

# Ethical experiments

**Murat Karkın and Gökhan Gökçe of YükselKarkınKüçük explain why Turkey's pharmaceutical regulations are good for business**

In Turkey, the Law on Pharmacy and Medicinal Products 1262, which was enacted in 1928, governs the basic rules on pharmaceuticals. Over the years, various amendments were made to the Law. However, due to its narrow scope and outdated provisions, it is still being criticised, and attention is frequently drawn to the need for a new law. Public institutions, in particular the Ministry of Health (MoH), have gained a significant level of knowledge and experience due to their long administrative history. The MoH is in charge of regulating and conducting the administrative processes in the pharmaceutical field. It has published several regulations and in practice most issues regarding pharmaceuticals are being conducted pursuant to such regulations. Especially within the harmonisation process of Turkish legislation with *acquis communautaire*, such regulations have been harmonised with the EU directives, in particular Directive 2001/83/EC of the European Parliament and of the Council of November 6 2001 on the Community Code Relating to Medicinal Products for Human Use. Also the government also has issued decrees regarding pricing and the MoH has published communiqués accordingly. The laws, decrees, regulations and communiqués are the main pieces of Turkish legislation on pharmaceuticals.

In the past decade the need for pharma law services in Turkey has notably increased because of the economic growth and positive developments in the healthcare business, new MoH regulations, harmonisation with EU rules, and the judicial and administrative investigations in the pharma sector. Some pharmaceutical companies have employed in-house counsels, while others increased the flow of their work with external law firms. The different segments of Turkish pharma law are licensing, pricing, packaging and labeling, promotional activities and clinical trials and observational studies.

## Licensing

The granting of marketing authorisations to pharmaceuticals is regulated by the Regulation on Licensing of Medicinal Products for Human Use. It was published in the Official Gazette dated January 19 2005 as number 25705, and superseded the previous licensing regulations. The Licensing Regulation reflects the same approach as Directive 2001/83. It lists the documents that shall be submitted for licence applications, sets forth the procedure for examining such applications and the rules for transfer of product licences, the criteria for granting of licence, the reasons for rejection of licence applications, and the reasons for suspension and cancellation of

licence. However, unlike the EU Directive in which marketing authorisation is enough both for the licensing and marketing of a pharmaceutical, it is necessary to obtain a sales permit following the grant of a licence. In other words, the marketing authorisation stipulated in Directive 2001/83 corresponds to both product licence and sales permit under Turkish Law.

One of the most recent amendments in the Licensing Regulation has been that data exclusivity was introduced for the first time in 2005. Pursuant to Article 9, a term of data exclusivity has been granted for original products that were licensed for the first time in a country within the EU Customs Area after January 1 2001, provided that no generic licence application was made in Turkey by January 1 2005; and for those products that would be licensed for the first time in a country within EU Customs Area after January 1 2005. The data exclusivity term is six years starting from the date of first registration in the EU Customs Area, which is limited to the patent protection term in Turkey. Although the Licensing Regulation stipulated the data exclusivity term, a debate continues regarding the status of the previous applications. There are rumours that a number of generic applications, even without the required documents, were submitted to the MoH before January 1 2005 to be exempted from data exclusivity.

## Pricing

In recent years, one of the hottest topics in Turkish pharma law has been the pricing of pharmaceutical products. From 2005 on, several investigations regarding the pricing of pharmaceuticals were carried out both in the administrative and criminal investigation channels. Until the beginning of 2004 prices of pharmaceuticals were determined on a cost basis. A certain margin as profit was added to the

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manufacturing/importation costs of the products to determine the ex-factory prices. Profit rate margins were again applied to find the wholesaler and retail prices. In February 2004, a reference system was introduced for pricing, in which prices were determined by reference to EU countries.

The most recent decree on pricing is Decree 2007/12325. It was published in the Official Gazette on June 30 2007 followed by a Communiqué published on December 29 2007. Under these regulations ex-factory prices of pharmaceuticals are determined by applying the lowest ex-factory price in the reference countries (between five and ten EU countries) and determined by the MoH every year. Until the end of 2008, Spain, France, Italy, Greece and Portugal are determined as the reference countries.

Although both original and generic products are included in the reference-price system, products that were licensed 20 years ago, non-prescribed products, blood plasma products, nutritional products, allergic products and orphan drugs are excluded from the reference-price system and continue to be subject to cost-basis calculation, subject to MoH approval.

