Orphan Drugs: R&D Challenges with Updates from Turkey and Middle East Countries

PEER REVIEWED

Introduction

Rare diseases (RDs) are an important public-health issue and a challenge for the medical community. They are called 'health orphans', because RDs have been neglected for many years, mainly due to the research and development (R&D) challenges.[1] In the 1960s, amendments were made to existing federal laws in the US, mandating that all drugs must be shown to be safe and effective through 'adequate and well-controlled studies' before receiving market approval[2]. Then raising the cost of drug development resulted in drugs for small disease populations being 'orphaned' by many major drug companies. Modern society still has a lack of options for the effective treatment of patients with RDs. As one of the consequences of this, the demand for public health protection has increased the economic burden of patients suffering from RDs[3].

The interest of the pharmaceutical industry in developing OMPs is fairly low due to the challenges specific to orphan drugs. Also, big pharma is paying increased attention to the orphan drug market in this decade[4]. However, there are major challenges in accessing these markets with reliable and comprehensive clinical data that needs to be obtained from well-defined clinical trials.

This article aims to present a review of the social and scientific need for the R&D of OMPs, discuss the management of the challenges, and propose the considerations to make the future better for meeting the medical needs in this area, with status updates from Turkey and the Middle East (ME), in an environment of rising improvement of the healthcare priority in this region.

Definition of Rare Disease and Orphan Drug/Medicinal Product (OMP)

There is no single orphan disease definition that is accepted all over the world, as it is outlined by the legislations adopted by each region or country. Overall, orphan diseases are often chronic, progressive, disabling, even life-threatening, and most of these have no effective or curative treatment, having low prevalence and high complexity.[5]

In the US, the Rare Diseases Act of 2002 defines rare disease strictly according to prevalence, specifically "any disease or condition that affects less than 200,000 persons in the United States (US)[6] or about 1 in 1500 people.[7] This definition is essentially like that of the Orphan Drug Act (ODA) of 1983, a federal law that was written to encourage research into RDs and possible cures[8]. In Japan, the legal definition of a rare disease is one that affects fewer than 50,000 patients in Japan, or about 1 in 2500 people.[9] However, the European Commission (EC) defines RDs as "life-threatening or chronically debilitating diseases which are of such low prevalence" that special combined efforts are needed to address them.[10] The term low prevalence is later defined as generally meaning fewer than 1 in 2000 people. The definitions ranging from 1/1000 to 1/200,000 used in the medical literature and by national health plans are similarly divided.

Looking at Turkey, an RD is defined in the Ministry of Health (MOH) Pricing Statement as a disease that has not been fully defined yet affecting less than 1/100,000 persons in a country.[11] In the ME countries Jordan, Lebanon, Egypt and Saudi Arabia, there is no available reference for 'rarity' of diseases in official sources. The US FDA defines an "orphan product" as a drug, biologic, device or medical food that is used for the prevention, diagnosis, or treatment of a rare disease. [12] An orphan drug is defined in the 1984 amendments of the ODA as a drug intended to treat a condition affecting fewer than 200,000 persons in the US, or which will not be profitable within seven years following approval by the FDA.[13] In Turkey, an orphan drug is stated as any drug that is used in these RDs.[11]

Generally speaking, an orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease.[14]

Rare Diseases May Not Be so 'Rare'!

Although we name these disorders orphan or rare diseases based on the prevalence data, the numbers giving details on these suggest that these might be more common rather than rare. For example, there are 5000-8000 RDs known so far. There are approximately 30 million Americans and 30-40 million Europeans affected by these diseases.[15] It has been reported that there are 250 new rare cases explored each year; however the acceptable treatment is available only for 200-300 orphan diseases.[15] In Turkey, as there is not enough available detailed epidemiological data about individuals having orphan diseases so far, it has been estimated that approximately 5 million people have at least one RD.[16]

It is known that the 80 % of the RDs are of genetic origin, and the rest have environmental, bacterial, viral, or unknown origin. [15, 17]

A number of medical disciplines with a lot of healthcare professionals are involved in the rare disease concept from diagnosis to treatment. Besides, the pharmaceutical industry has the responsibility to develop new and effective molecules to treat these diseases better in spite of the challenges of the medicinal product in this 'niche' area. More importantly, there are millions of patients and even more family members suffering from RDs trying to get fast diagnosis and effective treatment.

Research and Development Challenges of the Medicines to cure Rare Diseases

The challenges specific to OMPs, where pharmaceutical and biotech companies focus on OMP research and development, are discussed below:

1 Regulatory Framework and Scientific Approaches

There is a certain need for stimulus for the OMP R&D for pharmaceutical and biotech companies.[18, 19] For this purpose, several countries have implemented legislations to promote the development of medicinal products for RDs. In Table 1, the comparison of the various policies on orphan drugs worldwide is shown.

