

Turkish Pharmaceuticals: An Industry In Transition

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I. INTRODUCTION

While the Turkish pharmaceutical industry holds a prominent status in the global pharmaceutical market,¹ it is beset with a variety of political and regulatory issues that affect and potentially threaten its operation, functionality, and international relations. A primary source of concern in all of these areas lies within Turkish patent law, or the lack thereof, with specific regard to patent protection in the pharmaceutical arena. These regulatory problems also extend to Turkey's problematic development of clinical trial procedures.² These issues in the Turkish pharmaceutical industry have remained a source of political contention with respect to Turkey's pending ascension into the European Union since membership negotiations began in 2005.³

The Turkish pharmaceutical industry is quite large and represents the principal pharmaceutical market in the Middle East.⁴ In fact, Turkey ranks sixteenth among the world's thirty-five top pharmaceutical producing

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1. See AN OVERVIEW OF TURKISH PHARMACEUTICAL SECTOR, <http://www.egonzehnder.com/global/knowledge/articleindex/article/id/11900260> (last visited Mar. 20, 2012).

2. See WAY TO A NEW ERA FOR CLINICAL TRIALS IN TURKEY, <http://www.mondaq.com/404.asp?404;http://www.mondaq.com:80/x/144078/Healthcare/Way+To+A+New+Era+For+Clinical+Trials+In+Turkey&login=true> (last visited Mar. 20, 2012).

3. HARVARD INTERNATIONAL REVIEW, <http://hir.harvard.edu/turkey-s-membership-in-the-eu-realistic-or-merely-wishful?page=0,1> (last visited Mar. 20, 2012).

4. EGON ZEHNDER INTERNATIONAL, <http://www.egonzehnder.com/us> (last visited Jan. 5, 2012).

countries.⁵ It is projected that by 2020, Turkey's pharmaceutical market, along with that of the other E7 countries, will account for twenty percent of global pharmaceutical sales.⁶ E7 countries include China, Indonesia, Russia, Turkey, Brazil, India and Mexico, and are known for having fast-growing economies and aging populations that demand better healthcare.⁷ Not surprisingly, the Turkish pharmaceutical market is the fastest growing in the Mediterranean region.⁸

This paper will address the regulatory issues Turkey's pharmaceutical industry overcame by implementing industry-wide reforms. Specifically, this paper will describe the patent concerns Turkey faced, followed by a discussion of clinical trial reforms, and their impact on the pharmaceutical industry. Finally, this paper will discuss Turkey's issue with Adverse Drug Reactions (ADE's) and how the implementation of a national drug policy will alleviate this problem.

II. GOVERNANCE AND PATENT CONCERNS

Turkey's pharmaceutical industry is governed by the Ministry of Health (MoH), within which lie The General Directorate of Pharmaceuticals and Pharmacies (GDPP).⁹ The GDPP has sole authority for the registration, marketing approval and authorization, pricing, legal classification, and inspection of pharmaceuticals, manufacturers, wholesalers, and retail

5. *Id.*

6. Pharma 2020: The Vision: Which Path Will You Take? (last visited Jan. 3, 2012), <http://www.pwc.com/gx/en/pharma-life-sciences/pharma-2020/pharma-2020-vision-path.jhtml>.

7. Lesley J. Burgess & Marli Terblanche, *The Future of Pharmaceutical, Biological, and Medical Device Industry*, OPEN ACCESS JOURNAL OF CLINICAL TRIALS (2011), available at <http://www.doaj.org/doi/func=abstract&id=815417>.

