ACCESS TO ORPHAN DRUGS IN GUATEMALA:

A GAP ANALYSIS FROM AN INTERNATIONAL PERSPECTIVE

Yolanda Cabrera-Sybesma

United States of America (USA)

51st International Course in Health Development
Master of Public Health (ICHD/MPH)
September 22, 2014 – September 11, 2015

KIT (ROYAL TROPICAL INSTITUTE)
Vrije Universiteit Amsterdam
Amsterdam, The Netherlands

ACCESS TO ORPHAN DRUGS IN GUATEMALA: *A GAP ANALYSIS FROM AN INTERNATIONAL PERSPECTIVE*

A thesis submitted in partial fulfillment of the requirement for the degree of

Master of Public Health

by

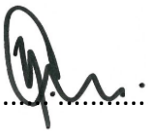
Yolanda Cabrera-Sybesma

United States America

Declaration:

Where other people's work has been used (either from a printed source, internet or any other source) this has been carefully acknowledged and referenced in accordance with departmental requirements.

The thesis titled *"Access to Orphan Drugs in Guatemala: A Gap Analysis from an International Perspective"* is my own work.

Signature:  .....

51st International Course in Health Development (ICHD)

September 22, 2014 – September 11, 2015

KIT (Royal Tropical Institute) / Vrije Universiteit Amsterdam

Amsterdam, The Netherlands

September 2015

Organized by:

KIT (Royal Tropical Institute), Development Policy & Practice Amsterdam, The Netherlands

In co-operation with:

Vrije Universiteit Amsterdam/ Free University of Amsterdam (VU)

Amsterdam, The Netherlands

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

FIGURES

TABLES

ABBREVIATIONS

ATM	Access To Medicines
CBG-MEB	Medicines Evaluation Board (CBG-MEB)
PROAM	Drug Access Program (Programa de Acesibilidad a Medicamentos, or PROAM in Spanish)
EHCI	Euro Health Consumer Index (EHCI)
EU	European Union
EMA	European Medicinal Agency
EML	Essential Medicines List
EURORDIS	European Rare Disease Information Service-a Patient Organization
PEC	Expansion of Coverage Program
FDA	Federal Drug Administration
GDP	Growth Domestic Product
GP	General Practitioner
HDI	Human Development Index
IGSS	Instituto Guatemalteco de Seguridad Social in Spanish-Social Security System
IRPs	international reference prices
MSPAS	Ministro de Salud Publica y Assistancia Social in Spanish-Ministry of Public Health and Social Assistance
MOD	Ministry of Defense
NGO	Non-Governmental Organization
NHI	National Institutes of Health
NME	New Medicinal Exemption
NORD	National Organization for Rare Diseases
OD	Orphan Drugs
OECD	Economic Co-operation and Development (OECD)
OOP	Out of Pocket
OOPD	Orphan Product Designation (OOPD)
RDs	Rare Diseases
RSM	Rational Selection of Medicines
RUM	Rational Use of Medicines
SIAME	Authorization System of Medications (SIAME in Spanish)
THE	Total Health Expenditure
TRIPS	Trade Related Aspects of Intellectual Property Rights
USA	United States of America
WHO	World Health Organization

ACKNOWLEDGEMENT

I would like to take this opportunity to extend a special thanks and sincere gratitude to my family and friends, the Royal Tropical Institute coordinators, secretaries, thesis advisor and back stopper and colleagues whom for the past year have guided me and inspired me to persevere during one of the most difficult periods of my life. Thank you all so very much for your unconditional support and helping me get through this challenging Master's study.

I am forever grateful to the Royal Tropical Institute (KIT) ICHD Director, Dr. Prisca Zwanikken, MD, PhD, MScCH for her kind words of encouragement and believing in me, for without her this masters study would have not been possible. Moreover, to my beloved, husband Hielke Hayo Sybesma whose unconditional love and words of wisdom became the pinnacle for me to do my thesis on this subject matter.

I would like to express a heartfelt thanks to my daughter *Stella and son Michiel,* who throughout this intense year were always understanding of my absence.

I dedicate this work to all those suffering from a rare disease.

ABSTRACT

Background: For an estimated one million patients with rare diseases (RDs), access to orphan drugs (ODs) represents a major public health problem just as it has been for most low-middle income countries. Patient groups have raised concerns as they struggle with huge challenges to be treated. However, the health authorities are not yet aware of the burden and access to ODs is not a priority.

Objective: To identify, describe and analyze access to ODs in Guatemala.

Methodology: A literature review was conducted by adapting the WHO Equitable Access to Essential Medicines Framework.

Findings: Rational use of ODs in Guatemala is very limited due to the absence of a national body to coordinate OD use, compounded by lack of an essential medicines list and RDs clinical treatment guidelines. Affordability of ODs globally as well as in Guatemala is still a huge challenge due to very high prices and the long-term nature of the diseases. Moreover, while sustainable financing of essential medicines is already under pressure, financing ODs is even more difficult. ODs are not covered in existing payment schemes and the current health and supply system fails to promote OD access in Guatemala.

Conclusion and Recommendations: Guatemala has not recognized RDs as a public health burden and the essential basic foundations for better access to ODs is lacking. The mentioned gaps that hinder access to orphan drugs should be addressed. Moreover, I recommend that RDs be a priority within Guatemala's Health System and further research in the area of ODs and RDs is urgently needed.

Keywords: Orphan Drugs, Rare Diseases, Access to Orphan Drugs, Health System, Guatemala

Word count: 13,046

INTRODUCTION

Orphan Drugs (ODs) are medicinal products intended for diagnosis, prevention or treatment of life threating or very serious diseases or disorders that are rare. While in Europe, an OD is defined as a medicinal product that would not be developed without incentives because its sales are unlikely to generate sufficient return on investment.[1]

In most of the literature, the ODs market is often characterized by an unequal access to ODs.[2] Despite the international and European Medicinal Agency (EMA) centralized regulation on access to orphan drugs; to them unequal access is related to factors of labeling, pricing, and reimbursement mechanism designed and implemented at the national level.[2]The most reliable indications of OD accessibility is its presence in the patient's home country.[3] Drug affordability is linked to early access and national incentives and health systems policies on reimbursement of ODs.[2,3]

The drive for me to write this thesis on access to orphan drugs stems from a National Institutes of Health (NIH) research fellowship that I did on Knowledge, *Behavior and Access to HIV/AIDS treatment in Petén, Guatemala*. During my tenor in Guatemala, I gained knowledge of what the locals needed in order for a clinical research program to be successful. The need to raise awareness and educate indigenous people was very rewarding for me. I clearly remember visiting an orphanage where kids were suffering from a rare disease or had some form of handicap, who were abandoned by their family by virtue of their physical appearance. I have always felt that I could be a voice for those who desperately needed access to orphan drugs and this experience solidified my interest and passion in clinical research. For the past 18 years, I have been working In the Pharmaceutical and Contract Research industry and I had the opportunity to manage Global Compassionate Use Programs which enhanced my interest in lobbying with pharmaceutical experts in the aim to raise awareness for orphan drugs accessibility. For me being able to contribute by helping provide an orphan drug to a child who is suffering from a rare disease has been an overwhelming experience, one that would forever change the way I thought about the value of life. I have often thought about how I could be making a difference in the lives of those who feel hopeless due to the suffering of a rare disease. Often asking myself, do we really need to add a monetary sign to life? Do low-middle income countries have a proper strategic framework that treating physicians can follow to expedite the process of access to treatment for people suffering from a rare disease? What are the issues affecting access to OD? What are the necessary steps to ensure ODs are available and affordable to low-middle income countries like Guatemala?

It is the challenge to raise awareness and help families in low-middle income countries gain access to orphan drugs that motivate me to write this thesis. This literature review intends to shed light into possible gaps in access to orphan drugs in Guatemala and provide recommendations that I hope will contribute to understanding the factors that influence access to OD in Guatemala.

CHAPTER 1. BACKGROUND INFORMATION

1.1 GEOGRAPHY AND DEMOGRAPHY

Guatemala is a Central American country boarded to the north and west by Mexico, surrounded to the northeast by Belize, and a short coastline of the Caribbean Sea, to the east by Honduras, the southeast by El Salvador, and to the south by the Pacific Ocean (Figure 1).[4]

Guatemala means 'land of trees'. Its geography is heavily forested and mountainous. Over a thousand years ago the Maya civilization flourished, and its impressive ruins dot the landscape. By contrast, the rest of the population are known as, Ladinos (mostly mixed Maya-Spanish ancestry).[6] Its indigenous Mayan people live in the western highlands and are considered poor farmers.[6]

Figure 1. ***Map of Guatemala***

Source: http://www.mapsopensource.com/guatemala-map 2014

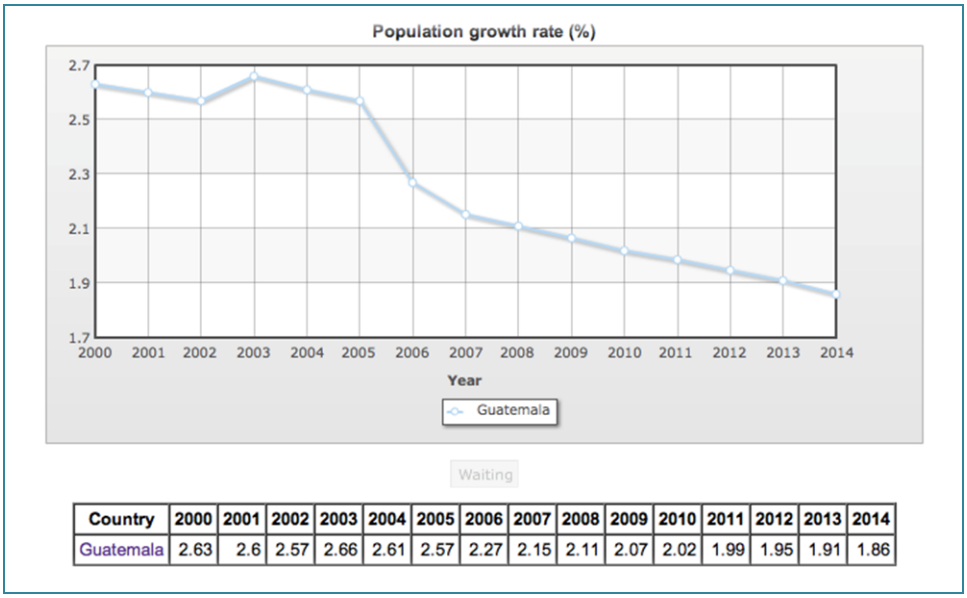
Apart from its characteristically attractive geography, it is the most populous country in Central America and 68th on earth, having a population of 16.2 million (2015); the majority (50%) is of Mayan ethnicity.[4] Guatemala has a constitutional democratic republic, whereby the president is both the head of state and government. Its capital is Guatemala City.

Demographically, Guatemala is a low-middle income country and more than half of the population lives below the poverty line.

According to the World Health Organization (WHO), Guatemala struggles in many areas of health including; infant, child and maternal mortality, malnutrition, women's health, and access to medicines.[6] This disproportionately affects the large indigenous population. Guatemala has the highest fertility rate in Latin America.[8]

Figure 2 below illustrates the reported 2014 population growth rate of 1.86%; this statistic is an indication of how the Guatemalan population has been growing over the past years.[4,6,6] Almost half of the Guatemala's population is under the age of 19, making it the youngest population in Latin America.[8]

Figure 2. Guatemala Population Growth Rate 2000-2014



Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Guatemala	2.63	2.6	2.57	2.66	2.61	2.57	2.27	2.15	2.11	2.07	2.02	1.99	1.95	1.91	1.86

Source: indexmundi.com: Guatemala population growth rate 2014

1.2 GENERAL SOCIO-ECONOMIC SITUATION

Guatemala is a low-middle income country.[9] GDP per Capita in 2011 was $6,989.52; placing Guatemala at 133 among 187 countries in the Human Development Index HDI, and last in its region.[9] According to the World Health Organization (WHO), more than half of the population lives in poverty and 13% of the population lives in extreme poverty. The indigenous groups account for 73% of the poor, with 22% of them living in extreme poverty.[9] Guatemala's high Gini coefficient (55.1) reflects an unequal income distribution.[9]

Guatemala has the biggest economy in Central America. However, it is reported to have the highest levels of inequality in Latin America, with many poverty indicators especially in indigenous and rural regions.[10,11]

1.3 HEALTH STATUS

Health Status: The health status of the Guatemalan people varies significantly between groups with reported health care challenges affecting the indigenous, rural and poor populations the most.[10,11] According to WHO, life expectancy continues at a steady rise and in 2013, stood at 72 years.[10] However, numerous health-related problems such as chronic malnutrition, infant, child and maternal mortality, communicable and non-communicable diseases plaques the country. Chronic malnutrition and mother and child mortality rates are amongst the highest in the region.[11] The total infant mortality rate for 2013 is 30 per 1000 live birth, while the main cause of death in the general population are chronic diseases.[10,11]

1.4 HEALTH SYSTEM OVERVIEW

Guatemala's Constitution is said to guarantee its entire population access to free health services. The Ministry of Public Health and Social Welfare (MSPAS[1]-in Spanish), is constitutionally responsible for the health care of Guatemalans.[12]

Figure 3, illustrates an adapted version of The Guatemalan health system which shows how it is compartmentalized.[13] Often considered in the literature as a fragmented system consisting of a public and a private sector. The public sector is comprised of the following three main branches;[13]

- MSPAS which has 1300 health facilities and covers 70% of the population, while
- Government Institute of Social Security (IGSS[2]-in Spanish) which has 139 facilities cover 18% of the population, and
- The Military Health Service has their own hospitals and clinics and cover 5% of the population). All of which are financed from tax revenue, grants, contributions either through employee or employer to the IGSS, or Loans for MSPAS.