In the US and EU

The successful implementation of the ODA has inspired the implementation of orphan drug legislation in other countries to address the unmet medical needs of patients suffering from RDs, hence the legislation in Singapore (1991), Japan (1993), Australia (1998), and in the European Union (EU) (2000).[4]

The EU Reg. (EC) No 141/2000 defines that medicines intended for the treatment, prevention or diagnosis of RDs (i.e. those conditions affecting less than 5/10,000 individuals in the EU) can be designated as orphan drugs (ODs).

The EC has, on Rare Disease Day 2013, announced €144 million of new funding for 26 research projects on RDs. The projects will help improve the lives of some of the 30 million Europeans suffering from a rare disease. The goal is to pool resources and work beyond borders, to get a better understanding of RDs and find adequate treatments.[20]

In Turkey:

Today, the Turkish MOH has been working on recognising a national plan with reference to "rare diseases" and "orphan drugs". Health services are provided by the MOH (state universities, universities, private hospitals and organisations) to all citizens, mainly free of charge. Currently the work in the Turkish MOH is ongoing to outline the legal infrastructure for certain incentives and providing the guidance documents.[21]

Encouraging the growth of the domestic pharmaceutical industry and attracting foreign investment are good options for Turkey and the ME. In this context, from 1990 onwards Scientific and Biotechnological Research Parks have been established in Turkey; 32 of these are actively operating to achieve the purpose of providing a common research environment for universities, research institutes and industry, to enable information and technology exchange.[22]

The Scientific and Technological Research Council of Turkey is one of the partner institutions in the E-RARE Project (ERA-Net for Research Programs on Rare Diseases) that is supported by the EC. The purpose of the project is to provide coordination of the national supporting institutions, to develop common support mechanisms in rare disease research, and to enable sustainable and long-term collaboration amongst partner countries. Being a member of this partnership, Turkey will be contributing to the global research and development of the rare disease treatment options and will extend awareness in the country.[23]

Turkey is planning to establish national networks for the prevention, surveillance, diagnosis and treatment of RDs. One promising example from Turkey is the first National Database Project for Pompe Disease, initiated under the coordination of industry, the Turkish Neurology Association Neuromuscular Diseases Scientific Working Group. With the 1st Pompe Disease database and follow-up study, it is planned to have 45 centres in Turkey, with the purpose of determining the prevalence, gender distribution and country-specific mutation types.

At the MOH level, the high priority sustainable investment in the projects of biotechnological drugs, oncology drugs and blood products manufacturing is supported by governmental grants in a way specified in the relevant directive.[24] This is an open channel for the orphan drug R&D steps to get the governmental driving force to enable the orphan drugs R&D processes in Turkey.

Patient access to the orphan drugs, if not licensed yet, is possible in certain ways in Turkey. One of these is the 'off-label use' which is defined in guidelines available on the Turkish MOH official web page. This process is a patient-specific application which is initiated by the primary physician of the particular patient. The other way for rare disease patients to get access to the orphan drugs is the compassionate use programme, a very well-defined process by Turkish MOH, which is a patient-based humanitarian programme enabling the patient free of charge

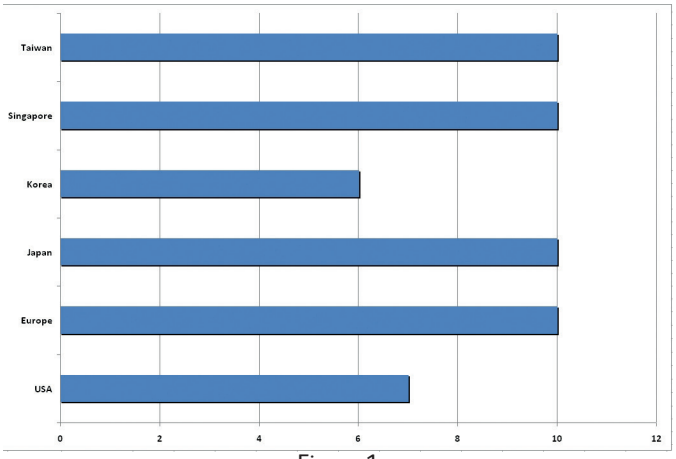

Figure 1

Figure 2: Turkish Regulatory Authority Orphan Drug Trials Applications in 2012 by Therapeudic Areas