8. EGON ZEHNDER INTERNATIONAL, *supra* note 3.

9. Andreas Seiter, *Health, Nutrition and Population: Turkey: Pharmaceutical Sector Analysis*, WORLD BANK, 5 (2008), <http://siteresources.worldbank.org/INTHSD/Resources/376278-1250623752714/Turkeypharmaceuticalsectoranalysis.pdf>.

pharmacies.¹⁰ In carrying out these functions, the GDPP is assisted by a number of committees whose functions are primarily consultative in nature.¹¹ Additionally, as a member of the World Trade Organization (WTO), Turkey is subject to certain trade agreements,¹² which play a large part in the current patent issues facing Turkey's drug industry. One such agreement is the Trade-Related Aspects of Intellectual Property Rights (TRIPS), which introduced minimum protection standards for protecting and enforcing most forms of intellectual property rights, including patent protection for pharmaceutical products.¹³

In general, pharmaceutical companies rely heavily on patents for their products, and these intellectual property rights have been dubbed a "major international battlefield."¹⁴ TRIPS protects data and production exclusivity, and WTO members benefit from reduced tariffs on their exports in exchange for granting patents on certain products and processes, including pharmaceuticals.¹⁵ TRIPS mandates that "patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application."¹⁶ Despite its WTO membership, historically, Turkey employed policies that failed to grant pharmaceutical patent protections.¹⁷ As a result, until approximately 2005, when new licensing

10. Directorate, General for Trade, *Commission Report to the Trade Barriers Regulation Committee: TBR Proceedings Concerning Turkish Practices Affecting Trade in Pharmaceutical Products*, at 16 (Sept. 13, 2004), available at <http://trade.ec.europa.eu/doclib/html/119478.htm>.

11. Seiter, *supra* note 9.

12. See David Henry & Joel Lexchin, *The Pharmaceutical Industry as a Medicines Provider*, 360 LANCET 1590, 1593 (2002).

13. *WTO and the TRIPS Agreement*, WORLD HEALTH ORG. (last visited Jan. 3, 2012), http://www.who.int/medicines/areas/policy/wto_trips/en/index.html.

14. Henry & Lexchin, *supra* note 13.

15. *Id.*

16. WORLD HEALTH ORGANIZATION, http://www.wto.org/english/docs_e/legal_e/27-trips_04c_e.htm (last visited Jan. 3, 2012).

17. See Office of the United States Trade Representative, *TURKEY 622* (2006), available

regulations took effect, copies of patent protected drugs in the United States and European Union were legally introduced in the Turkish pharmaceutical market.¹⁸ As such, Turkish pharmaceutical companies did not need to make any significant research and development investments, and consequently, the domestic sale of these drugs was a large source of profit.¹⁹ Thus, Turkish pharmaceutical companies were able to make sizeable profits at the expense of the R&D investments of foreign pharmaceutical companies.²⁰ This lack of intellectual property protection was part of a complaint against Turkey by the European Federation of Pharmaceutical Manufacturers and Associates (EFPIA), which resulted in an investigation into Turkish pharmaceutical practices by the European Commission.²¹ The investigation revealed that Turkey's lack of data exclusivity resulted in losses for "originator companies" between 128 and 135 million USD annually.²² The EFPIA concluded that Turkey was in "clear violation" of the TRIPS agreement, and to fulfill its obligation, Turkey must provide data exclusivity for a "reasonable period of time."²³

Today, while the pharmaceutical industry is not without problems, it has undergone several years of reform to bring the industry into compliance with international agreements.²⁴ In fact, Turkey already introduced several

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http://www.ustr.gov/archive/assets/Document_Library/Reports_Publications/2005/2005_NTE_Report/asset_upload_file512_7503.pdf.

18. Seiter, *supra* note 11, at 7-8.

19. Seiter, *supra* note 11, at 8.

20. *Id.*

21. Mere Perez Pugatch, *Dialogue on Ensuring Policy Options for Affordable Access to Essential Medicines Bellagio: Intellectual Property and Pharmaceutical Data Exclusivity in the Context of Innovation and Market Access*, UNIVERSITY OF HAIFA, ICTSD UNCTAD (Oct. 12-16, 2004) available at http://www.iprsonline.org/unctadictsd/bellagio/docs/Pugatch_Bellagio3.pdf.