While the private sector includes two main branches:

- For-profit and,
- Non-profit providers.

The for-profit private sector consists of hospitals, clinics, pharmacies, nursing homes and, Laboratories which are authorized by the MSPAS. The non-profit private sector is made up of Non-governmental organizations (NGOs), which currently total more than 1000, and traditional medicine practitioners.[14]

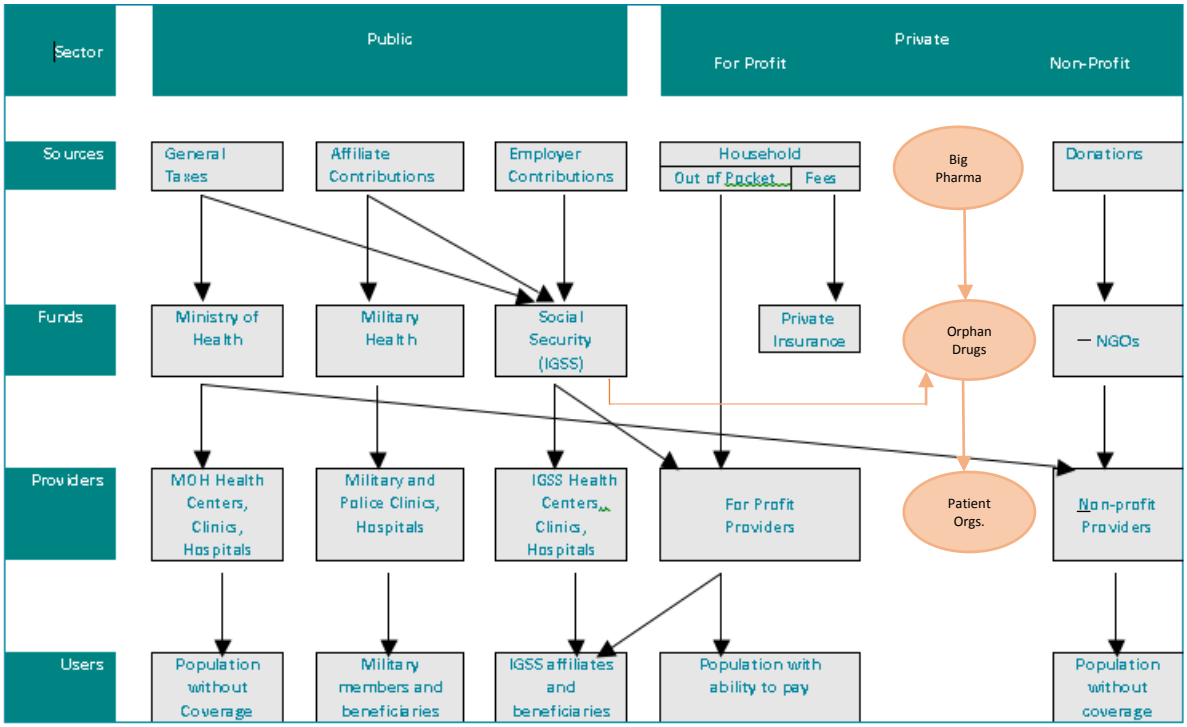
The MSPAS and IGSS deliver health care in their hospitals, clinics and health centers; however, there are no coordinating services between the units of these institutions. This often leads to fragmentation and division of services in different areas.[13]

Figure 3 illustrates an adapted version of Guatemala's health system. Here one can see that the delivery of MSPAS health care services includes three levels of care; the levels work through a referral system. In this model, Becerril-Montekio best describes these as:

- The first level care consists of health clinics and primary care centers, NGOs.
- Second-level care services are provided institutionally by health centers and comprehensive maternity centers (CAIMI).
- Third-level care services are provided by hospital centers – at the district, departmental, regional, and national levels.
    - IGSS have programs for disease, maternity, disability, old age, and preventive and curative care for members' children who are under 5 years of age.

[1] MSPAS is the Ministro de Salud Public y Assistencia in Spanish
[2] IGGS is the Instituto Guatemalteco de Seguridad Social in Spanish

Figure 3. Guatemala's Health System - *Organizational Structure*



Source: Adapted by the author; taken from Becerril-Montekio et al. 2011

According to the WHO, Guatemala's health-care system relies on private expenditure, primarily out-of-pocket spending approximately 52%.[14,13] This translates to Guatemala having the highest level of private expenditure as a proportion of total health expenditure of any Latin American country.[10] Only the elite 'urban' members of society have private health insurance.[17]

CHAPTER 2. PROBLEM STATEMENT, JUSTIFICATION, OBJECTIVES AND METHODOLOGY

2.1. PROBLEM STATEMENT

Orphan Drugs (OD) are drugs developed for the treatment of rare diseases (RDs). The definition of rare diseases varies; to the European Medicinal Agency (EMA), a rare disease is rare when a prevalence of 5 in 10,000 people are affected and they are often life-threatening or chronically debilitating conditions,[1] while in the United States of America (USA) the threshold that defines a rare disease is from 7 per 10,000 people.[18] More than 80% of the identified rare diseases are of genetic origin and 95% do not have a single Federal Drug Administration (FDA) approved drug treatment.[19]

At present, approximately 7000 rare diseases have been identified and that number is increasing according to advances in medical technology. Because of their low prevalence, only a small number of people are affected for each rare disease. However, together, rare diseases affect between 6% and 8% of the global population (or 420 million to 560 million people), half of them are children.[19] It is thus accepted as a significant, growing global health burden.[19]Although the total number of people suffering from a rare disease is not known for Guatemala, we estimate a calculated extrapolation of 972,000 to nearly 1.3 million from a population of 16.2 million in 2015.[19] Guatemala uses the EU definition of rare diseases.

Rare diseases have specific clinical and patho-genetic characteristics, but their social and health impact share a number of common features, which make RDs as a whole a public health issue.[20] The most common characteristics of RDs are; being life-threatening, chronic, progressive, degenerative and disabling.[18] People with RDs also face many common problems in access to information, diagnosis, treatment and care. For healthcare providers and authorities, RD related challenges include difficult and lack of research projects due to limited resources devoted to the single RD; difficulties in setting up clinical studies due to the scarcity of patients and weak interest in developing medicinal products targeting these conditions due to the unfavorable marketing conditions.[21,18]

Patients with rare diseases in Guatemala face huge challenges when it comes to access to orphan drugs. In principal, the country has been struggling with attaining all of the United Nations (UN) Millennium Development Goals (MDGs), which include eradicating extreme poverty and hunger; reduce child mortality; improve maternal health; combat HIV/AIDS, malaria, and other diseases; and develop a global partnership for development.[22] Furthermore, information related to ODs in Guatemala is very scarce and there is very limited awareness of the burden of RDs by the population and the health authorities. This leads to very low prioritization of rare diseases in Guatemala health system which in the long term affects the equitable access to ODs for patients suffering from a life threating disease.

This study aims to find the gaps on access to orphan drugs by comparing findings from literature review with Guatemala's situation. It applies the strategy of assessing the health system framework within the context of on orphan drugs and rare diseases and aims to: First, identify, describe and analyze access to orphan drugs in Guatemala's Public Health System and second to provide recommendations that may enhance access of orphan drugs in Guatemala.

2.2. JUSTIFICATION

Timely and correct diagnosis and management of rare diseases are very important for affected people to be able to maintain a good quality of life. Increase accessibility to orphan drugs is crucial for the better well-being of patients with RDs as well as contributes to reducing unnecessary expenses and waste of health resources.

In Guatemala, rare disease patient organizations have raised concerns on accessibility of ODs and have been debating the issue of 'the rights to Access' at the public health level. According to PROCRECE Guatemala and Asociación Para Todos, two of the most recognized patient organizations in Guatemala the topic of rare diseases is relatively unknown in Guatemala.[23] Patients need to travel outside the country to get proper clinical diagnostic tests, treatment, and medicines, however, many patients die because of lack of access to basic health care needs.[23,24] The Organization Para Todos state that from the 325 patient cases registered in their organization, five have died due to no access to orphan drugs in Guatemala.[24] Moreover, there is not enough information regarding RDs to be able to raise awareness and knowledge of health authorities especially on access to orphan drugs.[23]

The findings from this study will provide an overview on the status of RDs and ODs from an international perspective and look at the current Guatemala health system and the gaps which can influence raising awareness on access to ODs for patients with rare diseases.

2.3. GENERAL OBJECTIVE

To identify, describe and analyze access to orphan drugs in Guatemala's Health System with an international perspective.

2.4. SPECIFIC OBJECTIVES

1. To identify and describe the situation about access to orphan drugs in Guatemala's health system.
2. To identify, describe and analyze the gaps in access to ODs in Guatemala's health system using the WHO Access Framework.[25]
3. To provide recommendations that enhances access of orphan drugs in Guatemala.

2.5. METHODOLOGY

The methods and conceptual framework used for this study are described in this section.

2.5.1. LITERATURE REVIEW

A literature review was conducted to collate the most current research and health care policies in the area of orphan drugs in Guatemala.

Search strategy: Electronic database search of primary research literature was conducted using Medical Subject Headings (MESH) terms Orphan drugs, equitable access, essential medicines, World Health Organization and Guatemala. A search of bibliographies was also done. A few articles collected were not accessible due to fees for download policies in

websites. There were many articles that were made available only in the Spanish language. However, as Spanish is my native tongue, I was able to read and understand all the literature available.

The main search strategy was driven by three main MESH themes: orphan drugs, access, and Guatemala. These were combined with specific search terms, which when searched yielded a total of 2064 titles. These were then shortlisted by available abstracts for review. A total of 182 abstracts were retrieved and reviewed. These were then shortlisted to 101 full text studies and linked to the four basic puzzle pieces of the WHO Access framework used in this thesis. I screened all 101 studies/presentations/articles by title and/or abstracts and then selected the most relevant ones for review. The global search was limited to PubMed 1996–2015; and from local government documents dating back to 1996. Results, which were focused on bio-efficacy of ODs or full Research and Development (R&D), were excluded, as they were not a priority at this time.

Keywords used in this thesis were in combination with some of the following terms: access, affordable prices, essential medicines, sustainable financing, reliable health and supply system, orphan drugs, rare diseases, equitable access, generic policies, clinical treatment guidelines, Guatemala.

Limitations of the study: For this study, most of the data available on OD access was retrieved through the WHO, Orphanet or other similar 'patient' organizations. Most of the available literature is structured on the overall global or international market. The exploration on the impact that pharmaceutical companies have to help bridge the 'access' gap for patients in urgent need of treatment, especially in low-middle income countries like Guatemala is a limitation in this study. This is not something that was explored.

2.5.2. CONCEPTUAL FRAMEWORK

The conceptual framework for this study was taken from the WHO model on Access to Essential Medicines (Figure 4.).

Figure 4. Equitable Access to Essential Medicines – WHO Framework

Source: www.who.com[28]; [Accessed on May 2015]

The rationale for choosing the *WHO Equitable Access to Medicines framework* is threefold: First, It is a simple model that helps to explain a complex theme, Second, It is well recognized and used, and Third, It is the one framework that relates to the pharmaceutical industry which is responsible for development of orphan drugs for the treatment of rare diseases; the main topic of this thesis.

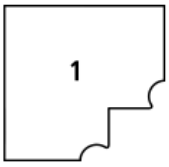
CHAPTER 3. FINDINGS

The treatment of rare diseases is closely linked to the organization of the basic health care needs, because treatment of RDs can only be effective if other medicines and (at least) basic health services can be provided. Therefore, a national health system has to build on the foundations and structures of the health system in place in order to provide access to orphan drugs. Access to medicines is defined by the WHO as "having medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour's walk of the population".[25]

For a country to optimize the coverage, countries and their governments should have national or local essential drug lists and corresponding treatment guidelines for proper rational medicines selection and use. Hence, equitable access to essential medicinal products, vaccines and technologies is one of the vital building blocks that a well-functioning health system needs and which provides the foundation for a system enabling equitable treatment of patients with a rare disease. Moreover, '*the prices should be affordable by all; and 'sustainable financing for the medicines component of health care should be ensured through adequate funding levels, to ensure that poor people do not face proportionally higher costs than the better off; and finally, reliable health and supply systems need to be in place*.'[28,27]

In this chapter, the findings concerning access to orphan drugs in Guatemala are presented and analyzed with an extended international perspective[3] and according to the main four headings of the WHO Access Framework: 1. Rational Selection, 2. Affordable Prices, 3. Sustainable Financing and 4. Reliable Health and Health Systems. The findings also take into account the gaps identified within Guatemala's health system and aims to provide the links between each 'puzzle' block of the conceptual framework used.

3.1. RATIONAL SELECTION AND USE OF ESSENTIAL MEDICINES



The basics of rational selection and use of medicines within a health system is important to be able to understand how access to orphan drugs could be analyzed within Guatemala's health system. Over many decades, medicines have been positively affecting health and quality of life of many people. They save lives, promote health as well as prevent epidemics and diseases. At the same time, there are also strong and abundant evidences of negative implications for people especially due to the way medicines are used.[28]

[3] International Perspective in this section 3.1 is interchangeably used with the term 'global'.

