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Turkey Modernises its Pharma Law

A new report finds that Turkey is taking steps to bring its pharma regulations into line with the European Union, but still has some way to go, says *Melek Bostancı Onol*.

Since 2004, the Turkish authorities have taken a number of important steps towards aligning the country's pharmaceutical legislation with that of the European Union (EU), both in drug licensing and in pricing and reimbursement procedures. But much remains to be done to increase the transparency of drug regulation in Turkey, and separating drug licensing from pricing procedures has become a top priority. This is all the more significant now in view of the fact that on 12 June 2006 Turkey began full negotiations on its proposed membership of the EU.

The situation of the Turkish pharmaceutical regulatory framework has been described in a report from the Istanbul Ekonomi consultancy firm, entitled *Transparency in Regulatory Bodies: Drug Industry Dimension*¹. The following article presents the main observations, conclusions and recommendations put forward in this report. The report was prepared after extensive interviews with Turkish officials in Ankara and EU officials in Brussels, and includes the results of a survey of the Turkish association of research-based pharmaceutical companies, but all the opinions as to what needs to be done with regard to the Turkish legislation are those of the authors.

A number of changes have been made to Turkish pharmaceutical legislation since 2004, with the dual aim of harmonising the laws with those of the EU, and effecting the transition to a general health insurance system as part of the reform of the social security.

Licensing

In the licensing area, the main piece of legislation is the *Licensing (Regulatory Affairs) Regulation No 25705* of 19 January 2005. Applications for a marketing licence are evaluated on the basis of efficacy, reliability, contribution to existing treatments and technical pharmaceutical characteristics of the drug. Applications are made to the ministry of health, general directorate of pharmacy and pharmaceuticals. The ministry checks whether the application file is complete, and informs the applicant accordingly within 30 days. The ministry completes the evaluation process within 210 days of accepting the file. Evaluations by administrations other than the health ministry are not included in the 210-day period.

If the applicant is asked for additional information or documents, the ministry requests verbal or written clarification, or product ingredients need to be tested in a laboratory, the period of 210 days is suspended until these activities are complete.

An application for a marketing licence can be refused for a number of reasons:

- if the potential risk of the drug is greater than its therapeutic effect under normal conditions of use;
- if its therapeutic effect is inadequate or cannot be proven or demonstrated adequately;
- if bioavailability is not adequate in certain drug products;
- if the product does not make a contribution to the existing treatments; or
- if its qualitative and quantitative formulae do not match the information given in the application file.

If an application is refused, the decision is notified to the applicant, together with the reasons. The applicant has the right to file a written objection against this decision within 30 days and the objection must be evaluated and answered within 90 days. Decisions taken as a result of an evaluation of the objection are final and cannot be appealed. Marketing licences are valid for five years, which may be extended by an application made three months before the end of the initial term of validity.

Although alignment with EU legislation has indeed been improved through changes to laws on both the licensing and pricing of drugs, it is still not possible to say that the Turkish legislation has been fully harmonised with that of the EU, the report says. One particular problem is that the licensing and pricing systems are not separate procedures: pricing is in fact part of the licensing process.

An illustration of the differences between Turkish and EU legislation on drug licensing is presented below. This comparison covers only the differences in principle – those encountered in daily practice will be dealt with separately.

Separating drug licensing from pricing procedures has become a top priority in Turkey

The main piece of legislation is the licensing regulation of January 2005

Applications can be refused for a number of reasons, including poor risk:benefit profile

Turkish legislation has still not been fully harmonised with that of the EU

Melek Bostancı Onol is the Turkish correspondent for *The Regulatory Affairs Journal – Pharma*.