22. Directorate, General for Trade, *supra* note 10, at 48.

23. Directorate, General for Trade, *supra* note 10, at 46.

24. *An Uncertain Future for Pharmaceutical Companies in Turkey*, BUSINESS TURKEY TODAY (Mar. 15, 2011), available at, <http://www.business-turkeytoday.com/an-uncertain-future-for-pharmaceutical-companies-in-turkey/>.

regulations to align its patent laws with the EU.²⁵ Specifically, the Government of Turkey issued best practices²⁶ in a number of pharmaceutical sectors including manufacturing, drug research, product registration, and packaging and labeling.²⁷ Furthermore, Turkey instituted a requirement that pharmaceutical companies have data exclusivity over new molecules for a period of no less than six years after entering the Turkish pharmaceutical market for the first time.²⁸ Thus, while this waiting period could begin within the existing twenty-year international data exclusivity agreements, production of the generic form of a molecule new to Turkey could potentially have a waiting period of up to twenty-six years.²⁹ These reforms substantially impacted the pharmaceutical market and resulted in significant profit losses for Turkish drug companies. The MoH addressed this issue by increasing drug subsidies to Turkish pharmaceutical companies from 4% to 41%.³⁰ It seems that this solution was effective in light of the massive adjustment because drug manufacturers were able to sell their products to pharmacies at even cheaper prices than before.³¹

The sweeping reforms to Turkish patent law in the pharmaceutical context have certainly been successful; if only because they brought Turkey into compliance with international agreements, such as TRIPS.³² However, more should be done to strengthen patent protections, particularly in light of

25. Rajesh Chhabara, *Transforming the Turkish Pharma Market* (Jan. 17, 2011), available at, <http://social.eyeforpharma.com/marketing/transforming-turkish-pharma-market>.

26. Best practices are guidelines that seek to identify the best or ideal practices in a sector or industry. USLEGAL, <http://definitions.uslegal.com/b/best-practices/>. (last visited Mar. 20, 2012).

27. Chhabara, *supra* note 25.

28. Interview with Seda Serin, Biologist, MN Pharmaceuticals, in Istanbul, Turkey (Mar. 5, 2012).

29. *Id.*

30. *Turkey: Pricing Dispute Between Government and Drug Manufacturers Resolved*, BUSINESS TURKEY TODAY (Dec. 19, 2011), available at, <http://www.businessturkeytoday.com/turkey-pricing-dispute-between-government-and-drug-manufacturers-resolved.html>.

31. *Supra* note 30.

32. *Supra* note 24.

Turkey's pursuit for EU membership. At a council debate in 2001, Turkish officials acknowledged "marketing exclusivity [is] not covered by Turkish legislation as it is the case in the EU and the US. Only patented product is protected by the patent law until the due date of the patent expires."³³

In the EU, member countries provide said protection with Supplemental Protection Certificates (SPCs).³⁴ SPCs provide additional protection for a period of time to manufacturers whose patents have expired.³⁵ SPCs were introduced in the EU to compensate pharmaceutical companies for lengthy regulatory approval and authorization periods.³⁶

While Turkey did institute the six-year data exclusivity protections mentioned *supra*,³⁷ that protection is narrow as it only applies to molecules new to Turkey, and was not applied retroactively.³⁸ Accordingly, should Turkey join the EU, it would have to implement additional patent protections inclusive of marketing exclusivity clauses and SPCs.³⁹

III. CLINICAL TRIALS AND THE PHARMACEUTICAL INDUSTRY

In addition to the regulatory issues plaguing Turkish patent law, regulatory problems in the Turkish pharmaceutical industry also affected the development of clinical trials.⁴⁰ Clinical trials play an important role in the pharmaceutical industry, as they are vital to the development of new drugs.⁴¹ Recent clinical trial legislation in Turkey has been the subject of

33. Directorate, General for Trade, *supra* note 10, at 37.

34. LONDON SCHOOL OF ECONOMICS, *Pharmaceutical Reimbursement Policy in Turkey* (Sept. 2005), available at <http://www.suvak.org.tr/kitap-2ingilizce.pdf>.

35. MPA BUSINESS SERVICES, EU SPC'S (2006), available at <http://www.mpaservices.co.uk/eu-supplementary-protection-certificates.html>.

36. *Id.*

37. *Supra* note 33.