Important elements of the WHO strategy on rational use of medicines (RUM)[4] are: correct drug, appropriate indication, appropriate drug considering efficacy, safety, suitability for the patient and cost, appropriate dosage, administration and duration, no contraindications, correct dispensing, including appropriate information for patients and patient adherence to treatment are all the major components for the rational use of medicines.[28,29,30,31]

Ensuring rational use of ODs in turn ensures access to ODs by the rare disease patients in a way that is appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community.[33,34,35] In order for the rational use of ODs, the information about the existing ODs should be available, these ODs must be available, appropriate diagnosis should be made and proper treatment should be provided.

WHO estimates that one third of the global population does not have reliable access to medicines.[32,33] according to the WHO the poorest countries of Africa, India and Asia lack of access to medicines can be as high as 50% of the population.[36,37] The factors that influence access to medicines could be linked to how health systems are organized. In the case of Guatemala we found that national policies on use of medicines and treatment guidelines are not existing. This leads to not only the lack of access to medicines in general but to irrational use for the small fraction of population who would have access to medicines.

The Guatemalan Ministry of Health and Social Services network is a publically funded group of primary, secondary and tertiary healthcare centers that render services to approximately 70% of the population in Guatemala.[25] Medicines are made available through tertiary care hospitals free of charge, but only on inpatient basis.[25] Guatemala has a national program, in which the government, the civil society and professional bodies are involved, to monitor and encourage the rational use of medicines. This program is the Academic Scientific Network for the Rational Use of Drugs, University of San Carlos Guatemala. But the network has not been convened in the past three years.[41,42] According to the Central American Association for Pharmaceutical Industries, the profile for selection and rational use of medicines in Guatemala is not well documented.[41]

In order to promote rational use of medicine, WHO has been advocating the following 12 key interventions:[28]

- *"Establishment of a multidisciplinary national body to coordinate policies on medicine use*
- *Use of clinical guidelines*
- *Development and use of national essential medicines list*
- Establishment of drug and therapeutics committees in districts and hospitals
- Inclusion of problem-based pharmacotherapy training in undergraduate curricula
- Continuing in-service medical education as a licensure requirement
- Supervision, audit and feedback
- Use of independent information on medicines
- Public education about medicines
- Avoidance of perverse financial incentives
- Use of appropriate and enforced regulation
- Sufficient government expenditure to ensure availability of medicines and staff".

[4] World Health Assembly (WHA) resolution 39.27and WHA54.11, both on (revised) drug strategy.

In this chapter 3.1, the first three points of the WHO key interventions (in italics above), which are most relevant to ODs rational use, will be discussed.

3.1.1. ESTABLISHMENT OF A MULTIDISCIPLINARY INTERNATIONAL AND NATIONAL BODY TO COORDINATE POLICIES ON MEDICINES USE

Being rare and geographically spread, no single institution and in most cases, no single country has sufficient number of patients for generalization of clinical and translational research. Most rare diseases are not included in international classification systems which are the obstacles for the knowledge on rare diseases. Recent conferences in Europe and the United States of America (USA) recognized the importance of rare diseases registries and called for their wide expansion. With the aim that the nature of rare diseases should be directed towards a global registry.[43]

Worldwide, establishment of international bodies such as Orphanet, national RD committees, patient registries, advocacy groups and patient groups have made significant improvement in quality of lives of many RD patients by means of increasing availability and access to treatments for rare diseases. One of the success examples was the ground breaking approval of the 1983 U.S. Orphan Drug Act which was due to incredible effort of an advocacy group, NORD (National Organization for Rare Disorders). That success was followed by further development and establishments of policies and regulations in other parts of the world.[45,46,47]

The common goal of the international and national patient advocacy groups and registries is to help rare disease patients get access to orphan drugs and necessary care and support. They work together with patients, families, other groups, healthcare centers, government and policy makers to facilitate access and development of new treatments to become available to the RD community. Current database of NORD has collected over 300,000 contacts and over 1,200 patient organizations and the potential for increase in future registries have been growing.[45]

In 2006 the international Rare Disease Taskforce that is operated Orphanet provided an overview of the issues surrounding Patient registries. According to them and patient organizations, registries constitute key instruments for RDs clinical research, and improvement of patient care and healthcare planning as well as social, economical and provide a basis for looking into quality of life outcomes.[86] They state that registries of patients treated with ODs are ‘relevant because they allow the gathering of evidence on treatment effectiveness and possible side effects, and for many patients registries help them determine how difficult it could be for them to obtain access treatment for a specific RD.[48]

A registry is an organized system that uses 'observational study methods to collect uniform data (clinical and other). It evaluates specified outcomes for a population defined by a particular disease, condition or exposure and serves one or more pre-determined scientific, clinical or policy purposes'.[48,49,50] According to Orphanet, one of the most recognized reference portals for information on rare diseases and ODs, the distribution of registries by coverage totaled 651 rare disease registries in 2015, comprising of 77 regional, 454 national 45 European, 71 global and 4 not defined registries.[52] (Table 1). This accounts to less than 10% of the globally identified rare diseases.

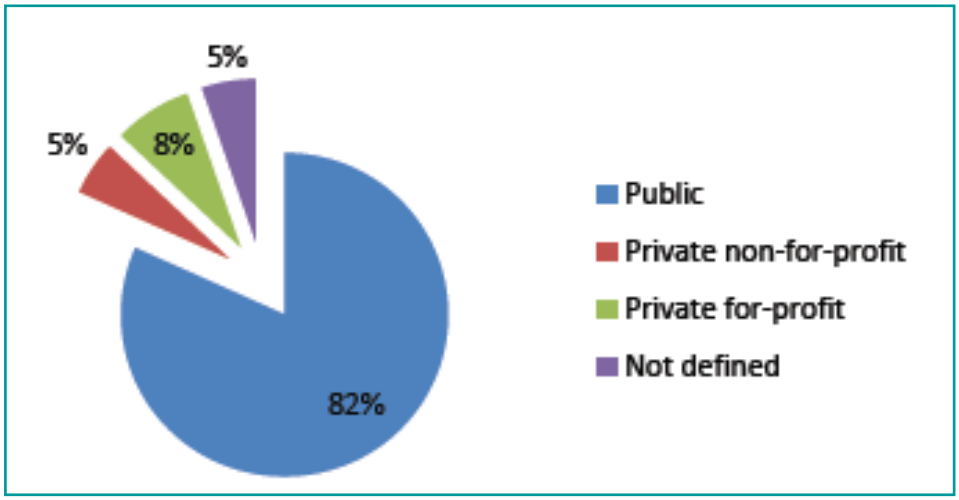
Table 1. Distribution of Registries by Coverage

COVERAGE	NUMBER OF REGISTRIES
Regional	77
National	454
European	45
Global	71
Not defined	4
TOTAL	651

Source Orphanet, Rare Diseases Registries in Europe, January 2015, Orphanet report series [Accessed July 2015]

The number of patient registries has been growing worldwide. Nearly 82% of all registries are academic/public, private for profit is 8% and private not-for-profit and not defined registries are 5% each.[52] (Figure 5).

Figure 5. Distribution of Registries by Affiliation



Source: Orphanet, Rare Diseases Registries in Europe, January 2015, Orphanet report series [Accessed July 2015]

In Guatemala, there are 12 patient rare disease registries. However, many of these registries are implementing in different platform with no uniform standards. In this case we found that all patient registries work in absolute isolation in different disease areas with variable quality of data and there were some cases of duplication of registries. For example the patient organization Para Todos relies on the European EURORDIS and Orphanet organizations to raise awareness and educate their patient population on RDs. However, like many, the main challenge for these registries are funding and there is no system of sustainable is funding for most of them.[48]

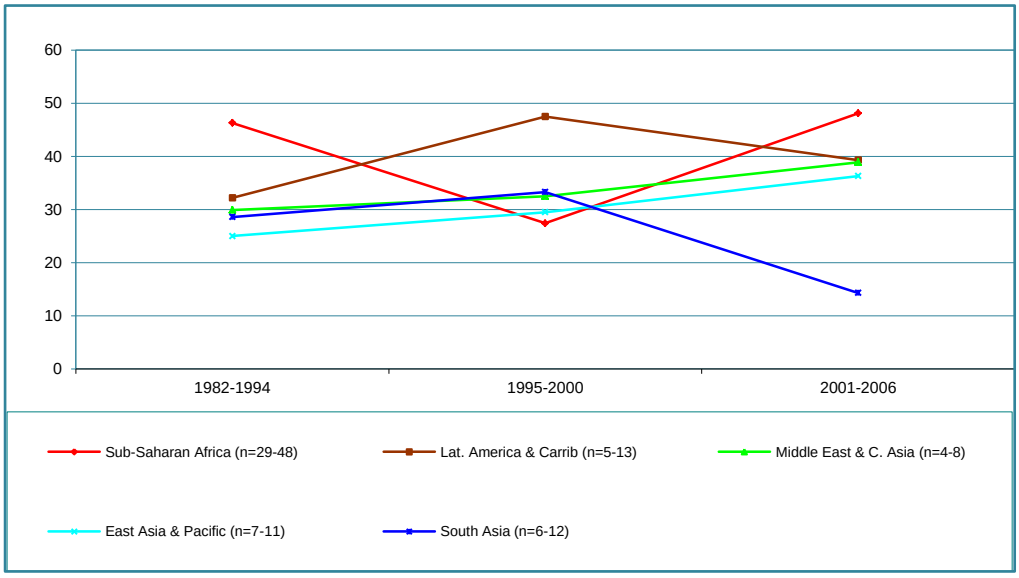
3.1.2. AVAILABILITY OF CLINICAL TREATMENT GUIDELINES

Clinical treatment guidelines are not available for most of the rare diseases and according to one literature, only less than 5% of RDs have clear treatment.[35] The literature on collective information about RD clinical guidelines and treatment is very limited. Web search in Orphanet's website showed 43 emergency guidelines available for rare diseases. These emergency guidelines are expert-authored and peer-reviewed and intended to guide health

care professionals in emergency situation and are also available through the National Organization for Rare Diseases (NORD).[50,51] However, literature on RD treatment guidelines for Guatemala could not be found. Although, most patient organizations do use the guidelines that are posted in Orphanet or NORD because it is the only means for providing their patients with information once a clinical diagnosis has been confirmed. The lack of treatment guidelines available affect patients with a rare disease, because the lack of knowledge of their direct health care provider impairs the treatment substantially and prolongs their suffering. Moreover, if ODs happen to be available and clear treatment guidelines are missing, this can lead an ineffective treatment and, hence, to irrational use of scarce ODs.

Irrational use of medicines means inappropriate, improper and incorrect use of medicine and is a very serious public health problem that we are facing worldwide. According to the World Bank, compliance with guidelines in certain WB-regions during 1982 and 2006 is not more than 50% (Figure 6) [33,53]

Figure 6. % Compliance with guidelines by WB region



Source: Department of essential medicines and pharmaceutical policy, TBS 2009, WHO [Accessed on July 2015]

According to the World Medicines Situation 2011 (WHO), over half of all countries worldwide still need to promote implementing many of the basic policies to ensure appropriate use of medicines including regular monitoring of drug use, regular updating of clinical treatment guidelines and establishing a medicine information center for prescribers or drug and therapeutics committees in respective areas.[20]

3.1.3. ESSENTIAL MEDICINES LIST AND ORPHAN DRUGS

Since 1977, WHO published and has been updating the Model list of Essential Medicines (EML) every two years.[54] "Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amount, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual

and the community can afford."[55] According to WHO Director-General Dr. Margaret Chan, 'When new effective medicines emerge to safely treat serious and widespread diseases, it is vital to ensure that everyone who needs them can obtain them and placing them on the WHO Essential Medicines List is a first step in that direction." The purpose of EML is to guide the prioritization of medicines from a clinical and public health perspective to ensure that these are actually available to patients."[54,56,57]

The essence of EML is dominated by public health priorities, cost-effectiveness and also on evidence-based medicines whereas ODs are primarily focused on individual patients, disease driven and strong evidences are difficult to get. The EML contains some products which are indicated for RDs, e.g., Factor VIII and Factor IX which have been in use for many years to treat hemophilia. Although specifically indicated, some medicines in the list can also be used for rare diseases, such as mineral corticosteroids, to treat Addison's disease. However, for global selection mechanism, ODs cannot be part of the EML if current terms for selection of essential medicines are applied strictly.[56,58,59] For Guatemala this proves to take away the priority of ODs within its health system.[23]

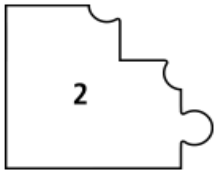
There have been discussions regarding the inclusion of ODs as part of the essential medicines lists, however this is not been fully elaborated on by the WHO or other international organizations.

In summary, when we apply the WHO Access Framework to ODs and RDs, the findings suggest that the recognition of rare diseases is lacking within the Guatemala's health system and the development of OD registries are instrumental to building knowledge and experience with respect to the treatment of rare diseases. Moreover, the 12 Guatemalan OD registries are struggling with funding and a standardized platform. In addition, lack of national clinical treatment guidelines that cover RD and describe treatment (with OD) for RD impedes the ability for patients to get the proper treatment they need on a timely basis. More importantly ODs are not included in any national medicines lists in Guatemala which makes access to ODs ever more challenging for patients. This often leads to the question of affordable prices of medicines which is discussed in the following section.