Oncology-Hematology	12
Genetic Disorders	4
Eye Disorders	2
Others	5

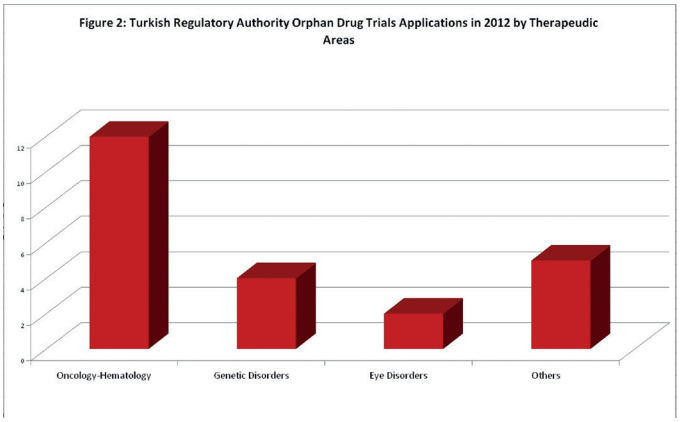

Figure 2

access to the unlicensed drug. The compassionate use programme covers the patients who are suffering from diseases that were not successfully cured by the existing licensed medications, and have no possibility of entering a clinical trial to have access to a medicinal product which the patient requires which has not been licensed in Turkey. The compassionate use programme application is made to the Ministry of Health per patient by the physician who confirms the diagnosis and maintains responsibility for patient

care. [25] Clinical trials are also very important for patient access to unlicensed orphan drugs. According to recent data from the Turkish Medicines and Medical Devices Agency in MOH, there were 162 clinical trial applications in 2012, and 24 of these trials (14.8 %) are stated as being in orphan drug research and/or the disease is stated as a rare disease. The therapeutic areas and the therapeutic indication of these trials are shown in Figures 1 and 2.[26]

In Some ME Countries:

At the moment, there is no legal framework specifically describing RDs and orphan drug research and development in ME countries such as Lebanon, Jordan, Egypt and Saudi Arabia. In one of the ME countries, the United Arab Emirates, in Dubai, a Biotechnology and Research Park (DuBiotech) has been established and has been providing the environment for life sciences companies to set up organisations in ME and to collaborate in productive partnerships, potentially with local companies.[27]

2 Insufficient Cooperation between Stakeholders Centralising Patients

The natural stakeholders in RD management include, but are not limited to, regulatory authorities, patient advocacy groups, academic environment, public organisations, consortiums, and governmental or private funding institutions. The organisations centralising patients suffering from RDs are considered of major importance. We will discuss two of the important ones here; Orphanet and EURORDIS.

Orphanet is a database of RDs which was established in 1997 in France and has been supported by the EU Commission. The printed directory is sent to these experts, to all relevant hospital departments (public and private), healthcare authorities, and patient support groups. The directory is also available online.[28] The aims of this study were (i) to determine how the directory is used to refer patients and send specimens, and (ii) to investigate its impact on patient referral. The Orphanet directory is used to refer patients and specimens, especially by experts and patient organisations.[29]

Turkey has been one of the Orphanet partner countries from 2007 onwards, with the academic support of Istanbul University. Turkey is joining the cooperation and collaboration activities in the organisation, aiming to increase awareness of RDs in Turkey, and to provide standardised, quality data to the Orphanet database. Turkey constitutes a unique place here, because none of the Middle East and North African (MENA) countries are involved in this collaboration, yet. Turkey is currently in the process of establishing national networks for the prevention, surveillance, diagnosis and treatment of RDs with the cooperation of the MOH, healthcare professionals, academia, patient advocacy groups, and industry.

Patient registries contribute to the accelerated research and development for rare disease data, because concentrated and standardised data can be achieved from the well-managed patient registries.[30] According to the Orphanet Jan 2013 Report, there are 588 disease registry studies being conducted in total in the world. Figure 3 shows the distributions of registries by country. There are four registry studies on RDs in Turkey which are seen in Table 2. There is no MENA country listed in the participant country list of

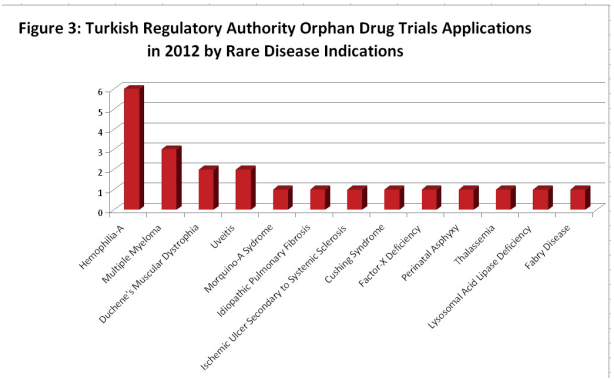

Figure 3

Figure 3: Turkish Regulatory Authority Orphan Drug Trials Applications in 2012 by Rare Disease Indications	
Hemophilia-A	6
Multiple Myeloma	3
Duchene's Muscular Dystrophia	2
Uveitis	2
Morquino-A Sydrome	1
Idiopathic Pulmonary Fibrosis	1
Ischemic Ulcer Secondary to Systemic Sclerosis	1
Cushing Syndrome	1
Factor-X Deficiency	1
Perinatal Asphyxy	1
Thalassemia	1
Lysosomal Acid Lipase Deficiency	1
Fabry Disease	1