Besides the ex-factory prices in the reference countries, if the ex-factory price in the country from which the product is imported or where the product is manufactured is below the cheapest reference-country price, then the ex-factory price in that country should be taken as the reference price. If the product is not licensed and marketed in the reference countries or in the country of origin or import, then the cheapest ex-factory price in the EU countries where the product is marketed should be applied as reference.

As with generic products, the prices are 80% of the ex-factory prices of the original product determined as stated above. In determining the wholesale price of a product, a profit margin of between 2% and 9% according to the price of the product is added to the ex-factory price. Likewise, to determine the retail price, a profit margin of between 12% and 25% ranging according to the price of the product is added to the wholesale price.

### Packaging and labelling

The Regulation on Packaging and Labelling has laid down what information should be inserted on the inner and outer packages of the pharmaceuticals. Furthermore, the Regulation lists the requirements for the usage instructions (prospectus) and for the labels of the pharmaceuticals.

Another pivotal issue regarding the

## Author biographies



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pharmaceuticals is barcoding. Recently EU countries have struggled with the counterfeit products and endeavoured to find new barcoding strategies to fight counterfeited products. Following this trend significant amendments were made in the Regulation on Packaging and Labelling on February 1 2008. Before the recent amendment, pharmaceutical companies in Turkey used linear bar codes voluntarily to prevent their products being counterfeited.

This amendment introduced new identification and traceability requirements and stipulates that medicinal products shall have an identifier and data matrix type 2-dimensional barcode (2D barcode). As stated in the Regulation, the 2D barcode and identifier should be placed on pharmaceuticals for promotional purposes, sample medicinal products, products for hospital use, prescribed and non-prescribed products, products included in reimbursement list and the nutrients. Moreover, a new clause has been inserted into Article 16 of the Regulation, which sets forth that identifiers should also be used on conveyance packages and parcel packages

describing the conveyance packages or showing the 2D-barcode information of the pharmaceutical products included in the conveyance packages.

It is worth mentioning that a transitional period is accepted by the regulators, and licence holders of the medicinal products should start inserting 2D barcodes in their products at the latest on January 1 2009. However it should be noted that the sale of products that have already been manufactured without a 2D barcode will be allowed until December 31 2009.

In accordance with Article 19 of the Regulation, A Guide on Implementation of Identification and Barcoding of Pharmaceutical Products for Human Use has been drafted to explain the application of the 2D-barcode system and to set out the principles for identification and barcoding of pharmaceutical products for human use. The Guide regulates the 2D-barcoding requirements in detail.

The MoH plans to introduce a new drug-tracking system in order to use the 2D-barcoding system efficiently for fighting counterfeited products and fraud in the social security institutions. However this drug tracking system has not yet started operating.

**Promotional activities**

Promotional activities regarding pharmaceuticals are regulated by the Regulation on Promotion of Pharmaceuticals, which was published in the Official Gazette dated October 23 2003 and abolished the previous promotion regulation. Pursuant to the original text of the Promotion Regulation and in contrast with the promotion of prescribed products, the promotion of non-prescribed products (OTC products) to the public was allowed, as it is the case in EU Directive 2001/83.

However in 2003 directly after the publication of the Promotion Regulation, the Association of Pharmacists filed a lawsuit before the Council of State (the highest administrative court in Turkey), requesting the cancellation of the provisions of the Regulation that allow the promotion of non-prescribed products to the public. The claim was based on the argument that the Law 1262 had prohibited the promotion to the public of both prescribed and non-prescribed products.

In its decision the Tenth Chamber of the Council of State annulled the provisions of the Promotion Regulation on the grounds that the promotion of non-prescribed products should not be allowed since

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otherwise it would contradict Article 13 of Law 1262. In light of the foregoing, promotion of both prescribed and non-prescribed products to public is prohibited under Turkish Law for the time being.

On the other hand, the Promotion Regulation allows the promotion of medicinal products, including those that are not prescribed, to healthcare professionals – doctors, dentists and pharmacists. The remaining provisions lay down the rules concerning what kind of promotion materials may be provided to healthcare professionals, and the procedure and requirements for convening meetings exclusively for the attendance of healthcare

professionals. As the Council of State suspended some of the provisions of the Promotion Regulation because of non-conformity with Law 1262, a change in Law 1262 is needed for promotion of non-prescribed products.