3.2. AFFORDABLE PRICES

Secure and sustainable access to medicines is highly dependent on affordable prices "to ensure that the drug expenditure of governments, other health care providers and consumers is cost effective and represents best value for money."[37,87] Even if the orphan drugs are available, if these are not affordable, it is of no use. One of the biggest challenges and a major obstacle to access to ODs has been the prices of ODs.[33,60,62] In this section; we would like to discuss why OD prices are high and what are the efforts of governments and everyone involved to make the prices reduced as much as possible. The following sub-headings of the WHO Access Framework are considered the most relevant when we look at ODs access in Guatemala: 1. Pricing, 2. Pricing policies, and 3. Negotiation pricing and Procurement for Guatemala.

3.2.1. PRICING

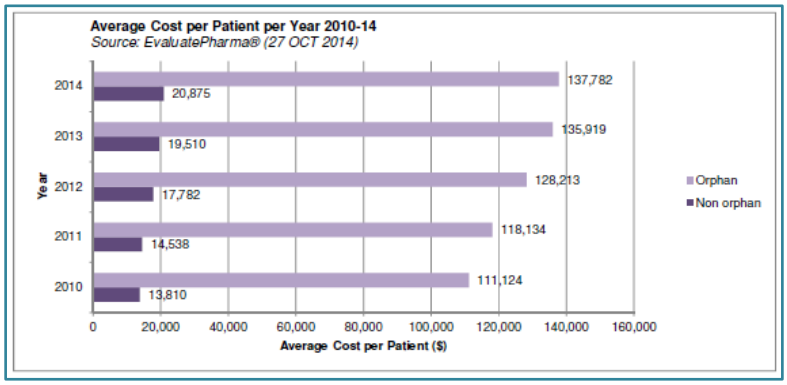


One of the crucial factors for access to medicines is their prices. In its report on 'Measuring medicine prices, availability, affordability and price components, Second Edition', WHO/Health Action International (HAI)[61] mentioned that the price and availability of medicines to those who need them are the critical factors that the policy makers need to pay more attention to. The prices of drugs are simply too high for poor people and the products for diagnosis, treatment or prevention are often not available.[62,20] The price of medicines can determine whether a sick person will be treated or not.[63]

Considering the complexity of both supply and demand structures for pharmaceuticals, pricing mechanisms of ODs are far from straight forward. Research activities for ODs are often difficult and extensive, development projects for the drug meet difficult obstacles because of the rarity of the disease and, because of the specialty of the drug, the production processes of drugs might not be simple as well. Once an orphan drug ready to be placed in the market the supplier of the drug is confronted with factors of: 'current and planned indications for treatment, the existence of alternatives, off-label indications and total estimated and registered number of patients.'[64] The rarer the disease, the more expensive the treatment is, because of the smaller number of patients from whom the costs for R&D are to be recovered. In order to stimulate the development of a cure against a certain rare disease, governments or other organizations might provide subsidies or similar incentives and regulating bodies could give certain country-specific marketing-exclusivities. The supplier tries to take all factors into account when it establishes a certain price for the ODs and assesses the accompanying risks with it too.

Together this constitutes a complicated process, which also gives rise to debates and controversies on the price of orphan drugs. According to Orphan Drug Report 2014 by EvaluatePharma, the median price differential between an OD and non-OD was 19.1 in 2014.[65] This report also estimated that the average cost per patient per year in 2014 for an orphan drug was $137,798 versus $20,875 or 7 times higher for a non-orphan drug. Figure 7 showed the difference in average cost per patient per year among ODs and non-ODs as well as the increasing trend of drug prices of all types from 2010-2014.[24] Orphan drugs with multiple orphan indications, which can demonstrate improvement in overall survival or quality of life and which are for chronic treatment are found to be associated with higher treatment cost.[68]

Figure 7. Average Cost per Patient per Year 2010-2014



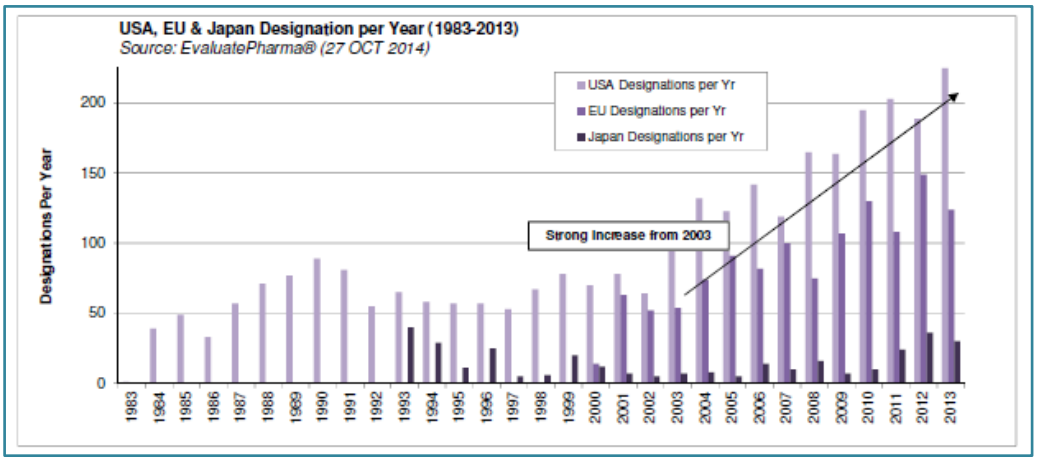
Another factor that is also very important to note is the actual prices that the end-users need to pay for medicines. In countries where patients have to pay for medicines themselves, the end-users have to pay much higher prices than the international reference prices (IRPs): 5.3 times IRPs in the Eastern Mediterranean Region to 20.5 times in the European Region for originator brand medicines and 1.9 to 5.3 times in the Eastern Mediterranean and Western Pacific Regions for generic drugs. In many situations, availability of medicines in the public sector is low and patients have no other choice except to purchase them in the private sector.[63] The literature regarding actual OD prices for end-users cannot be found so far, but it is very likely that the situation is similar and it is important to consider regarding assessing access to ODs in Guatemala.

3.2.2. PRICING POLICIES

Policies regarding pricing for orphan drugs have to be considered on the cost structure, cost effectiveness, relative effectiveness and economic viability of ODs.[64] There are quite a number of regulations which were developed for development and research of orphan drugs. With historical passing of the 1983 Orphan Drug Act in the US, which was followed by those of other countries like Japan, EU, and Australia, the OD related laws include market exclusivity, tax credit for clinical trial costs, fee waiver for regulatory activities to set-up programs for new orphan drugs research and development and marketing authorization of orphan drugs. In addition, companies are offered protocol assistance, advice on the development and access to specific grants.[43,44]

There have been some controversies regarding affordability and the value of ODs. Many studies described the higher remuneration of the OD market because of the lower cost of clinical trial for orphan drugs and also due to lack of alternative therapies for rare diseases. Furthermore, there is reduction of cost in development of ODs because of the tax incentives and other market favorable regulations. As a result, OD-designations continue to increase in 2014 (Figure 8) and by 2020, the forecast on sales of ODs is predicted to be $176 billion.[68] Since the enactment of EU Orphan and Medicinal Product (OMP) regulation in 2000, More than 1,000 medicines are approved for OMP designation in the EU.[69]

Figure 8. Global (USA & Japan Designation per Year from 1983-2013



There has been health policy debate on rare diseases with the perception that OMPs are highly priced and much more expensive than non-orphan drugs, and budget impact of OMP is high.[69]

For Guatemala the pricing policies on medicines was presented to legislative board on May 2014. The proposals aim is to regulate what would be the final price of medicines and MSPAS would then be responsible for verifying prices and quality of medicines. However, this proposed policy received criticism because it was an exact copy of the generic medicines policy from EL Salvador and could not be approved by the ministries of health.[70] Discussion on this topic are currently ongoing in MSPAS.

3.2.3. NEGOTIATING PRICING AND PROCUREMENT IN GUATEMALA

Even though the prices of ODs distributed through the hospital pharmacy are not regulated in most European countries, the price negotiations happen between the individual hospital and the manufacturer. Some hospitals jointly purchase ODs from the manufacturers to be able to negotiate better. In Belgium, Italy and Greece, price control measures are imposed on ODs distributed through the hospital pharmacy. In the United Kingdom, prices are controlled by means of Pharmaceutical Price Regulation Scheme and pharmaco-economic guidelines.[64]

The negotiation of pricing and procurement in Guatemala is managed by MSPAS and collaborated with the Pan American Health Organization (PAHO). The MSPAS has attempted several strategies to bring down the prices of needed medicines. A finding for this study showed that the PAHO provides Guatemala with medicines at lower prices.[71]

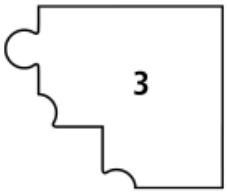
There are such policies that allow Guatemala the right to wave taxes on certain drugs. Although there is no information that could be found regarding negotiating pricing on ODs there is a policy decree 16-2003 that permits negotiating and waiving import taxes on AIDS drugs.[71]

Decree 16-2003 includes a section on open contracts negotiations. This law permits free competition in medicines including *"non-national producers, facilitating imports in order to lower prices".* This law also opens the possibility for the retail sale of generic drugs purchased by the Social Security Department and the State.[72] While another domestic laws such as that titled law 66-2007 set what are known as financing controls, limiting the government to pay no more than 20% of a medicinal order at a time. Thus, challenging the MOH's ability to purchase through current suppliers.[72] Moreover, making it more difficult for Orphan Drugs to be purchased at lower prices than developed.

In summary one of the biggest challenges for improving access to drugs in general has been affordable pricing. For ODs affordability is an even bigger issue considering the high cost and the length of the treatment. Pricing policies can bring down the cost of ODs and often incentives are provided to generate sufficient return to justify the necessary investment in development.[74] In Guatemala, the MSPAS with the assistance of PAHO, attempt to bring down prices of needed medicines, but is challenged by domestic law 66-2007, laying the rules on financial controls.

For equitable access to ODs, in addition to rational use and affordable prices, it is crucial to know how international and Guatemala is doing for sustainable financing of ODs which will be discussed in the following section.

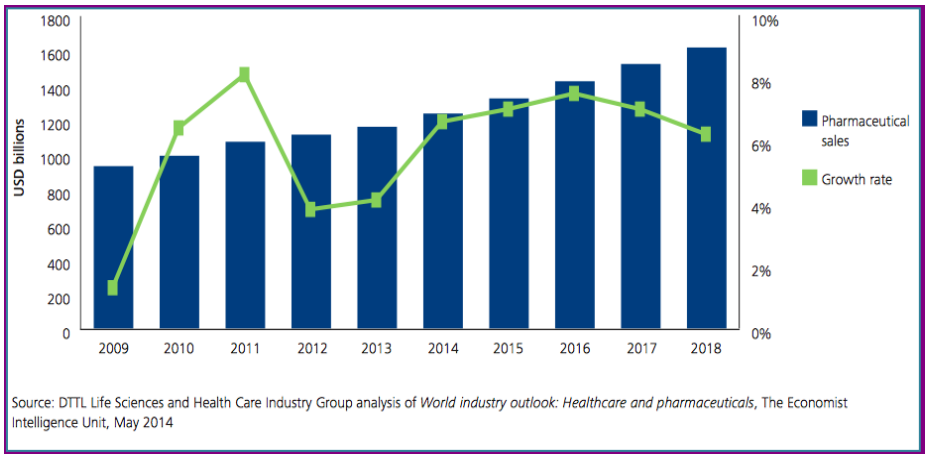
3.3. SUSTAINABLE FINANCING



Sustainable financing of Orphan drugs cannot be reviewed outside the context of the overall health care financing. The choice of a health-financing system should be made within the particular context of each country, and it is important to regulate and maintain the three core functions of revenue collection, pooling of resources and purchasing of services.[25,75]

According to the Economist Intelligence Unit (EIU), it was estimated that the global pharmaceutical segment revenues are projected to increase at an average of 6.9% every year over 2014-2018, surpassing the estimated global health care spending rate of 5.2% during that same time period.[75] (Figure 9).

Figure 9. Global pharma segment revenues



[Accessed July 2015]

The WHO framework stipulates that there are opportunities for low- and middle-income countries to both better and more public spending on health and essential medicines [76] by way of; 1. Increased public funding, 2. Out-of-pocket spending and cost sharing with patients, 3.Health insurance, 4. Donor assistance and development loans and 5. Donor funding and donations of medicines.[78]

Financing orphan drugs is closely related to the country specific financing mechanisms. Moreover, equitable funding is particularly important with respect to ODs, implying that the risks that individuals face with respect to health care costs are distributed according the ability to pay and not according to the risk of disease. A sustainable finance system permits risk sharing and offers financial protection. WHO Resolution WHA58.33.[75] recognized the importance of financial protection and set the goal of universal coverage for its member states and defined three dimensions of universal coverage: the population covered, the services covered and the proportion in which they are financially covered. So far, the way treatment of rare diseases relates to the goal of universal coverage has been generally neglected. Orphan drugs coverage represents a major challenge in developing the financial mechanisms that offer effective financial protection.[79]

In order to grasp the insights on how internationally and in Guatemala sustainable financing for ODs is addressed, 1) current public funding, 2) out-of-pocket and cost sharing, 3)

external and other funding sources and 4) health insurance and funding for research and development will be presented in this chapter.