the registries. It can be concluded from this that the RDs having respective high prevalence in this region are neglected. Local or national-level studies may be up and running in the region, but the data from these are not incorporated with the global data, and they are not serving a global dataset for researchers.

EURORDIS is a patient-driven alliance of patient organisations representing 561 rare disease patient organisations in 51 countries. EURORDIS promotes information services adapted to the situations and special needs of people living with RDs[31]. Currently there is only one member from Turkey, the Turkish Mucoplysaccharidosis and Similar Lysosomal Storage Disorders Association (from 2009 onwards), in the member associations list in EURORDIS. Considering the fact that the very valuable information exchange and contributing to or shaping up the policies of healthcare and rare disease research within EURORDIS provides remarkable improvements, it would be reasonable to expect to have more patient advocacy groups in EURORDIS from Turkey. Currently, there is no membership from MENA countries here. Although this is a European organisation, as rare disorders have no borders it is necessary for some MENA patient associations to be members of this organisation. In this way the overall purpose of 'adopting the scattered patients of RDs' is achieved by providing them with adequate, up-to-date scientific, social and medical information all over the world.

In ME countries, however, there are some initiatives aiming to increase the public awareness for the RDs and to attract the attention of healthcare professionals.

In Bahrain, for the first time, Al Jawhara Center for Molecular Medicine and Genetic Disorders/Arabian Gulf University, in collaboration with the MOH, celebrated Rare Disease Day in Manama on 28th of February 2013. The event included a scientific

symposium at Al Jawhara Center on the 26th of February and a public awareness campaign day on the 28th of February.

In Cyprus (Southern), the Cyprus Alliance for Rare Disorders, founded in 2010, has taken significant steps towards a proposal for a national strategy for RDs. This was accepted by the Ministerial Council in 2012, and the newly established National Committee on Rare Diseases has been working towards the creation of the rare disease management strategy.

The Rare Disease Foundation of Iran is a four-year-old private institution that provides services for rare disease patients in Iran. Its aim is improving the life quality of rare disease patients and increasing public awareness about the burden of RDs on patients, their families and the community. It collaborates with the medical system and research centres to provide an information bank of rare disease patients, and to disseminate information about RDs to inform all health professionals and educate patients, their families and the general public.

The Lebanese Association for Neuromuscular Diseases is a unique association of voluntary parents' and professionals' support groups that will spread awareness and help patients and families affected by neuromuscular diseases. LAND is committed to the identification, treatment, and cure of rare disorders through programmes of education, advocacy, research, development, and outreach.

The Palestinian Starfish Orphaned Charity for Rare Disorders started in 2013, offering all individuals and their organisations activities and events that help in continuing the progress on rare disorders in Palestine. Some are fundraising projects that can be held in local communities; some will raise public awareness and support for rare disorders; some will educate and engage healthcare professionals, school students, families and patients; and all will help to provide opportunities for understanding and supporting rare disorders.[32]

3 Still Secret Natural Histories of Rare Diseases

The natural histories of most RDs are not fully known, as seen in mucopolysaccharidosis type I, II, III and some other lysosomal disorders.[33]

Mucopolysaccharidosis type III is a family of autosomal recessive lysosomal storage disorders. MPS IIIB (Sanfilippo B Syndrome) is similar to other LSDs with an accumulation of substrate in a number of tissues and cell types, which results in cell and tissue dysfunction.[34] As seen in most LSDs, a considerable variability has been observed in the clinical course of Sanfilippo B Syndrome. Children with the classical and more severe form of Sanfilippo B Syndrome often have normal or near normal development, and initially present with a slowing of development and behavioural problems beginning around two years of age. This is followed by progressive intellectual decline and loss of morbidity.[33] There is no currently approved therapy for the treatment of Sanfilippo B Syndrome; additionally, the options for clinical symptoms management are limited due to the diversity of the phenotypes of the disease. As is the case for more RDs, the natural history of the disease needs to be clarified, including the clinical, biochemical, genetic, molecular characteristics and the course of disease progression for all phenotypes remains to be investigated to define the most adequate treatment options, such as enzyme replacement or gene therapies. This will contribute to scientifically and ethically well-designed clinical protocols that will eventually lead to reliable and standard clinical data from trials.