There are also Guides on Promotion of Medicinal Products to Healthcare Professionals prepared by both the Association of Research-Based Pharmaceutical Companies (innovator companies) and the Employer Association in Pharmaceutical Sector (generic companies). These Guides have laid down the restrictive rules for promotion in detail and explain the provisions of the

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Promotion Regulation, considering ethical standards in promotion to healthcare professionals. Although these Guides are not legislative, violation of them may cause application of inter-disciplinary sanction by the Associations. Therefore, pharmaceutical companies in Turkey are sensitive about complying with the provisions of the Guides.

### Clinical trials

Clinical trials are the studies that are carried out on human beings to search and evaluate the benefits and/or adverse effects, absorption, dispersion, metabolism and excretion of pharmaceuticals. The rules and procedures regarding clinical trials have been set forth under the Regulation on Clinical Trials dated January 29 1993 (CT Regulation). The purpose of the CT Regulation is to set out the rules and procedures that apply to the phases of the clinical trials conducted on volunteer subjects with synthetic, herbal and biological-sourced substances and combinations of them, and the liability provisions that may arise due in such studies.

The CT Regulations comprise three sections: General Provisions, Clinical Trial Phases, Ethics Committees and Clinical Trial Protocol and Miscellaneous and Final Provisions. In these sections, various subjects have been regulated – trials that require permission, pre-clinical searches, the phases of the clinical trial phases and definitions of such, adverse-event reporting, the qualifications of investigators, and local and central ethics committees.

All clinical trials performed during the pharmaceutical development process are carried out at general training hospitals, which should comply with the standards of equipment, personnel and laboratories that would enable the security of the trial subjects and proper follow-up after the trial. Pursuant to CT Regulation, it is required to obtain permission for all clinical trials regarding pharmaceuticals that have not been licensed by the MoH, new indication studies regarding the pharmaceuticals that have already been licensed by the Ministry, application studies on a patient group that has not been worked on yet, and high dosage studies. In the permission process the principle is that application must be made to the local ethics committee of the relevant trial centre. If the committee approves the application, it relays it to the central ethics committee of the MoH for approval. Only for Phase IV trials does the central ethics

committee report for information purposes.

In Turkey, a limited number of search and development activities are being carried out for new drugs. Therefore, the proportion of Phase I and Phase II studies is relatively small, while a significant number of multi-centred Phase III studies are being conducted.

Considering the nature of clinical trials, which require detailed regulations, the current CT Regulation is being criticised as it does not meet all the technical aspects of such studies. In this respect, the MoH has started to draft a new regulation. Although a significant period of time has passed since the first discussions, the new regulation has still not been published. All the relevant parties (trial centres, investigators and the industry) are eagerly awaiting the new regulation. On the other hand, observational (non-interventional) studies are being carried out within the scope of ongoing routine treatments to monitor various aspects of marketing-authorized products, exploring questions of safety, clinical effect and cost-benefit efficiency.

Like in most of the countries, observational studies are accepted as different from clinical trials. In this respect, they have not been included in the scope of CT Regulation. However Turkey is one of the countries that have a detailed set of rules regarding observational studies. Following the application of certain administrative rules on observational studies, the Ministry of Health issued a Guide on Observational Studies that stipulates the rules and procedures for such studies.

Below is a summary list of the provisions stipulated by the Guide, which was published on January 23 2008.

- It is not possible to impinge on the doctor's discretion, as in principle the treatment should have started before the decision to include the subject in the

observational study was made.

- Observational studies cannot be carried out by the marketing departments of the pharmaceutical companies. Thus, such activities cannot be performed to increase or promote the use of pharmaceuticals. Otherwise, it would be an unethical promotional activity and subject to administrative sanctions.
  - Permission from the MoH must be obtained, together with a study programme and budget, and reporting should be performed on developments in the study.
  - It is not required to inform or obtain informed consent from subjects separately unless their personal information is being processed or additional information needs to be provided regarding the requirements of observation.
  - No incentive of financial benefit can be provided to the subjects to convince them to participate in the observational studies.
  - The final report of the study should be retained for five years and the information of the subjects should be kept confidential.
  - The MoH audits the observational studies in order to control whether they are being carried out in accordance with the legal and medicinal requirements and the necessary precautions are being taken.
  - All the legal, criminal and financial liabilities shall be borne by the supporter entity and by the coordinator doctor in studies without supporter entities.
- As the Guide has been published quite recently, the administrative practices have not yet been settled. However, being one of the leading countries, it is believed that Turkey will benefit from this administrative legislation, taking the rapidly increasing number of observational studies into account.

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