3.3.1. CURRENT PUBLIC FUNDING FOR ESSENTIAL MEDICINES AND ORPHAN DRUGS

Although the information on total pharmaceutical expenditures are not available for many low-income countries, most studies indicate that high-income countries spend more on medicines than the less wealthy countries.[80] In general, global pharmaceutical expenditure is increasing and it accounts for about 15% of health care spending. But the cost of ODs and other biologics are increasing even more at 20-25% per year.[58] Within the existing public drug plans, orphan drugs account for less than 1% of all drug plan budget. Even in the European countries where RD patients are considered to have best access, ODs take up only 2.5 to 3.5% of the drug budget.[81,82] The information on total pharmaceutical expenditure for Guatemala was not found from available literatures in this study. Data from 2006 showed that Guatemala's (per capita) public expenditure on pharmaceuticals was US$ 9.18 while the regional average was US$ 27.48 and that of private expenditure was US$ 45.13 while regional data was US$ 74.1.[63]

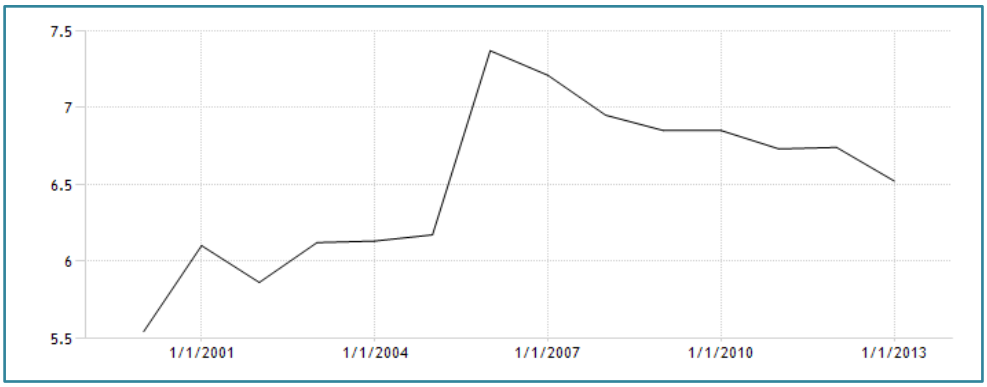
Table 2. Health Finance Indicators: Guatemala

Table 2. Health Finance Indicators: Guatemala	1995	2000	2003	2005	2007	2009	2012
Population (thousands)	10.016	11.237	12.099	12.717	13.359	14.034	15.083
Total Health Expenditure (THE, in million current US$)	538	1079	1397	1755	2456	2663	3405
THE as % of GDP	4	6	6	6	7	7	7
THE per capita at exchange rate	54	96	115	138	184	190	226
General Government expenditure on health (GGHE)							
as % of THE	36	40	37	35	33	36	36
Out of Pocket spending as % of THE	59	53	53	54	54	51	53
Private insurance as % of THE	2	2	2	3	3	4	3

Source: World Bank, WHO, Global Health Expenditure Database; National Health Accounts, Guatemala

The World Bank Health Finance Profile of Guatemala shows that Guatemala's indicators are improving (table 2).[17] Total Health Expenditure (THE % GDP) is the most common health finance indicator and is rising over the last 17 years. Nevertheless, according to 2013 WHO health systems financing, Guatemala is still one of the Central American countries that spends the least amount on healthcare compared to its neighboring countries.[83,84] According to the World bank, THE in Guatemala was last measured at 6.52% in 2013 (Figure 10).[11] Overall, the total health expenditure in Guatemala is estimated at $226 per person per year, which, according to the 2013 World Bank study is only one third of the Latin American average. This low figure suggests that not enough resources are mobilized for health and that access to health care (including orphan drugs, because of how expensive they are) is insufficient.[25] This number also shows the sharp contrast with the very high costs of orphan drugs referenced earlier in section 3.2.

Figure 10. Total Health Expenditure (% GDP) in Guatemala



Source: World Bank: Total Health Expenditure (% of GDP) in 2013 [Accessed July 2015]

Like most low and middle-income countries, Guatemala uses a diverse set of health and drug financing mechanisms. The WHO estimates that the 2012 public and private shares of total health expenditures are 36% and 64 %, respectively, (Table 2). From the public sector, the sources of funds come from general taxes, affiliate contributions and employer contributions while from the private sector the funds come from households (out of pocket-OOP and Fees) and from non-profit donations.

In Guatemala, the health financing of orphan drugs is managed through the social security system (IGSS), whereby patients contributions to IGSS are deducted or when the patient pays out of pocket (privately) for the use of orphan drugs. For patients with rare diseases this means that coverage for the cost of treatment is provided as long as the patient is a member of the system and as long as the drugs are enlisted with the IGSS; like shown in chapter 1 the coverage of IGSS is only 18%. Consequently, the general coverage for the high cost of ODs is restricted.

In order to raise funding for ODs, several financial mechanisms can be explored. In a study on financing options for orphan drugs in Chile four options are reviewed associated with different contribution mechanisms with regards to the financing of high-cost of drugs for the treatment of rare diseases: general taxation, mandatory contributions, voluntary contributions and innovative financing mechanisms (like special levies, special purpose tax on ODs).[13,26]

For Guatemala, the literature review shows that main attention is put at raising public funding. The analysis of the Expansion of Coverage Program (PEC) by the World Bank (2013)[85] shows that since 1997 a lot of effort has been placed to increase the funding to expand health and nutrition services throughout the country. Unfortunately, the WB-study concludes also a chronic underfunding of the program mainly due to variable political support and Guatemala's limited fiscal space. Moreover, "significant and sustained health coverage expansion in terms of areas and population groups covered, and types of services offered, will require significantly more of the government's resources and commitment." [85] With a lot of attention to the funding of basis health goals, the fiscal possibilities for raised funding for the treatment of rare diseases will be limited. Traditionally, lack of public funding seems to be solved in Guatemala by private out-of pocket spending, which therefore is already high.

3.3.2. OUT-OF POCKET SPENDING AND COST SHARING WITH PATIENTS

Even in Europe where the universal access to and coverage of health care is broadly practiced; very high personal financial contribution has to be made for diagnosis and treatment.[86] Access to treatment in many low and middle-income countries is further compromised when people have to pay out-of-pocket for their treatment. Although Guatemala is used to a diversity of private and public funding, its high OOP cannot be regarded as a sustainable way of financing ODs and can lead to expenditures with high financial impact for families of patients with a rare disease.[58] According to WHO out-of-pocket expenses is a result of failure by the government to allocate sufficient resources.[25]

As previously mentioned, THE (% GDP) of GDP has risen in the last 10 years and the Guatemalan health-care system relies significantly on private sector expenditure, primarily out-of pocket spending. It means that Guatemala has the highest level of private expenditure as a proportion of total health expenditure of any Latin American country.[76]

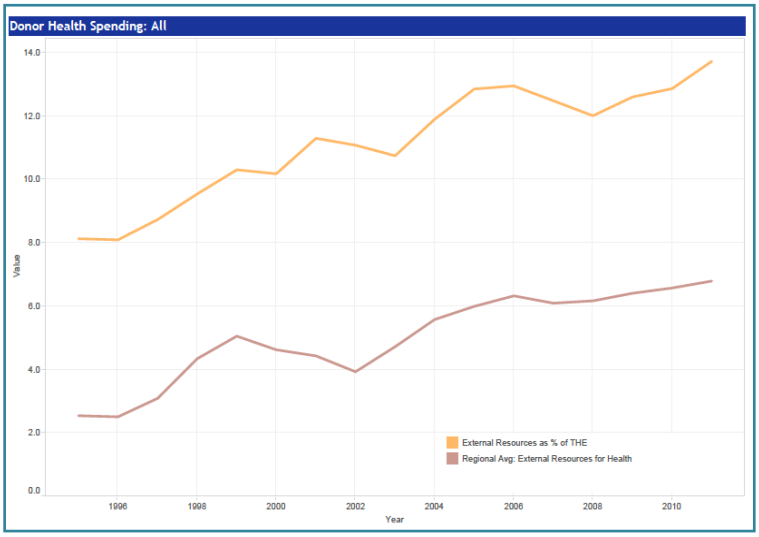
Large out of pocket payments have adverse implications for financial risk protection and likely to result in significant impoverishment for households that incur them. In a study that analyzed the health finance systems of Guatemala, it was reported that the poor paid five times more than the rich in terms of health payments as a percent of income levels.[72] Much more common than user fees are direct payments by households to health care providers in the private sector for consultation, diagnostics and drugs. For the insured this may sometimes take the form of co-payments.[76] The perceived main advantage of such out of pocket payments is that, if all else are the same, they would promote efficient use of health care. However, in practice, the informational advantages that providers of health services enjoy can lead them to promote unnecessary care, diagnostics and drug use as a way to raise revenues. When such charges are not reimbursed or otherwise covered by insurers, they will lead to inequity in access to care.

In a study conducted by Flores et al in 2007, they showed that out of pocket spending on medicines is present across all income groups, with the highest income quintile paying on average 63% and those in the lowest income quintile paying on average 80%. Hence, they concluded that the poor are allocating a much greater portion of their out of pocket spending on drugs compared to the rich.[72] Furthermore, out of pocket spending is a challenge for Guatemala's Policymakers with regard to Health Financing because people are not covered by any form of insurance except by means of access to subsidized public services which leads to high shares of out of pocket spending by private households.[72] An alternative for private out-of-pocket spending could be found in other funding sources.

3.3.3. EXTERNAL FUNDING AND OTHER FUNDING SOURCES

According to WHO and USAID, Guatemala is more dependent on donor resources for health than the average country in its region. USAID reported that Guatemala's donor spending on health as a percentage of "THE in 2011 was 2.1, compared with the regional average of 1.13 and the lower-middle income group average of 2.62" (Figure 11).[25,73] Nonetheless, the level of donor resources hardly forms a solution to raising funding for orphan drugs, unless specific OD-donor programs can be identified; this literature review did not provide any insights.

Figure 11. Donor Health Spending (Time series) for Guatemala and regions



Source: Based on data from WHO-Global Health Observatory (2012)[28] [Accessed July 2015]

3.3.4. HEALTH INSURANCE AND FUNDING SOURCES FOR RARE DISEASE RESEARCH

As the prices of ODs can be as much as 19 times higher than non-orphan drugs and most of the RDs are chronic nature, there is a rising worry on how to absorb the costs and about how third party payers are going to pay for patients with RD.[49]

Health insurance is one of the core functions for better accessibility of medicines stipulated by the WHO.[76,77] Escalating health care costs especially costs of orphan drugs are raising concerns of the third-party payers.[49] For equitable access to ODs, it is imperative that the risks that individuals face with respect to health care costs are distributed according to the ability to pay and not according to the risk of disease.[79] As table 2 showed, the participation of Guatemalans in (private) health insurance is very low (3%).[79] As referenced in chapter 1, only a small upper part of society participates in private insurances, creating only a very small basis for a general widespread insurance system that could help funding ODs.

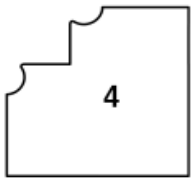
Between 2000 and 2008, OMP research and development expenditures in the EU have tripled.[69] There are three major funding sources for health research in RDs: public sector funding, non-profit private sector funding (charities and foundations) and for-profit private sector (pharmaceutical companies) funding. But very little is known about the funding situation regarding RDs and which are the priorities. According to some studies in Europe, main funding sources turn out to be the disease advocacy groups (non-profit private sector) followed by the European Commission (public sector). Experimental biological studies are much more likely to receive funding than other research categories like clinical observational studies and sociological health economic studies.[88]

In summary, a sustainable financing of health systems permits risk sharing and offers financial protection. The latter is especially important for patients with a rare disease, because of the high cost of the ODs. To raise funding for ODs, different financial mechanisms (general taxation, mandatory or voluntary contributions or innovative financing

mechanisms) exist. Guatemala has put a lot of attention in raising public funding for the general Expansion of Coverage program (PEC), but did not yet succeed to reach a sufficient and sustainable level of funding for fulfillment of the general health goals. Total health expenditures rely for almost two third on private (out-of-pocket expenses) and participation in private insurances is very low. Equitable funding of ODs would imply that financial risks of rare diseases are distributed according the ability to pay and not according to the risk of disease. Considering the very high out-of-pocket spending by Guatemalans, the fact that participations in health insurance is very low and the report that the poor pay five times as much that the rich in terms of health payments, equitable funding of ODs does not seem to exist in Guatemala. Although public and private funding of health expenditures is trending up, the funding of ODs do not seems to benefit from it.

Financing ODs in sustainable manner and equitable access to ODs cannot be achieved without a reliable health and supply system which will be discussed further in detail in the following section.

3.4. RELIABLE HEALTH AND SUPPLY SYSTEMS



Weakness in health management system is widely perceived as an important cause for inadequacy and inequity in medicine access. According to WHO, the issues of high prices and low availability of medicines can be addressed through improved procurement efficiency and adequate, equitable and sustainable supply systems.[58]

Reliable health and supply systems means “incorporating a mix of public and private supply services, to ensure regular supply of essential drugs of assured quality in health care facilities and sufficient research and development for new drugs”. In addition to above-mentioned three crucial factors (3.1, 3.2 and 3.3), the last factor, the reliable health and supply system, is the main engine to ensure equitable access to ODs. It is even more important for ODs due to many challenges unique to rare diseases and orphan drugs. For this section the following sub-headings are considered the most relevant when we look at ODs access in Guatemala: 1. National Plans, Regulations and Drug Policies, 2. Supply Delivery Approaches, 3. Purchasing Schemes and Quality Control, and 4. Research and Development (R&D) of orphan drugs.