4 Low Prevalence

As RDs are seen in a limited number of persons in the population due to its low prevalence, it is quite difficult to calculate the adequate sample size, in other words enrolment figures, to be included in the clinical trials. Moreover, patients are dispersed across the world as seen in the cases of Spinal Muscular Atrophy (SMA) and Duchenne Muscular Dystrophy (DMD). This also makes it difficult to organise a clinical trial.

The prevalence data for RDs is of crucial importance for companies having orphan drug research and development in their pipeline while planning clinical trials. Epidemiology studies focusing on RDs have been helping companies to make decisions on the location and the number of human subjects for clinical studies of drug development. Population characteristics are important for the determination of rare disease prevalence. The population of Turkey and other parts of the ME region is characterised by large family size, older maternal and paternal age, and high rate of consanguineous marriages.[35]

Consanguineous marriages are one of the major risk factors in rare disease incidence, and carriage constitutes an attention point for researchers. The global distribution of consanguineous marriages data are summarised in Figure 4.[36]

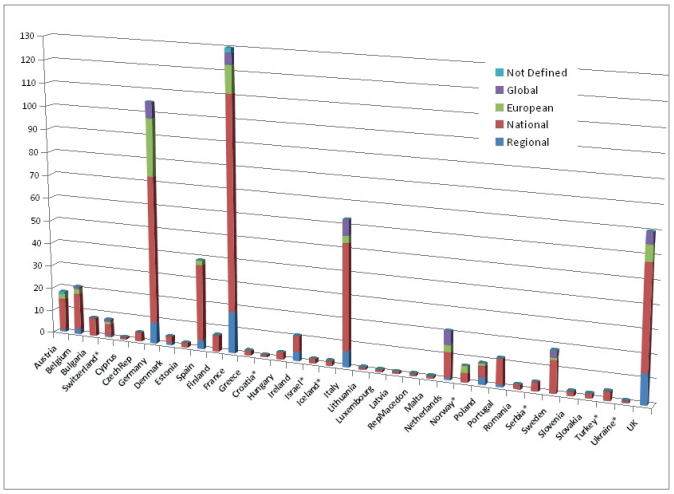

Figure 4

There are differences between regions in means of consanguineous marriages in the world: the lowest rates of consanguinity are found in Western Europe, North America and Oceania, where less than 1 % of marriages are consanguineous (i.e. unions between couples related as second cousins or closer ($F \geq 0.0156$)). In some parts of Southern Europe, South America and Japan, 1–5 % of marriages are consanguineous, depending on local geography and social customs.[37]

The highest rates of consanguineous marriage have been observed in North Africa, the ME and much of Central and South Asia, where more than 25 % of the world's population lives, and unions between couples related as second cousins or closer can account for 50 % of all marriages.[38]

Increased prevalence of α- and β-thalassemia, rare complex haemoglobinopathies and other hematological disorders (including coagulation deficiencies and acute lymphocytic leukemia in childhood) have been reported for consanguineous offspring in different countries. A wide range of inborn errors of metabolism have been reported in indigenous and migrant populations, including lysosomal storage disorders and cerebral lipidoses.[39] The consanguineous marriage rate in Turkey is reported as 17 % in Ankara, Istanbul and Izmir. According to the evaluation of the regions in Turkey, this rate is lowest in the Western region (12.8 %) and the highest in the Southeastern region (35 %).[40]

Disease carriage is also important for RDs. Some of the RD carrier rates in MENA are shown in Table 3.[41] This is especially crucial for the hemoglobinopathies. Thalassemia, an autosomal recessive hemoglobinopathy, is one of the commonest genetically transmitted disorders throughout the world. Collective measures including carrier identification, genetic counselling and prenatal diagnosis are required for preventing thalassemia.[42]

As recently reported by the Turkish Regulatory Authority, the majority of orphan drug and/or rare disease clinical trial applications are in the Hemophilia-A disease indication (six trials). This is followed by Multiple Myeloma (three trials), Duchenne Muscular Dystrophy (two trials), Uveitis (two trials), Morquio-A Syndrome, Idiopathic Pulmonary Fibrosis, Ischemic Ulcer secondary to Systemic Sclerosis, Cushing Syndrome, Factor X Deficiency, Perinatal Asphyxia, Thalassemia, Lysosomal Acid Lipase Deficiency, Fabry Disease (Figure 2).[26]

Genetic disorders such as hemoglobinopathy, glucose-6-phosphat dehydrogenase deficiency, autosomal recessive syndromes, and several metabolic disorders have a presence throughout the Middle East.[34] Other rare diseases resulting from viral or bacterial infections and allergies, or autoimmune reasons such as Behcet's disease, Lichens Planus Pigmentosus, and Pemphigus are all seen more in the Middle East region than the rest of the world.[43]

Having these data in mind, the sponsor companies need to plan the locations of the potential clinical sites for the targeted clinical studies for OMPs in their pipeline.