Some assessment periods differ, as do interpretations of the time allowed

- the EU legislation states clearly that economic and other issues are outside the scope of the drug licensing process, but in Turkey the legislation makes no reference to such issues;
- in Turkey, the process of checking whether the approval application file is complete is finalised within 30 days, a period that is not included in the total evaluation period of 210 days. In the EU, by contrast, the checking process is completed in 10 days;
- the Turkish legislation says that the time spent on evaluation of the application by public authorities other than the ministry of health is not included in the period of 210 days, while in the EU there is no such provision. Furthermore, it is not clear what the phrase "public authorities other than the ministry of health" means, what issues these authorities will evaluate, or for what purpose;
- in Turkey, the 210-day period is expressed as "business days", while the EU refers to "calendar days".
- in Turkey, the criteria for refusing a licence include the following: if a drug offers "no contribution to the existing treatments" and "if the bioavailability is not adequate in certain products deemed necessary". This is not true of the EU;
- the time allowed for an applicant to object if a licence application is refused is 30 days in Turkey and 60 days in EU, while the period for review and re-evaluation following an objection is 90 days in Turkey and 60 days in the EU;
- in case of a second refusal of an application, the decision is final and cannot be appealed in Turkey, while in the EU the applicant has legal remedies and can take its case to court;
- in the EU, information on all decisions, whether positive or negative, is publicly accessible, while in Turkey reasoned decisions are not open to public access; and
- the EU publishes clear information on the committees involved in the licensing process and their decision-making processes, but Turkey does not clearly specify which criteria are used in the committees' decision-making processes, or which decision-making mechanism is employed.

There is also no appeal against applications that are turned down a second time

Pricing

There are also a number of differences in the areas of pricing and reimbursement procedures, as follows:

In Turkey pricing applications are dealt with during the licensing procedure

- in the EU, price applications are made upon receipt of a marketing licence, while in Turkey they are made during the licensing process;
- price approval, increase and reduction requests are dealt with in Turkey within 10 business days, which is shorter than the 90 days stipulated by the EU;
- if the product is being licensed for the first time, and if the proposed price is not found acceptable by the ministry, the price evaluation process is completed within 90 business days in Turkey, while this period is 90 calendar days in the EU;
- in the EU, each member state publishes information about its rules for deciding whether a drug should be reimbursed, but in Turkey there are no known predetermined criteria, nor are reasons given if a product is refused reimbursement;
- if a drug is not included in a European reimbursement system, the applicant is told how to appeal against the decision, but in Turkey no such methodology has yet been determined; and
- EU member states have to inform the European Commission about the criteria used in the social security system with regard to the therapeutic classification of drugs, but the Turkish authorities do not publish such criteria.

Problems in practice

It is still too early to say "whether the new regulation has improved the situation"

One of the purposes of the new regulation is "to ensure harmonisation with the relevant EU legislation", and it is intended to make the process more efficient and predictable than before. However, the consultancy firm notes that as one may only see the changes and improvements brought by the new regulation after the first licensing decisions are made, it is too early to make a comment on this point. Nonetheless, there are some issues that could lead to problems in actual practice.

First of all, officials from the ministry of health say that the period of 210 days referred to in the regulation is to be understood as business days, not calendar days. It is legally objectionable to interpret this period as "business days" as no such reference is contained in the regulation; moreover, the corresponding period in the EU is expressed in "calendar days". This would defeat the main underlying objective of having a set period of time for evaluations, ie to speed up the

licensing process, the report says.

A survey conducted among the members of AIFD (the Association of Research-Based Pharmaceutical Companies) reveals that over the past three years the average licensing time varied between 24 and 30 months. Some companies have even said that this period could extend up to 63 months. Although it is estimated that the new regulation will shorten this period, the period of 210 days must be considered as "calendar days" for the sake of full harmonisation with the EU legislation.

Another problem encountered in the licensing process is the fact that the ministry does not have detailed, comprehensive and publicly accessible guidelines or Standard Operating Procedures (SOPs). This is a very serious deficiency in terms of transparency, the consultancy says. For instance, the European Medicines Agency (EMA) has detailed guidelines for all processes, and the agency tries to conduct evaluations in line with the periods and criteria set down in these guidelines.

In Turkey, the results (positive or negative) of marketing approval applications are not made public, nor are the reasons for decisions made clear. This constitutes another very important deficiency in transparency. Publishing the decisions and the reasons for them is an important way of informing healthcare professionals and the public in general.

Pricing part of licensing process

As for pricing, Turkey took a significant step forward by implementing reference prices in 2004. The new legislation is founded on a more transparent base than its predecessor, and this is of course an improvement. In addition, the period of 90 days cited in the pricing decree for pricing decision was inspired by EU legislation.

However, there are some differences between Turkish practices and the EU's price transparency directive. In Turkey, the initial pricing process is part of the overall licensing procedure. In other words, when a drug is licensed, its price is also determined. At first glance it may be thought that the Turkish practice saves time, but in fact it can result in some drawbacks in terms of transparency, according to the report.