Generally, pharmaceutical distribution to meet the health-care needs of people in need within many developing countries is inadequate. The challenges of accessibility to medicines ranged from rational selection, pricing, procuring medicines at the national level, to receipt, storage and distribution until they reach the end-users. The health systems and infrastructures are often inadequate to manage the processes necessary for access to medicines. The critical importance of a well-functioning pharmaceutical management system cannot be emphasized enough.[58,89]

3.4.1. NATIONAL PLANS, REGULATIONS AND DRUG POLICIES

As increasing number of RDs are identified, researchers, health care professionals, policy makers and legislators have to raise their concerns for access to treatment. In recent years, much progress has been made especially in some developed countries such as EU, UK, US and some parts of Asia including Australia, Japan, Singapore, South Korea and Taiwan

regarding access to ODs with the introduction of regulatory frameworks, national rare disease plans and strategies as well as revision and considering of orphan drugs in national drug policies.[90]

In 1983, the FDA Orphan Drug Act passed in the United States in which the definition of rare disease or condition in US was developed. That reflected the recognition on the needs for development of drugs for RDs. It was followed by Singapore in 1991, Japan in 1993, Australia in 1998, Europe in 1999-2000 (the European Union Orphan Drugs Regulation), Taiwan in 2000 and South Korea in 2003. It was also noted that China is actively promoting the regulation of RDs. To develop ODs, pharmaceutical companies are provided with various incentives including tax incentives, market exclusivity and facilitation in registration.[24,92] The recognition by policy makers have also increased in other middle and low-income countries. In some countries such as Canada, the requirement of a separate policy for ODs was previously rejected citing that the OD access could be achievable under various existing policies and legislations.[91] However, these mechanisms were found to be not sufficient and their RD patients faced high challenges in gaining access to ODs. Throughout this literature review, we found that national plans for RDs have been developed in many countries in Europe, The United States, Canada, and some Asia and Latin American Countries but for Guatemala, it does not exist.

The introduction and implementation of OD policies and regulations have great impact on OD development, marketing, distribution and consequently for access to ODs by end users. Since the 1983 Orphan Drug Act in the US, there has been significant progress in development of orphan medicinal products and hence the treatment of rare diseases. In the US, over 2600 products have been approved as orphan designation and more than 400 products have been approved as therapy for over 200 RDs indications. In EU, about 1000 products were designated as orphan medicinal products, of which 70 products for around 45 indications received marketing authorization. In Japan, 269 drugs were designated as orphan for more than 100 diseases. Despite these progresses, the treatment for most of the rare diseases is lacking or highly insufficient.[93]

In 2005, the Expert Committee on Selection and Use decided on the issue of OD selection that the "recognition of rare diseases may increase in importance as diagnostics improve, access to health systems increases and communicable diseases decline in importance." They encouraged the member countries to seek advice from WHO on how to address this issue and WHO had established a Topic Advisory Group for Rare Diseases.[94]

Guatemala does not have an official national drug plan or policy. However, there are regulations that address the topic on essential drugs.[38,41] Access to essential medicines and technologies as part of fulfilling the right to health is recognized in the national legislation and there are official guidelines written for drug donations.[38,39] According to the 2012 Guatemala Pharmaceutical Profile,[40] an updated electronic version of the list can be found in their Authorization System of Medications (SIAME [5] in Spanish). Guatemala's pharmaceutical industry lists drugs by their International trade names.[95] Like MSPAS, the IGSS has its own list of drugs according to their interests and there is only a basic list of most common medicines used and not a National List of Essential Medicines as recommended by the WHO.[42] This leads us to the understanding what approaches Guatemala uses to supply the delivery medicines.

[5] SIAME is the Sistema Automatizado de Medicamento, (see www.medicamentos.gob.gt) in Spanish.

3.4.2. SUPPLY DELIVERY APPROACHES

In Guatemala there are different channels of medicine supply within the health system. In general, the MSPAS operates PROAM[6] or pharmacies that offer medicines from a basic list (*Lista Basica-in Spanish),* to ensure access to quality medicines at good prices. According to the patient organization Para Todos (in Spanish), ODs are not within this 'basic list'', hence, it is very difficult for patients with RDs to receive timely and appropriate treatment.

Findings from studies in some developed countries showed that ODs are installed within health systems and governments negotiate pricing with pharmaceutical companies. In this study, we found that ODs are not part of Guatemala's health system. Moreover, the supply of ODs is mainly through the private sector, most commonly NGOs, unregistered dispensaries, and patient organizations such as Para Todos. Therefore, the government is not able to distribute ODs needed to stock pharmacies which are subsequently sold to consumers.[96] The supply delivery approaches that are used in Guatemala could be linked to purchasing schemes and the quality control systems that are in place in the country.

3.4.3. PURCHASING SCHEMES AND QUALITY CONTROL

The MSPAS controls medicines purchasing for the public sector. The MSPAS identifies the categories and quantities of medicines it expects to use in the coming year and invites suppliers to submit bids to procure these medicines. Suppliers and prices are established through an open, public bidding process known as *Contrato Abierto* (Open Contract).[97]
The purchasing scheme follows a bidding procedure were bids submitted are open by a panel at a public meeting and eight of the lowest bids in each therapeutic category are selected. MSPAS and IGSS procure their drugs through these vendors with an ordering limit of three-month supplies of medicines. Exceptions apply when a drug of interest is not on the Open Contract list or when some suppliers may elect not to fulfill their contracts, for whatever reason. In these cases, both price and supplier are unknown. In 2007 there were approximately 730 medicines on the Open Contract list for Guatemala.[97]

In Guatemala quality assurance of medicines is done by *the MOHs Department of Regulation and Control of Pharmaceutical and Allied Products*. Whose role is to regulate and control the pharmaceutical companies that import, Research and Development (R&D), manufacture and market medicines in Guatemala.[98]
In the following sections we address R&D of ODs, from the international perspective. Providing a description of translation of rare diseases into OD R&D and factors that influence the rational use of ODs towards R&D and give a brief overview of Patents in Guatemala.

3.4.4. RESEARCH AND DEVELOPMENT (R&D) OF ORPHAN DRUGS

There is no available literature regarding orphan drug R&D in Guatemala and therefore, not much is going on in Guatemala in this area. However, we would like to discuss the general overview on international situation.

[6] PROAM is the Programa de Accesibilidad de Medicamentos in Spanish.

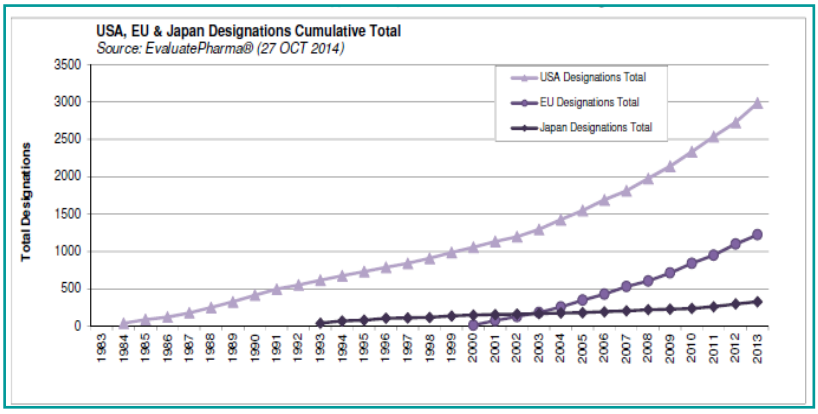
To date, for most rare disease, the etiology is still unknown, which makes rare diseases a genuine global health issue. Lack of understanding for many rare diseases such as the cause, pathophysiology, semiology, natural history of disease and epidemiological data significantly influence the ability for diagnosis and treatment. Due to its rareness, only a few pharmaceutical companies engage in investing in fundamental research of rare diseases.[15]

Furthermore, the patients with rare diseases as well as the professional experts are also scattered all over the world and consequently the existing research efforts are fragmented. Many physicians have never heard of many rare diseases and there still is no adequate coordinating mechanism to integrate the scarce knowledge and expertise. These factors affect the proper diagnosis and treatment.[99]

Translation of Disease Understanding into Orphan Drugs R&D

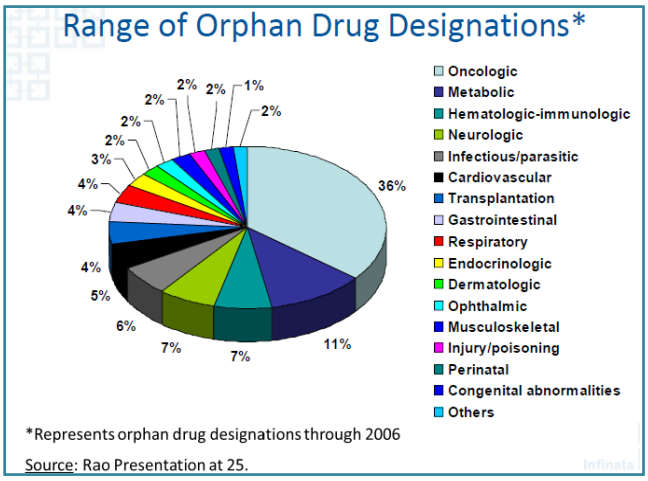
From 1973 to 1982, only 10 new drugs were developed for rare diseases. However, after 30 years of Orphan Drug Act (US), there were 432 approved drugs and 2820 designated orphan drugs in the US and in 2008, these account for 38% of all FDA-approved NMEs.[15,100] According to the Office for Orphan Product Designation (OOPD), from 1983-2013 the number of OD designations and marketing approvals continued to increase (Figure 12) and 36% orphan drug designation was allocated to Cancer (Figure 13).

Figure 12. USA, EU & Japan Designations Cumulative Total



Source: EvaluatePharma, 2014
[Accessed July 2015]

Figure 13. Range of Orphan Drug Designations



Factors that influence rational selection of drugs towards research and development

The key factors that influence the rational selection of orphan drugs unlike other diseases like asthma or diabetes, is that the rarity of a disease significantly complicates the clinical development stage. As Vrueh et al illustrated in a background paper on Priority Medicines for Europe; the small number of patients, the logistics involved in reaching widely dispersed patients, ethics (e.g. use of placebo), poor diagnostics, limited clinical expertise and expert centers are some of the problems the world is faced with when it comes to OD development.[15,16] The current pipeline of products for rare diseases (2012) are mentioned in the following abbreviated Table 3 (extended list of approved ODs to date could be found in www.orpha.net).[15,17]

Table 3. Designated and Approved Orphan Medicinal Products in USA, Japan, Australia and EU

Jurisdiction	OMP Status	OMP Market Authorisation
USA	2609	403
Japan	269	173
EU	1000	70
Australia	231	62

Source: Franco P., Orphan drugs: the regulatory environment. Drug Discov Today. 2012 Sep 5. doi: 10.1016/j.drudis.2012.08.009. [Epub ahead of print]

Note: MA, Market authorisation ; OMP, Orphan medicinal product Status, the product has the status of OMP, but its safety, quality and effect has still to be analysed by a committee before the product may be registered.

Patents-brief overview

Guatemala is one of Central American countries that participate in The World Trade Organization Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement, which provides patent protection for medicines. TRIPS can only be used if the country decides that a disease is a public health emergency. In that case they can produce the medicine in the country as a generic and if the country does not have the capacity, they can buy it from another country that produce generic medicines (like India or Brazil). TRIPS could provide countries like Guatemala with safeguards to compulsory licensing, to help them override patents whenever there is access to medicines. Results from a study conducted by N. Ford, however, show that countries such as South Africa, Thailand, Kenya and Guatemala are challenged by the TRIPS Agreements because 'it underscores the vital role played by civil society in defending the right to access affordable medicines'.[45,66,67]

In summary, gaining access to treatment of RDs is often extremely difficult and Guatemala lacks an official national drug policy that supports the availability and access to ODs. ODs are not on the basic list and effectively in no part of Guatemala's health system, which makes it difficult for patients with RDs to receive timely and appropriate treatment. The MSPAS purchases its essential medicines through an open public bidding process (Contrato Abierto), however because the number of ODs requested is low in comparison to general medicines they never make it on the bidding lists. The pipeline of new OD development is filling, but clinical development of ODs is significantly complicated by the rarity of the disease. For balancing development and sufficient use of ODs patient protection for medicines is regulated by 'TRIPS' in which Guatemala participates.

CHAPTER 4. DISCUSSION

In this chapter, literature findings on the current situation and gaps in access to ODs in Guatemala's health system will be systematically organized and discussed using the conceptual framework.

4.1. **RATIONAL SELECTION AND USE OF OD** - *Current situation and Gap identified*

Medicines save lives, promote health and prevent diseases but at the same time, they also impose negative affects if they are not used properly. Worldwide, over half of all countries still require extensive measures to ensure appropriate use of medicines. Irrational use of medicines is a very serious public health problem that we are facing currently.