5 Difficulties in Diagnosis of Rare Diseases

The disease itself is complex and hard to diagnose, thus enrolment in a well-defined clinical trial protocol is very difficult; 30 % of the patients receive the appropriate diagnosis in 3-5 years. More dramatically, 15 % of the patients receive a diagnosis in 7 or more years, and some of them remain misdiagnosed or undiagnosed in their lifetime.[1, 44]

In a survey of eight rare diseases (Crohn's Disease, Cyctic fibrosis, Duchenne Muscular Dystrophy, Ehlers-Danlos Syndrome, Marfan's Syndrome, Tuberous Sclerosis, fragile x syndrome), it was shown that 40 % of patients are misdiagnosed, and others had no diagnosis. This study suggested that appropriate information and medical expertise on RDs are often insufficient, and access to care is difficult. As a consequence, the risk for medical complications and late sequel is increased.[44]

Difficulties in diagnosis partly result from the sub-type of the diseases that have a mechanism that is not fully known. Another factor is scientific knowledge on RDs being scarce overall due to the rarity and complexity. 'Rare doctors' have adequate know-how to diagnose 'rare diseases'.

Turkey has a unique place in this area, having very well-equipped medical faculties, accredited hospital laboratories, and medical genetics research centres. There are striking examples, such as Hacettepe, Ankara, Istanbul, and Ege University Medical Faculty Hospitals departments of hematology, pediatric medicine, oncology, etc. The most recent perinatal and pre-natal diagnostic techniques have been used in these clinics to obtain diagnoses in a very early phase. Genetic tests also help 'rare doctors' to diagnose the case correctly, thus avoiding delays in curing RDs.

The other reason for diagnosis difficulties is the lack of a universally accepted special coding system for RDs. Although Orphanet has been presenting a classification on RDs[45] this is only available for reference to Orphanet members. OMIM (Online Mendelian Inheritance in Man)[46], and ICD-10 – the 10th International Classification of Diseases established by WHO – are other systems for coding.[47] The absence of a universally recognised coding system is an obstacle for reliable registration of patients in national or international databases.[47]

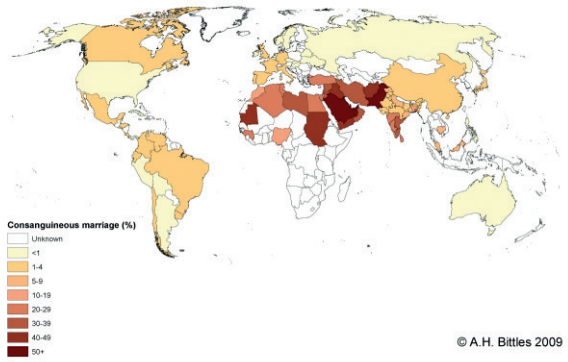

Figure 5

Conclusive Remarks:

Rare disease research requires a broad range of disease-related information for the discovery of causes of disorders. The rarity of cases makes it difficult for researchers and companies involved in R&D of orphan drugs to elucidate definite inception.

Taking patients and their advocacy groups centrally, the industry and healthcare professionals need to collaborate to define the unmet medical needs and to develop innovative treatment alternatives, specifically orphan drugs, for these. Inevitably, initiatives, incentives and an established legal framework by the rule-makers, the regulatory authorities, is required to achieve the goal of defining RDs and adequate data being obtained from well-designed clinical trials. Social and official media can also support public awareness of RDs and contribute to patients' accessibility to the correct and most current treatment options.

The national and transnational collaboration between the stakeholders may help to support the orphan disease research projects, funding them and providing them with reliable communication media. This would contribute to obtaining more correct prevalence and epidemiological data, helping healthcare professionals communicate more intensely, and increasing knowledge of the diseases and the diagnosis/treatment methods. Turkey is also the only example in the region of the participation

of international organisations such as Orphanet and ERORDIS. Taking the recent initiatives of healthcare professionals and patient advocacy groups in ME countries, the interest of the rule-makers, and the forming phase of the fully established legal framework outlining RD and orphan drug development into consideration, we can conclude that community awareness of RDs and R&D need in this region is growing.

Cooperation and collaboration between all stakeholders in rare disease and orphan drug R&D needs to be improved nationally and transnationally to achieve the ultimate global goal of providing adequate care for patients suffering from RDs, and promoting orphan drugs R&D. Turkey and ME countries are of central importance, having certain rare patient pools seeking treatment options and having communities ready to proceed, taking steps forward to participate in developing new treatment options.