38. LONDON SCHOOL OF ECONOMICS, *supra* note 33, at 13.

39. *Id.* at 44.

40. *Supra* note 2.

41. See Thomas Bodenheimer, *Uneasy Alliance—Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENGL. J. MED. 1539, 1539 (2000).

profound debates.⁴² So much so that, in 2009, the Turkish Medical Association (TMA) filed an action against certain provisions of clinical trial regulations.⁴³ The 10th Chamber Council of State presided over the action and issued a stay of execution, which prevented the implementation of certain articles from the regulation until the court rendered a final decision.⁴⁴ The stayed articles provided that: volunteers participating in clinical trials could not be paid; a person independent of the research team must inform volunteers about the clinical trial proceedings; changes in clinical trial protocols required GDPP approval; and that the High Council of Health's authority could not establish Ethics Committees through regulation.⁴⁵

During this time, the MoH and TMA filed a request for review with the Plenary Session of the Chambers for Administrative Cases (PSCAC), a branch within the 10th Chamber.⁴⁶ PSCAC held that the clinical trial regulations at issue were directly related to the "right to life and immunity of physical integrity," and as such, the regulations governed fundamental human rights.⁴⁷ Thus, the regulations intervened with the basic human right of physical integrity and could only be limited by law even with a volunteer's consent.⁴⁸ PSCAC explained that subjecting a person to scientific and medical experiments violated the Turkish Constitution, unless the experiments were authorized by law.⁴⁹ PSCAC's decision effectively invalidated the clinical trial regulations, and the MoH stopped accepting clinical trial applications in October 2010.⁵⁰

42. *Supra* note 2.

43. *Id.*

44. *Id.*

45. *Id.*

46. *Id.*

47. *Id.*

48. *Supra* note 2.

49. *Id.*

50. *Id.*

As a result of this decision, confusion regarding the status of ongoing clinical trials ensued.⁵¹ Educational institutions and universities decided to proceed with the clinical trials already in progress and took steps to form the independent ethics committees banned by the original regulations.⁵² The universities established Ethical Committees within the scope of their authority under Turkey's Higher Education Law.⁵³ This law grants universities the authority to conduct "scientific trials," including clinical trials.⁵⁴ Universities interpreted this to mean that Ethical Committees could be properly established under that authority.⁵⁵ After seeing these developments with leading Turkish universities, the MoH announced that it would begin accepting clinical trial applications once again.⁵⁶

Finally, in May 2011, the 10th Chamber of Council delivered its final judgment.⁵⁷ Contrary to PSCAC's ruling, the 10th Chamber held that the MoH has the authority to regulate clinical trials and that the rules promulgated by the MoH had the force of regulations.⁵⁸ Consequently, a law was enacted that provided the MoH with the legal authority to issue new clinical trial regulations.⁵⁹ The MoH acted quickly, and by August 2011, new regulations provided that: clinical trials cannot be conducted in, or by, private hospitals, but only by education, research, or government hospitals and healthcare institutions; either the pharmaceutical company sponsoring the clinical trial or the Contract Research Organization (CRO) must be a resident of Turkey; all clinical trials require approval by an Ethics Committee; and in the course of obtaining consent, a member of the

51. *Id.*

52. *Id.*

53. *Id.*

54. *Id.*

55. *Supra* note 2.

56. *Id.*

57. *Id.*

58. *Id.*

59. *Id.*

research team can inform participating volunteers.⁶⁰

In the EU, clinical trials procedures have slight variations from country to country.⁶¹ However, the EU Voluntary Harmonization Procedure (VHP), for which state participation is entirely voluntary, was created to streamline the application process.⁶² To date, all EU countries with the exception of Poland have recognized VHP as a “valid approach to gaining clinical trial approval. . .”⁶³ Under this procedure an application is submitted to the Clinical Trials Facilitation Group (CTFG) for review.⁶⁴ The CTFG is comprised of authorities from each member state where the clinical trial will be performed.⁶⁵