First of all, in the EU economic criteria are not taken into consideration at all in the licensing process, and licensing decisions are based purely on scientific and technical criteria. But in Turkey, deciding on the price of a drug during licensing inevitably brings financial considerations into the licensing process. There may be allegations that if the authorities believe the price of a drug is too high, they may delay the licensing decision, and this may in turn result in unofficial contacts with the applicant on the basis of non-transparent criteria. Moreover, if the goal is to have legislation harmonised with the EU, the pricing process must be completed in 90 calendar days, not business days.

Reimbursement

The most problematic area in Turkey in terms of transparency is reimbursement. In February 2005, the positive list came into effect for all reimbursement systems in Turkey, replacing the previous negative list of drugs that would not be reimbursed. The positive list is handled by the reimbursement committee that was formed under the 2004 pricing decree. The working procedures and principles of the committee were published in February 2006. However, it is not clear how the committee will operate, on which criteria it will take its decisions, and which scientific bodies will be involved.

The February 2006 document on Working Procedures and Principles of the Reimbursement Commission states that the committee members will be representatives of relevant administrations, and must be at least at the level of department head. However, it is not made clear which disciplines the committee's members should be drawn from, and on which issues they are expected to contribute to the activities of the committee. Likewise, the document does not identify the criteria that will be used to determine which drugs should be reimbursed.

Furthermore, the decisions of the reimbursement committee, and the reasons underlying them, are not published, and the route of appeal is uncertain. In addition, it is not clear whether it is a separate legal entity or not. If the same people are assigned to both the price and reimbursement committees, reimbursement issues could have an impact on the pricing process, which could impair the transparency of the whole process. For this reason, the report says, the document is still far from bringing the transparency required by the transparency directive.

The survey of AIFD members shows that applications for inclusion in the reimbursement list are dealt with in one to six months, or sometimes longer. This is far above the period of 90 days stated in the transparency directive.

The lack of guidelines and SOPs is a serious problem for transparency

Turkey now has a more transparent system based on reference prices...

...but including pricing in the licensing process could lead to problems

It is not clear how the reimbursement committee will operate in practice

Membership talks

The pharmaceutical sector will be high on the agenda of Turkey's EU membership talks

Detailed negotiations on Turkey's membership of the EU began on 12 June 2006 after foreign ministers agreed on a way forward that among other things addressed questions relating to relations between Turkey and Cyprus. EU membership will require harmonisation of Turkish legislation in the drug sector. The initial issues expected to be put on the agenda of talks about the drug sector are free movement of goods and intellectual property rights. The transparency directive will also be under discussion, particularly because of its impact on the free movement of goods.

Officials from the European Commission have said in various forums, including official meetings, that despite the progress recorded in recent years, Turkey has not yet fulfilled all of its responsibilities. With regard to the problematic areas affecting intellectual property rights, the commission has singled out in particular the problems faced in the licensing process and in protecting the confidentiality of marketing approval application dossiers during the period between 1 January 2001 and 31 December 2004.

It is not difficult to predict that the commission will closely follow these issues during the negotiations with Turkey, as they will have to be resolved before Turkey becomes a full member of the EU.

Through legislative changes since 2004, Turkey has shown a willingness to make great improvements in harmonisation with the EU; now is the time to implement the changes, particularly in terms of improving the transparency of the regulatory bodies.

One of the main problems is the lack of reliable data

One of the main problems affecting the drug industry in Turkey is the lack of data, something the study authors have felt acutely. The officials interviewed in Ankara have also admitted this. For this reason the industry and the public administration need to hurry up and begin working jointly to resolve these deficiencies.

Interviews with various parties revealed that the burden of drug expenditure on the public finance is a serious source of concern and plays a role in decision-making. In a developing country like Turkey, where the wounds caused by a deep economic crisis have not yet fully healed, the ratio of public debt to the gross national product is still too high and public expenditure has to be reduced as a requirement of commitments given to the International Monetary Fund, the sensitivity created by drug spending is easily understandable. Obviously this is not a problem unique to Turkey. As pointed out in the report with various examples, even the developed countries are trying to find alternatives for taking the drug expenditures under control. Of course, the most important thing to be always kept in mind must be the protection of human health. Exclusion from reimbursement systems of the drugs increasing efficacy in treatment will not be a feasible solution, but on the contrary will create a negative picture in terms of the public interest.