References:

1. Schieppati A. et al. Why Rare Diseases are an important medical and social issue, Essay Focus, Lancet 371:2039-41, 2008
2. Halffner, M.E. et al. Two decades of orphan product development. Nat Rev Drug Discov 2002: 1: 821-5
3. Halffner, M.E. et al. Adopting Orphan drugs: two dozen years of treating rare cases. N Engl J Med 2006; 354: 445-7
4. Kessel M. The problems with today's pharmaceutical business—an outsider's viewNature Biotechnology 29(1) 2011
5. Wastfelt et al. A journey of hope: lessons learned from studies on rare diseases and orphan drugs. J Internal Med 2006: 1-10
6. US Rare Disease Act (ODA), 2002
7. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm239698.htm (Accessed 25 Mar 2013)
8. Orphan Drug Act (US) 1983.
9. http://malattierare.regione.veneto.it/inglese/dicosaparliamo_ing.php Rare Diseases What we are talking about? (Accessed 25 Mar 2013)
10. http://ec.europa.eu/health/ph_information/documents/ev20040705_rd05_en.pdf (Accessed 20 Mar 2013)
11. Turkish MOH Pricing Statement, Official Gazette dated 22.09.2007 with number 26651
12. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm239698.htm (Accessed 20 Mar 2013)
13. FDA/CDER Small Business Chronicles Jul 13, 2012.
14. http://en.wikipedia.org/wiki/Orphan_drug, (Accessed 25 Mar 2013)
15. Stakisaitis D. et al. Access to information supporting availability of medicines for patients suffering from rare diseases looking for possible treatments: the EuOrphan Service. Medicina (Kaunas) 2007; 43(6)
16. Dundar M. et al. Turkiye'de Nadir hastaliklar ve yetim ilaclar: Medikal ve sosyal problemler, Erciyes Medical Journal 2010; 32(3): 195-200
17. Fatma Atalar et al. Orphanet and Orphanet Orphanet Turkey Presentation 2011
18. Sharma A. Orphan Drug: Development, trends and Strategies. J Pram Bioallied Sci. 2010 2(4): 290-299
19. Nistico G. Orphan Drugs Assessment in the Centralized Procedure. Ann Ist Super Sanità 2011 | Vol. 47, No. 1: 98-99
20. EUROPEAN COMMISSION PRESS RELEASE Brussels, 28 February 2013
21. Ozbek U. Presentation in Fourth Eastern European Conference for Rare Diseases and Orphan Drugs "Together for Integrative Approach to Rare Diseases" 13-14 June 2009 - Plovdiv, Bulgaria
22. Teknoloji Gelistirme Bolgeleri Dernegi (http://www.tgbd.org.tr/tr/teknopark-tanimi-16.html) (Accessed 15 Mar 2013)
23. http://www.fp7.org.tr/home.do?cid=25789,www.tubitak.gov.tr (Accessed 21 Mar 2013)
24. http://www.titck.gov.tr/Folders/TheLaws/Te%C5%9Fvik%20Y%C3%B6nergesi_2012_12_19_b45aa8c.pdf
25. Turkish Ministry of Health Compassionate Use Guideline (1 Jan 2009)
26. Yegin E., Ciba M., Hicdurmaz E., Ilbars H. Orphan Drug Clinical Trials Applications to Turkish Medicines and Medical Devices Agency in 2012, Poster Presentation in 1st National Clinical Trials Congress, 3-4 May 2013, Istanbul, Congress Booklet Page 91
27. DuBiotech (http://www.dubiotech.ae)
28. www.orpha.net. (Accessed 15 Mar 2013)
29. Nabarette H. Use of a directory of specialized services and guidance in the healthcare system: the example of the Orphanet database for rare diseases. Rev Epidemiol Sante Publique. 2006 Feb;54(1):41-53
30. Hollak C.E.M. Limitations of drug registries to evaluate OMPs for the treatment of lysosomal storage disorders. Orphanet J Rare Dis 2011, 6:16
31. http://www.eurordis.org (Accessed 20 Mar 2013)
32. http://orphandruganaut.wordpress.com/2013/03/06/orphan-drugs-and-rare-diseases-in-the-middle-east/ (Accessed 17 Mar 2013)
33. Valstar M.J. et al. Mucopolysaccharidosis type IIIB may predominantly present with an attenuated clinical phenotype. J Inherit. Metab. Dis 2010; 33:759-767
34. Ohmi K. et al. Activated microglia in cortex of mouse models of mucopolysaccharidoses I and IIIB. Proc Natl Acad Sci. 2003; 100(4): 1902-1907
35. Al Gazali L., et al. Genetic disorders in the Arab world Brit Med J 2006; 333: 831-34
36. www.consang.net (Accessed 20 Mar 2013)
37. Saggar K.A. et al. Consanguinity and child health, Pediatrics and Child Health 18:5, 2008
38. Zlotogora J., Hujerat Y., Barges S., Shalev S.A., Chakravarti A. The fate of 12 recessive mutations in a single village. Ann Hum Genet 2007 71: 202–8
39. Bittles A.H. Consanguineous marriage and childhood health. Dev Med Child Neurol 2003; 45: 571–6
40. Turkiye Aile Sagligi Planlama Vakfi, Gorunum Dergisi Ocak 2011, sayfa 2
41. https://www.counsyl.com/learn/middle-eastern/ (Accessed 18 Mar 2013)
42. Ansari S.H. et al. Molecular epidemiology of β-thalassemia in Pakistan: Far reaching implications. Indian J Hum Genet. 2012 May-Aug; 18(2): 193–197
43. Almalki Z.S. et al. Access to orphan drugs in the Middle East: Challenge and perspective 2012: 1(4):139-143)
44. EurordisCare2: Survey of Diagnostic delays, (Accessed Jul 2006)
45. Orphanet Classification of Orphan Diseases- March 2013 (http://www.orphadata.org/cgi-bin/inc/product3.inc.php)
46. www.ncbi.nlm.nih.gov/omim (Accessed 20 Mar 2013)
47. http://www.who.int/classifications/icd/en/ (Accessed 18 Mar 2013)
48. Song P. et al. Intractable and Rare Diseases Research in Asia. Biosci Trends, 2012; 6(2):48-51