From the WHO's advocating recommendations to promote RUM, establishment of multidisciplinary national body to coordinate policies on medicines use, use of clinical guidelines and development and use of national essential medicines list are most relevant factors for orphan drugs rational use. There is lack of basic understanding for most of the rare diseases which makes research very difficult and the rare disease patients as well as the rare disease experts are spread in the world. Therefore, for most of the rare diseases, there still is no treatment at all.

When we compared the data in this study to the international community and what is out there, we found that due to the rarity of RDs, many physicians in the world have never heard or encountered many rare diseases and there are high percentage of mis-and delayed diagnosis even in most developed countries. In addition, there are a large number of rare diseases (5000-7000) and adequate coordinating mechanisms to integrate scarce knowledge and expertise is still lacking. The clinical guidelines and clear treatment for RDs are available for only a small percentage of RDs (less than 5% of all RDs). Only 43 emergency RD guidelines are available in Orphanet website. Until 2013, about 500 medicines have been approved in USA, EU and Japan for RD treatment. The information regarding existence and use of proper clinical guidelines and clear treatment for RDs in Guatemala is not yet available.

Even though some medicines used for some RDs are included in WHO essential medicines list, majority of ODs cannot be part of the EML due to its strict selection terms. As diagnostics improves and access to health systems increases, and as the awareness on the high burden of RDs increased, recognition of ODs and the possibility of their inclusion in EML has been under the process of discussion internationally.

Another gap found was that there is no national essential medicine list and official national drug policy available in Guatemala. The consequences of this could be significantly impacting someone who suffers from a life threating disease. Due to lack of access to medicines, (either through availability or affordability), patients run a real risk to die. The essential and other drugs are controlled under the other health system regulations. The MSPAS and IGSS have their own lists of drugs for which the expenses are totally or partially covered. However, ODs are not on their list. Which as a consequence lowers IGGS's priority of for ODs

Rational use of orphan medicines requires that "patients with rare diseases receive medications appropriate to their needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community." However, for Guatemala, because an ODs policy is lacking, this lead to other gaps in infrastructure and coordination which are required for access and rational use of orphan drugs.

4.2. **AFFORDABILITY** - *Current situation and Gap identified*

There is limited data available on the actual figures that relate to affordability of pharmaceutical drugs in Guatemala. However, it is well documented that much is needed to improve access to affordable drugs to patients, especially for those who live in hard to reach regions.

The cost of treatment rises as the medicine prices are high and for the population who are living around and under the poverty line, it may mean a month or several months wage. For people with chronic conditions, the need to medicines/treatment will be long-term or even life-long and the affordability for the therapy becomes a virtually impossible challenge. Therefore, regulations and policies become very important to address affordability of medicines for those who need these. Eliminating duties and taxes on medicines, promoting use of quality-assured generic medicines and regulations to avoid excessive add-on costs in the supply chain are crucial factors to lower the prices in general and ODs in particular.[29]

The lack of affordability to ODs in Guatemala is a large gap that we found in this study.
The consequences for this are similar to what others studies stipulate in this respect. For example in a medicines price survey they determined that prices are higher in Guatemala, which they concluded, as an explanation for the lower access to medicines that was observed. Meanwhile, In this study we found that to ensure access to ODs for the treatment of rare disease, policy makers need to find a balance between the available resources to fund medicines and must be willing to negotiate the pricing of ODs for procurement. In this case, the fact that high-cost ODs are the only treatment options that patients with a life threating disease have, the problems of access are compounded. For a Guatemalan to privately purchase an OD becomes a huge financial burden to them and their families. The situation of ODs not being available in Guatemala reflect a huge gap in health system, which Guatemala aims to direct at universal coverage
In general, Guatemala is wealthier than Nicaragua and Honduras, which is the reason we expected to find access to ODs. However, the inequities in wealth confirm our findings which show that access to ODs is lacking in Guatemala.

4.3. **SUSTAINABLE FINANCING -** *Current situation and Gap identified*

Sustainable financing of Orphan drugs cannot be reviewed outside the context of the overall health care financing. Guatemala's Total Health Expenditure is only US$226 per person per year, which is much lower than neighboring countries and indicate that not enough resources are mobilized for health and drug financing. When sustainable financing of essential medicines are already under pressure, financing orphan drugs is even more difficult to establish. Although Guatemala is used to a diversity of private and public funding,

ODs are not covered in these schemes, furthermore, out-of-pocket expenses cannot be regarded as a sustainable way of financing ODs and can lead to unaffordable expenditures for families of patients with a RD. According to WHO a high degree of out-of-pocket expenses is a result of failure by the government to allocate sufficient resources.

Following the WHO increased public funding and donor funding can aid to raise health financing. It does not mean that Guatemala should "reallocate funds from prevention or other health priorities, but additional new public funding to the health sector" (WHO framework, figure 3). Guatemala has been raising funding for the Expansion of Coverage Program (PEC) but the funding of ODs are no part of this program. Since a widespread base for insurance is also lacking, a specific 'solidarity-program' for treatment of rare diseases maybe difficult to launch in Guatemala, but is worthwhile to explore. For orphan drugs connection and inclusion could be sought with global programs or globally available funding for the treatment of specific rare diseases. In this respect, donor funding or donations of medicines for RDs from other (high-income) countries or directly from pharmaceutical companies could be an effective step to treat RDs in Guatemala. Sharing adequate health research data on specific RDs in an adequate way, contributes to the available patient information to improve Research and Development on Orphan Drugs.

4.4. **HEALTH SYSTEM** - *Current situation and Gap identified*

Considering health system characteristics that affect potential access to medicines, for Guatemala out-of-pocket payment for health services and medicines is a burden especially affecting the poor.[99,54]
RDs are not recognized within the Guatemala health system in addition, there are no reported clinical treatment guidelines that cover RD and describe treatment (with OD) for RD. Moreover, we found that OD are not included in any national medicines lists.
In order to ensure regular supply of quality medicines as well as for development of new drugs, reliable health and supply systems are essential. Pharmaceutical distribution to people in need in many developing countries is inadequate. Weak and ineffective health systems and infrastructures are responsible for these. In cases of rare diseases, there needs to be health and supply systems which can effectively manage the complex and difficult nature of accessibility to high-priced orphan drugs.

There are a variety of medicine supply channels in Guatemala health system, in which MOH is the main responsible body to ensure access to quality medicines at good prices. However, ODs are not included in the basic list and the current systems do not have capacity to distribute required amount of ODs and hence, it is very difficult for RDs patients in Guatemala to receive timely and appropriate treatment. Quality assurance of medicines is managed in Guatemala by the MOH by means of regulation and control of the pharmaceutical companies that manufacture, import and market medicines.

The importance of RD registries has been widely recognized and their wide expansions have been called for. Currently, there are 651 RD registries in Europe and 71 of them are global registries that serve as RD registries and the number is increasing worldwide. While in Guatemala there are only 12 patient organizations. Globally, more than two-third of registries are operating by the public/academic sector and the rest by private non-for-profit (patient organizations and charity organizations) and private for-profit (pharmaceutical

companies). So far, these registries are operating with no uniform standards and are working in isolation. There also is a challenge in sustainable funding for them. No information about or collaboration of RD registries in Guatemala has been found in this literature review. Moreover, there are no national rare disease plans in place anywhere within the health system, in academia or non-government agencies. Most patients with rare diseases are relying on outside sources (like donations) in order to obtain access for treatment options.

Orphan drug access for rare disease patients is further compromised because of the inadequate health and supply system in Guatemala. There is no incorporation of private and public mixed supply services. Research and development in RD, OD and other operational research are also very weak in Guatemala.

CHAPTER 5. CONCLUSION

In spite of progress in health system development in the last decade, Guatemala still struggles to attain all the UN-millennium goals (MDG) and strives to fulfill the constitutional rights to universal access to health services. With still approximately 1 million people deprived from any access to health care services, understandably, the MSPAS is focused on expanding coverage and solving the main general health issues that affects its population.

Because a rare disease by definition concerns only a small number of patients, so far, the treatment of rare diseases has been generally neglected in Guatemala. Globally, only a small fraction of patients with rare diseases have access to necessary treatment and it is in itself not surprising that the scenario is much worse in a low-middle-income country like Guatemala Altogether though, we estimate around 1 million patients suffering from a rare disease in Guatemala, but the country's health system does not include an orphan drugs and RD-policy and lacks the establishment of a multidisciplinary national body to coordinate the irrational us of orphan drugs. Moreover, the system is not systematically registering rare diseases, national clinical treatment guidelines are lacking and orphan drugs are not included in any national medicine list.

With affordability already being one of the biggest challenges for improving drug access, in Guatemala the coverage of orphan drugs turns out to be even more complicated than in other countries in the world. The MSPAS (with assistance of the PAHO) tries to bring down the prices of ODs, but is challenged by domestic financial controls. The study findings indicate that equitable funding of orphan drugs does not exists in Guatemala and that people with a rare disease are financially significantly impacted, because they have to fund the treatment themselves. The private out-of-pocket health care expenditures in Guatemala are higher than in the rest of Central America and participation in health insurances is remarkably low and cost sharing with patients is not integrated in the health system.

Even when they are able to finance it, the RD treatment most likely becomes extremely difficult, since Guatemala lacks an official drug policy that supports the availability and access to ODs. Moreover, currently ODs cannot be part of the essential medicine list, which proves to take away Guatemala's priority of ODs within its health system.
In short, the study shows numerous health system gaps for Guatemala having a real issue with the treatment of rare diseases and the sustainable funding of the orphan drugs needed.

These shortcomings in Guatemala's health system reflect the need to ferment a sustainable policy for ODs and RDs which includes equitable access to ODs for patients suffering from a life threatening disease. A starting point would be for Guatemala to recognize that rare diseases represent a global health challenge and it affects many Guatemalans; the estimated number of patients with rare disease over one million warrants a much higher priority from the Ministries of Health and Social Assistance. From this study we conclude that a comprehensive approach is needed towards a sustainable health system with integrated orphan drug policies for the treatment of rare diseases. Moreover, steps need to be taken for the development of clinical guidelines which are urgently needed in order to improve the effective treatment of patients as well as the rational use of the scarcely available medicines. Further research is needed to help raise awareness and knowledge of RD and ODs in all levels of public health in Guatemala. For Guatemala, the government should set

up a strategic framework within the health system that incorporates innovative ways to fund orphan drugs such as cost sharing with patients, funding via tax incentives and support global partnerships and donations.

The pharmaceutical industry has traditionally been a main contributor to improving global health through the innovative medicines they develop. “They have a strong track record of sustaining programs to improve the health of patients in low and middle income countries”[102] In the case of Guatemala, pharmaceutical companies can help to bridge the gap between access to expensive orphan drugs by collaborating with all stakeholders, policy makers, patient organizations and encourage the MOH to recognize and place orphan drugs and rare diseases in their agendas as a priority for Guatemala.

CHATER 6. RECOMMENDATIONS

An estimate one million Guatemalan people suffer from a rare disease. With a lack of proper diagnosis, access to medicines and treatment, the Guatemalan people dying from a RD should be prioritized. From the gaps identified in this study and in order to meet the demands of RDs the following recommendations to enhance access to ODs should be considered for Guatemala:

1. *National policies and regulations*

- Establishment of RD expert committee
- National RD policy development and integration into National Health Plan
- National Pharmaceutical Plan development and integration of ODs in it.
- Establishment of RD registries which will enable:[48]
    - better understanding of natural history of disease which will be the foundation for successful OD development
    - support discussions with regulators and,
    - meet post-marketing safety commitments.
- Review and revision of current medicines pricing, procurement procedures and supply system for inclusion of ODs

2. *Sustainable financing*

- Ear-marked budget for RDs (government)
- Review of current reimbursement policies of MSPAS
- Expanding external (donor) funding
- Negotiation and cooperation mechanisms with pharmaceutical companies for better prices
- Investigate possibilities for a specific 'solidarity program' for the treatment of RDs (including use of alternative financing mechanisms)

3. *Implementation/Activities*

- advocacy and awareness raising on RDs to policy makers and the community for recognition of the burden of RDs
- review and revise of the basic medicines list including integration of suitable ODs
- development of RD clinical guidelines or adaptation of RD clinical guidelines from other countries according to Guatemala context
- awareness raising of healthcare providers and continuous medical education on RDs

4. *Coordination and Networking*

- Networking among existing patient organizations and coordination for implementation
- Networking among clinical professional organizations and patient organizations to share knowledge and expertise
- Expansion and promotion to establish more patient organizations

- Empowerment, protection and financial and technical support for patients and organizations
- Dialogue between patient organizations and policy makers
- Coordination with EURORDIS, ORPHANET and other international RD organizations for information sharing, expertise sharing and support for technical and other supports

5. Information and research

- Data collection through RD registries and dissemination and use of information
- Inclusion of RD data in National Health Information System Database
- Research to get better understanding on current situation of RDs, factors influencing on access to ODs and operational research
- Evidence-based planning for better accessibility to ODs

FUTURE RESEARCH

Leveraging access to orphan drugs can only be accomplished by policy makers contributing to sustainable health systems, procuring ODs and engaging in pricing practices that are realistic, affordable and available to the RDs patient populations.
In order for Guatemala to be able to meet the demands of OD access for RDs patients, the government should recognize the need to raise awareness, invest in research, the development of patient registries, and investing in good clinical research, providing a platform for future scientists to help break the barriers that are so often common in low-middle income countries.

