasury and Directorate of Social Security Authority. The Price Evaluation Commission shall evaluate whether the reference prices should be raised, reduced or maintained. Such Commission also determines the periodical foreign currency band, which is the basis of the reference prices. Such foreign currency band is currently between the lowest periodical Euro rate (lower limit) and the lowest periodical Euro rate plus 10 percent (upper limit).

A change in foreign currency rates up to 5 percent less than the lower limit and 5 percent more than the upper limit shall not affect the prices. However, if the change in the 90 day moving average of the foreign currency rate exceeds the above-mentioned 5 percent limits the Price Evaluation Commission may amend the prices.

The price of the original products without generics shall not exceed the reference price until the generics are placed on the market. The price of the original product with a generic product that has been licensed and placed on the market shall not exceed 60 percent of the base price registered under the Ministry of Health database.

The method of evaluating when to substitute prescribed pharmaceuticals with non-prescribed products is determined by protocols assigned by SSI, Ministry of Finance and the Turkish Pharmacists Association. As mentioned by the Turkish Competition Authority in the April 20, 2009 dated decision for Sanofi Aventis; the current practice in the market is for pharmacists to provide pharmaceutically equivalent generic products instead of the prescribed product.

As a matter of fact, it is an established practice for the pharmacists to direct customers to the lower priced equivalent generic product by indicating that they have the option to pay the extra price from the reference price determined by the Ministry of Health for the original product or buy the generic product, which is within the reference price determined. There are two legal bases for such application. First of all it is accepted that the generic product is the exact subsidiary of the original product and secondly, it is the practice of SSI and Ministry of Finance, which together holds approximately 80 percent of the pharmaceutical purchases in the Turkish market.

Comparison of Turkish and EU prices

Tariff Communiqué Article 2/h stipulated that prices of pharmaceuticals are determined based on the reference prices in five to 10 reference countries (among European Union countries) determined by the Ministry of Health. The reference price refers to the lowest warehouse sales price of the original and licensed product (exclusive of discount) in the reference countries. However, in case the 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, then the lower price shall be considered as the reference price.

Time frame for Price/Reimbursement Approval

According to Communiqué concerning the Tariff to be Applied to Pricing of the Pharmaceuticals (dated June 30, 2007 and numbered 26568) Article 4, the license holders shall apply to the Ministry of Health along with the Price Declaration Form as well as other documentation, which may be required depending on whether the product subject to price application is an original or a generic product. The applications to obtain an initial price shall be concluded within 60 days. Applications other than for the purposes of obtaining an initial price shall be concluded within 10 days.

Available reimbursements

With the radical change brought by the Code of Social Security Institution (dated May 16, 2006 and numbered 5502) which combined all social security institutions under the roof of the Social Security Institution (SSI), a list was published to indicate the pharmaceutical products to be reimbursed.

The list contains molecules against all kinds of diseases. Any product that is not included in the list will not be subject to reimbursement. On the other hand, the list is updated frequently (the latest update on August 22, 2012 being the 79th) and in this regard has been rapidly expanded since its first practice in 2005. New products entering into the market for the first time can be subjected to reimbursement upon approval of the Reimbursement Committee, which gathers at least quarterly to discuss and update the list indicating the molecules to be reimbursed. The Reimbursement Committee consists of doctors, pharmacists, public health experts, economists, statisticians, specialists, pharmacologists and biostatisticians who evaluate applications for reimbursement and amend the list of pharmaceuticals to be reimbursed according to the Directive on the Procedure and Principles of Practice of the Reimbursement Committee ("**Directive on Reimbursement Committee**").

The Communiqué on Health Implementations published by the SSI provides that the basic discount to be applicable to generic and original products shall be at a rate of 11 percent. As per the amendments to the relevant Communiqué on April 4, 2012, the following additional discount rates shall apply:

1. 29 percent until reference price is determined (a total of 40 percent) and 17 percent after the reference price is determined (a total of 28 percent) for products which have been released to the market before August 1, 1987 (twenty year products) and have a warehouse sale price of 6.79 TL and above.

2. 30 percent for original products of which generics have not been launched to the market (a total of 41 percent).

3. 17% for original products of which generics have been launched to the market (a total of 28%).

4. 17 percent for generic products (a total of 28 percent).

The above-mentioned Communiqué also stipulates the terms of reimbursement for pharmaceutical products. Accordingly, in order for a listed pharmaceutical product to be reimbursed, first the discounted price thereof shall be calculated. Following such calculation, the equivalents of such pharmaceutical product shall be determined. Pursuant to Article 6.4.2 of the relevant Communiqué, a reimbursement price band is applicable, which is between the lowest price in the determined equivalent pharmaceuticals group and 10 percent more than the lowest price in the determined equivalent pharmaceuticals group. However, we have been verbally informed by the officials in the Ministry of Health that for the pharmaceutical products placed on the market that have already been reimbursed based on a different reimbursement band before the introduction of the current reimbursement band, the products will continue to be reimbursed based on the original band.

Until December 3, 2010 the practice of the Ministry of Health was the base for evaluation of which products should be considered as original, generic, or 20-years-old (introduced into the world market for the first time before 1/8/1987). After December 2010, the Turkish Drug and Medical Device Institution is the authority to evaluate any amendments to groups of products.

Availability and Justification for Premium Prices

Pursuant to Article 6.4.1(10) of the Communiqué on Health Implementations, the provisions for lowest reference pricing and price ratio shall not be applied to non-prescribed products and/or products that are not within the list of products to be reimbursed. These products will be evaluated without differentiating whether they are original, 20-year, co-marketing or generic. Regardless, the price shall not be higher than the official highest warehouse sales price in the reference countries.

According to Tariff Communiqué Article 5/a, even if there is a price determined by the Turkish Drug and Medical Device Institution, reevaluation of the price may be conducted for products that may not be possible to import due to economic reasons and therefore threaten public finance and health, on the condition that it is proven with documents and determined by the Price Evaluation Committee. In such a case, the price of the product may be determined up to 15 percent higher than the price of the lowest reference price. If there is any other product used for the same indications, then the price of the closest option shall be the reference point. Even if the price gap between the product to be reevaluated and the product with the same indications is high, the new warehouse sales price determined based on the cost sheet approved by the certified public accountant shall not exceed 200 percent of the prior warehouse sales price.

Regulation of the Generic Price Level

Subsequent generic entrants to the market must price their product at a predetermined percentage of the original product (i.e. generic product). In that respect the Ministry of Health applies a reference pricing system to determine the prices of original and generic products.

In this regard, according to Article 4/1 (a) of the Tariff Communiqué the warehouse sales price of generic products without the original products released in the Turkish market can be up to 60 percent of the reference price registered to the Ministry of Health. Starting with the first generic product, all generic products may be priced on 60 percent of the original product reference price.

Market Observations

In general, most foreign investors prefer acquiring an existing and active Turkish company for their prospective activities in the pharma market; rather than establishing a brand new company. This is especially due to the Ministry of Health's practice towards the Turkish pharmaceutical market both in sales and marketing and the regulatory aspects, which results in foreign investors entering the Turkish market via acquisition of an already existing and well-established company.

Some recent acquisitions are:

- Acquisition of Dr. F. Frik by Yeni Recordati (with an EBITDA of 14)
- Acquisition of Biofarma ?laç by Biofarm
- Acquisition of Birgi by Mefar
- Acquisition of Mustafa Nevzat by Amgen
- Acquisiton of Yeni ?laç by Recordati SL. (seller side representation)