Hilal İ LBARS, Pharm. PhD was born in Ankara in 1970. Having completed her primary, secondary and high school education at TED Ankara College, she received her bachelor's degree in pharmacy as well as her master's degree in pharmaceutical toxicology from the Pharmacy of Gazi University in Ankara, Turkey. Currently, she has a PhD degree in pharmacy business administration discipline of the Pharmacy Faculty of Ankara University, Turkey. She worked in the Eğ irdir Osteopathic Hospital under the Turkish Ministry of Health for one year. She has been working in the General Directorate of Drug and Pharmacy of Turkish Ministry of Health for nineteen years in various departments by order of cosmetics, licensing, pharmacovigilance and clinical trials. Currently, she has been working as a Director of Clinical Drug Trials Department in Turkish Medicinal and Medical Devices Agency. She has been involved in various national and international meetings as speaker, also contributing to the publications in regards to the Pharma industry. She is the author of the book 'Clinical Trials Dictionary' published in 2013.Dr Ilbars is one of the founders of Clinical Research Association in Turkey. Email: hilalilbars@gmail.com

Duygu Kuyuncu Irmak, was graduated from the Uludag University Veterinary Medicine Faculty in 1990. She joined to Osmangazi University Medical Faculty in the same year and completed her MSc and PhD degrees at the Department of Histology and Embryology in 2000, while she has been working as research associate at the same time. She completed two thesis studies in reproductive medicine, and participated in multidisciplinary research studies during the academic experience. Dr Irmak was involved in various national and international scientific meetings as presenter of the studies and speaker. Dr Irmak joined the clinical research industry in 2003 and worked as Clinical Research Associate. She has been working as Clinical Operations Manager for more than 5 year as of now, and currently leading the MEK Consulting, a CRO operating in Turkey, Greece, Middle East and North Africa Region. Dr Irmak is an advisory board member of the Scientific and Technological Research Council of Turkey in 'New Medicine R&D Program' from July 2013 onwards. Email: dirmak@mekconsulting.com

Dr. Hamdi Akan is working as a Professor in the Hematology Department of Ankara University School of Medicine. He is an active member of EORTC and EBMT. He is a member of various national and international societies including, European Hematology Association (EHA), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), International Bone Marrow Transplantation Registry (IBMTR), Immunocompromised Host Society (IHS) and involved in multiple national and international clinical trials as an investigator or coordinator. He is currently the head and webmaster of Febrile Neutropenia Assocoation and Turkish Clinical Research Association (www.febrilnotropeni.net, and www.klinikarastirmalar.org.tr/en/). He is also the Editor of Clinical Trials Text Book and Turkish GCP Journal. Dr. Akan is the first ACRP certified clinical trial investigator in Turkey. He is one of the founders of Clinical Research Association and Akademika GCP Education Program in Turkey. He is the national representative of Educational Affairs of Turkish Society of Hematology in EHA. He has more than 60 manuscripts indexed in Index Medicus and SCI. Email: hamdiakan@gmail.com