Like in Turkey, Ethical Committees (ECs) in the EU play an important role in that they review clinical trial materials for things like discrepancies in protocol and informed consent documents.⁶⁶ The Clinical Trials Directive outlines their role and the clinical trials process in greater detail. It provides that a pharmaceutical company must submit an application to the EC documenting aspects of the trial including protocol, subject information, and consent.⁶⁷ Detailed requirements for each country are set forth in documents issued by the European Commission.⁶⁸ ECs then have sixty

60. *Id.*

61. Franz Buchholzer, *Implementing the EU Harmonization Procedure for Accelerated Clinical trial Approval*, PHARMANET: INVENTIVE HEALTH, <http://blog.pharmanet.com/post/Implementing-the-EU-Voluntary-Harmonization-Procedure-for-Accelerated-Clinical-Trial-Approval.aspx> (last visited Mar. 20, 2012).

62. *Id.*

63. *Id.*

64. Susan Bhatti, *EU Incentives for Simplifying Clinical Trial Approval Concerns and Initiative: An Overview*, available at http://www.premier-research.com/files/EU_Initiatives_for_Simplifying_Clinical_Trial_Approval.pdf.

65. *Id.*

66. *Id.*

67. National Health Service, *The Ethical Review Process for Clinical Trials in the European Union*, available at http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2010/06/WC500093372.pdf.

68. maRS, *Clinical Trial Authorization Process: EU (UK)*, available at http://www.marsdd.com/dmsassets/entrepreneurtoolkit/Regulatory-PDFs/Clinical_Trial_Authorization_EU.PDF.

days to issue an opinion upon receipt of a valid application.⁶⁹ In reviewing an application, the EC looks to the relevance and design of the clinical trial, the risks, benefits, and protocol, quality of the facilities, consent procedures, and subject information.⁷⁰ During this time the EC also has the option to request more information from the sponsor, which stops the sixty day clock.⁷¹ If the application is denied, a pharmaceutical company can appeal or submit an amended request for further consideration.⁷² All approved clinical trials are then registered in an online database called EudraCT, which makes certain clinical trial information available to the public.⁷³

As it stands now, it is apparent that significant differences remain between Turkish and EU clinical trial processes. While Turkey has instituted several reforms to address regulatory issues in its clinical trials process, Turkey should consider restructuring its clinical trial process to parallel those of the EU in light of ongoing negotiations for EU membership. Because each EU state has requirements that vary slightly in nature, Turkey would not have to completely reform its existing structure, but merely harmonize its application procedures and tweak the roles of its Ethical Committees to comply. Thus, the regulatory changes Turkey instituted, particularly with respect to consent, could likely remain intact. Adopting EU clinical trial processes would improve Turkey's potential for EU ascension, as well as streamline clinical trial procedures with other Western and European nations. Doing so may increase Turkey's potential for foreign investments and opportunity for development within the industry.

69. National Health Service, *supra* note 67.

70. *Id.*

71. *Id.*

72. maRS, *supra* note 68.

73. *Id.*

V. CONCLUSION

The Turkish pharmaceutical industry is at a pivotal point. Despite its prominent status in the global pharmaceutical market, a plethora of political and regulatory issues remain. These issues have the potential to transform Turkey's pharmaceutical industry and make it an even bigger international player, but also threaten the industry's growth and operation, as well as its functionality and international relations.

While Turkey's intellectual patent laws have made huge strides to comply with international agreements such as TRIPS, it remains to be seen whether these developments will continue to be enforced and progress as to satisfy the European Union standards. Patent reforms had a great impact on Turkey's pharmaceutical industry, but should continue to evolve, as they will likely continue to shape the industry in the near future.

Similarly, with respect to pharmaceutical research and development, clinical trials in Turkey underwent substantial changes in the past twenty years, which greatly affected the functionality of Turkish pharmaceutical operations.⁷⁴ Regulations were promulgated and re-promulgated as Turkey struggled to find the right balance between pharmaceutical companies conducting the trials and patient rights. These changes have transformed the Turkish pharmaceutical industry and will continue to do so for the foreseeable future.

74. *Supra* note 2.