Turkey's record on transparency in the drug industry is not very encouraging. In its Trade Barriers Regulation (TBR), the EU draws attention to deficiencies in transparency and asserts that Turkey does not reply to its questions, further reducing the transparency level.

Proposals

The report puts forward a number of suggestions to help improve transparency in the drug sector and harmonise Turkish legislation with that of the EU. These are detailed below.

The licensing process needs to be speeded up, confidential data must be protected...

- the licensing process must be completed within 210 calendar days rather than business days. Speeding up the licensing process will be in the interests of patients, the industry and the state;
- it must be clarified what is meant by "evaluation by the public authorities other than the ministry";
- the period of 210 days must cover the whole process. Transparency will be increased if all stages of the licensing process are regulated by publicly available guidelines;
- Turkey is not succeeding in fully protecting the highly confidential commercial data and information disclosed in marketing approval applications, so criteria for ensuring the confidentiality of information must be developed and efficiently implemented, and must be transparent and auditable;
- guidelines for assuring the competence and independence of the specialists involved in the licensing process must be issued; and
- the applicant must be duly informed about the routes of appeal and objection in cases where a licence application is refused. It must also be possible to appeal to the administrative courts against negative decisions.

...and more clarity is needed on routes of appeal and objections when a licence is refused

There is also a need for more information on the Turkish health ministry's activities in the pharmaceutical area. The EMEA publishes monthly and yearly reports, presenting detailed

information about its activities and sharing statistical data such as the number of applications received, the period of completion of the process, the number of drugs licensed, and the number of marketing licence applications refused. In addition, the EMEA makes such information public through periodic press bulletins. In Turkey, the publication by the health ministry of at least annual cumulative data would represent a serious step towards improving transparency.

In the pricing area, conducting the licensing and pricing processes jointly creates the impression that factors other than pharmacological considerations – particularly economic ones – may play a role in the licensing process. For this reason, it would be better that entirely independent bodies were responsible for licensing and pricing processes, the report recommends.

The non-independence of these processes also creates the impression that marketing approval for a product whose price is deemed too high may be delayed. Unless these two processes are made independent from each other, the periods referred to in the existing pricing regulation do not have any meaning, because the period of 90 days gets lost in the licensing process and is not measurable, according to the report.

Other improvements needed include:

- the routes of appeal and objection must be clarified and the rights to take legal remedies and go to court must be guaranteed;
- a list of international organisations and institutions that may be consulted for pharmaco-economic evaluations and assessments needs to be drawn up and made available to interested parties;
- the duties of the technical committees to be appointed must be defined in detail, and qualifications of specialists to be assigned thereto must be made known;
- the committees' decisions are only advisory opinions submitted to the relevant ministries. However, the reimbursement committee must have some legal liabilities and regulations are needed on this; and
- routes of appeal and objections against negative decisions must be clarified and the right to take legal remedies and go to court must be guaranteed.

Furthermore, the reimbursement committee decides which group of doctors is allowed to prescribe which drugs, but the criteria used in these decisions are not made clear to interested parties. If such decisions have to be taken, they must be made not by the reimbursement committee but during the licensing process (as in the EU). In any case, these criteria must not be economic, but pharmacologic. The decision must also take into consideration the distribution of specialists throughout the country and the extent of the public's access to them, otherwise it will restrict access to certain drugs. In summary, harmonisation of the reimbursement system with the transparency directive will be helpful in EU membership talks.

In fact, the great majority of the above suggestions can be implemented transparently only if the licensing, pricing and reimbursement procedures and structures are separated from each other. By this is meant not only the separation of the processes, but also the handling of evaluations by different bodies and different persons, the report says. The first duty of the ministry of health should be to ensure that effective, safe and high-quality drugs are made available to the public in the shortest possible time. The burden of these drugs on the budgets of the social security institutions is a separate matter which must be considered by other bodies such as the ministry of labour and social security and the ministry of finance, it concludes.

References

1. Istanbul Ekonomi Danismanlik Report, www.istanbul-ekonomi.com

There is also a lack of information on the health ministry's activities in the pharmaceutical area

Decisions on which doctors can prescribe a product must be taken during the licensing process, not by the reimbursement committee

It is the health ministry's responsibility to ensure safe and effective drugs are made available, not to look at financial aspects

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