REFERENCES

1. European Commission. Regulation (EC) No 141/2000*. The European Parliament and the Council: Orphan Medicinal Products*. Official Journal of the European Communities 2000;L 18/1; 16 December 1999.
2. Michel M, Toumi M. *Access to orphan drugs in Europe: current and future issues*. Expert Review of Pharmacoeconomics & Outcomes Research. University of Paris V, University ofLyon. 2012;12(1):23-29.
3. de Varax A, Letellier M, Börtlein G, *Study on orphan drugs: Phase I: overview of the conditions for marketing orphan drugs in Europe*. Alcimed, Paris. http://ec.europa.eu/health/files/orphanmp/doc/pricestudy/final_final_report_part_1_web_en.pdf (accessed 28 June 2015)
4. Thomas P. Anderson. *Guatemala.* Encyclopaedia Britannica. http://www.britannica.com/place/Guatemala. (accessed 3 August 2015).
5. World Population Review. *Guatemala population 2015*. http://worldpopulationreview.com/countries/guatemala-population. (accessed 3 August 2015).
6. Maps Open Source. *Map of Guatemala*. http://www.mapsopensource.com/guatemala-map-black-and-white.html (accessed 28 June 2015).
7. The World Fact Book, *Central America and Caribbean: Guatemala.* https://www.cia.gov/library/publications/resources/the-world-factbook/geos/gt.html (accessed 28 June 2015)
8. index mundi. *Demographics: Population Growth Rate, Guatemala*. http://www.indexmundi.com/g/g.aspx?c=gt&v=24. (accessed 3 August 2015
9. The United Nations Development Program (UNDP). *Human Development Report 2013, The Rise of the South: Human Progress in a Diverse World: Guatemala.* http://hdr.undp.org/en/countries/profiles/GTM (accessed 28 June 2015).
10. The Center for Disease Control. *CDC in Guatemala*. Fact sheet. http://www.cdc.gov/globalhealth/countries/guatemala/pdf/guatemala.pdf (accessed 28 June 2015).
11. Researchandmarkets.com. *Global Orphan Drug Pipeline & Regulatory Insight 2015*. January 2015 http://www.researchandmarkets.com/reports/3065833/global-orphan-drug-pipeline-and-regulatory (accessed 28 June 2015)
12. WHO, Geneva. *Monitoring the Building Blocks of health System. A Handbook of Indicators and their Measurement Strategies*. WHO; 2010. Pg 4-59 http://www.who.int/healthinfo/systems/WHO_MBHSS_2010_full_web.pdf (accessed 18 July 2015).
13. Becerril-Montekio Víctor, López-Dávila Luis*. The health system of Guatemala*. Salud pública Méx; 53(Suppl 2): s197-s197. http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S003636342011000800015&lng=en. (accessed 5 August 2015)
14. WHO, Geneva. SIXTIETH WORLD HEALTH ASSEMBLY WHA60.16; *Progress in the rational use of medicines; may 2007*; http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R16-en.pdf / (accessed 3 July 2015)
15. Cote T, Cote Orphan Consulting and Kurt Karst, Hyman, Phelps and McNamara, Moderated by Jennifer C. Smith-Parker and Anusha Kambhampaty, *The Do's and Don't of Orphan Drug Development*, BioPharmInsight Webinar Series; October 2013.
16. De Vrueh R, Baekelandt, E.R.F, and de Haan J.M.H., *Priority Medicines for Europe and the World 'A Public Health Approach to Innovation'*. Update on 2004 background Paper written by S. van Weely and Prof. H.G.M. Leufkens. background Paper 6.19 Rare Diseases; 2004.
17. Dr. Deena Class et.al, *Health Financing Profile Guatemala*, World Bank, Washington, July 2014
18. Fiorentino R, Liu G, Pariser A.R, Mulberg A.E, Cross-sector sponsorship of research in eosinophilic esophagitis: A collarative model for rational drug development in rare diseases,

Journal of Allergy and Clinical Immunology, September 2012, Volume 130, Issue 3, Pages 613-616.
19. Right Diagnosis. *Statistics by Country for Rare diseases.* http://www.rightdiagnosis.com/r/rare_diseases/stats-country.htm# (accessed 3 August 2015).
20. Holloway K, Liset van Dijk, Department of Essential Medicines and Pharmaceutical Policies, *The World Medicines Situation 2011, Rational Use of Medicines.* WHO, Geneva, and University of Utrecht, the Netherlands, [Internet]. (accessed 3 July 2015).
21. WHO, *The benefits of responsible use of medicines: Setting policies for better and cost-effective health care*, 2012. http://apps.who.int/iris/bitstream/10665/75828/1/WHO_EMP_MAR_2012.3_eng.pdf?ua=1 (accessed 3 July 2015).
22. The United States Global Health Initiative. The *USG Guatemala GHI Team*, Revision: December 11, 2010. http://www.ghi.gov/wherewework/docs/guatemalastrategy.pdf (accessed 16 July 2015).
23. Madelin R, *The Voice of 12,000 patients, Experiences and Expectations of Rare Disease Patients,* A report based on the EurordisCare2 and EurordisCare3 Surveys, Eurodis 2009. http://www.eurordis.org/IMG/pdf/voice_12000_patients/EURORDISCARE_FULLBOOKr.pdf (3 July 2015).
24. Hadjivasiliou A, EvaluatePharma, Orphan Drug Report 2014. [Internet]. 2015 [cited 3 July 2015].
25. WHO, Geneva. *Policy Perspectives on Medicines: Equitable Access to Essential Medicines – WHO Framework:* March 2004.
26. Bastias G et al, "Policy Brief, Financing Options for the treatment of rare diseases in Chile", Santiago, Chile: EVIPNET-Chile, June 30, 2011.
27. WHO, Geneva. WHO Medicines Strategy: Framework for Action in Essential Durgs and Medicines Policy - 2000-2003, 5.2 Access: *Ensure equitable availability and affordability of essential drugs, with an emphasis on diseases of poverty.* http://apps.who.int/medicinedocs/en/d/Jwhozip16e/8.2.html#Jwhozip16e.8.2. (accessed 15 August 2015).
28. Brahma D, Marak M, Wahlang J. Rational Use of Drugs and Irrational Drug Combinations. *The Internet Journal of Pharmacology.* 2012;10(1). http://ispub.com/IJPHARM/10/1/14081 (accessed 3 July 2015).
29. Sharma A, Jacob A, Tandon M, Kumar D. Orphan drug: Development trends and strategies. *Journal of Pharmacy and Bioallied Sciences.* 2010;2(4):290-299. doi:10.4103/0975-7406.72128 (accessed 3 July 2015).
30. WHO, Geneva. *WHO Medicines Strategy 2004-2007*. WHO, Geneva. WHO/EDM/2004.5.
31. IMS Institute for Healthcare infomatics,. *The Global Use of Medicines: Outlook Through 2016*. 11 Waterview Boulevard, Parsippany, NO 07054, USA. ://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMSInstitute for Healthcare Informatics/Global Use of Meds2011/Medicines_Outlook_Through_2016_Report.pdf (accessed 01 August 2015).
32. WHO, Geneva, *The Pursuit of responsible use of medicines: Sharing and Learning form Country Experiences*, WHO/EMP/MAR/2012.3. Technical Report prepared for the Ministers Summit. 2012.
33. WHO, Geneva, *Progress in the rational use of medicines*, Sixtieth World Health Assembly A60/24, 22 March 2007. http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_24-en.pdf (accessed 3 July 2015).
34. Winegarden, W. *A Primer on the Orphan Drug Market: Addressing the Needs of Patients with Rare Diseases* October 2012. www.pacificresearch.org (accessed 3 July 2015).
35. Dr. Deena Class et.al, *Health Financing Profile Guatemala*, World Bank, Washington, July 2014
36. Song P, Gao J, et al, Rare diseases, *orphan drugs and their regulationin Asia: Current status and future perspectives*, Department of surgery, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan, Policy Forum. 2012. DOI: 10.5582/indr.2012.v1.1.3 (accessed 3 July 2015).

37. Kerstin Westermark. Regulating Orphan Drugs in Europe, *European Oncology Nursing Society.* EONS Magazine, 2013 Autumn, Pg. 24-26. http://www.cancernurse.eu/documents/magazine/2013Autumn/EONSMagazine2013AutumnPage24.pdf (accessed 15 August 2015).
38. Instituto Guatemalteco de Seguridad Social; Lista de medicamentos. http://www.igssgt.org/ (accessed 3 July 2015).
39. WHO, Geneva. Chapter 4. Access to essential medicines. In: *Monitoring the Building Blocks of health System. A Handbook of Indicators and their Measurement Strategies*; 2010. Pg 60-70 http://www.who.int/healthinfo/systems/WHO_MBHSS_2010_section4_web.pdf?ua=1 (accessed 18 July 2015).
40. Perfil Farmacéutico de la REPÚBLICA DE GUATEMAL, Publicado por el Ministerio de Salud Pública y Asistencia Social de Guatemalaen colaboración con la Organización Panamericana de la Salud/OrganizaciónMundial de la Salud (OPS/OMS), Marzo de 2012.
41. rarediseaseday.org. *Rare Disease Day In Guatemala,* http://www.rarediseaseday.org/country/gt/guatemala (accessed 3 July 2015).
42. Asociación Para Todos. *Mas sobre las Enfermedades Raras en Guatemala,* Youtube video. HTTPS://WWW.YOUTUBE.COM/WATCH?V=ZAWVTWJXHTA: (accessed3 July 2015)
43. Gliklich R, Dreyer N, Leavy M, eds. *Registries for evaluating Patient Outcomes: A User's Guide.* Third edition. Two volumes. AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality; April 2014. http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm. (accessed 22 July 2015).
44. Pedro Franco, drugs: the regulatory environment: Drug Discovery Today, European Medicines Agency, London, UK, Orphan, *ELSEVIER* Volume 18, Issues 3-4, February 2013, Pages 163-172.
45. Sukirti Bagal, Patient Advocacy Group and Patient Registries: An Overview. *NORD National Organization for Rare Disorders*, Inc. Power point presentation. Day one-SessionvIV. (accessed 18 August 2015)
46. Simoens Steven, Pricing and reimbursement of orphan drugs: the need for more transparency, *Orphanet Journal of Rare Diseases* 2011, 6:42. http://www.ojrd.com/content/6/1/42 (accessed 20 July 2015).
47. Rollet P, Lemoine A, Dunoyer M, Sustainable rare diseases business and drug access: no time for misconceptions, *Orphanet Journal of Rare Diseases* 2013, 8:109, http://www.ojrd.com/content/8/1/109 (accessed 20 July 2015).
48. Orphanet, *The portal for rare diseases and orphan drugs. Emergency Guidelines,* http://www.orpha.net/consor/cgi-bin/Disease_Emergency.php?lng= (accessed 29 July 2015).
49. S. van Weely, Prof. H.G.M. Leufkens. *Priority Medicines for Europe and the World "A Public Health Approach to Innovation".* Background Paper 6.19, Rare Diseases. Update on 2004 Background Paper. 12 March 2013.
50. Wayne Critchley, *A Strategy for Rare Diseases in Canada. Where are we now? What else is needed?* Powerpoint presentation. CORD Board of Directors, http://www.slideshare.net/raredisorders/wayne-critchley-strategy-for-rare-diseases-in-canada-present?next_slideshow=1. (accessed 29 July 2015).
51. Vegter S, Rozenbaum MH, Postema R, Tolley K. Postma MJ. *Review of Regulatory Recommendations for Orphan Drug Submissions in the Netherlands and Scotland: Focus on the Underlying Pharmacoeconomic Evaluations*, Unit of PharmacoEpidemiology & Pharmacoliconomics, University of Groningen, the Netherlands; Tolley Health Economics Lid., United Kingdom and University Medical Centre Groningen, the Netherlands. 2010 Aug;32(9):1651-61. doi: 10.1016/j.clinthera.2010.08.006. (accessed 20 July 2015).
52. WHO, Geneva. Resolution WHA64.9, *Sustainable health financing structures and universal coverage*, Geneva, World Health Organization; may 2011.
53. Holloway K, Department of Essential Medicines and Pharmaceutical Policy, WHO, *Presentation on Rational use of drugs: An Overview,* November 2009. http://apps.who.int/gb/ebwha/pdf_files/A62/A62_23- en.pdf (accessed 3 July 2015).

54. WHO, Geneva, *Report on the 12th Expert Committee on the Selection and Use of Essential Medicines*, Geneva, 2002. http://whqlibdoc.who.int/trs/WHO_TRS_914_eng.pdf?ua=1 (accessed 25 July 2015).
55. WHO, Geneva. The Selection and use of Essential Medicines, *WHO technical Report Series 933, Report of the WHO Expert Committee, 2005* (including the 14th Model List of Essential Medicines), P 4, 5. http://archives.who.int/medicines/services/expertcommittees/essentialmedicines/TRS933SelectionUseEM.pdf (22 July 2015).
56. WHO, Geneva, *WHO moves to improve access to lifesaving medicines for hepatitis C, drug-resistant TB and cancers*. News release 8 May 2015, Geneva. http://www.who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/ (accessed 22 July 2015).
57. van den Ham Rianne, *Selection of Essential Medicines- a background paper for the World Medicines Situation 2010 report*, Universiteit Utrecht, the Netherlands, WHO Collaborating Centre for Pharmacoepidemiology and Pharmaceutical Policy Analysis., September 2009.
58. Kaplan Warren, Colin Mathers, *The World Medicines Situation 2011, Global Health Trends: Global Burden of Disease and Pharmaceutical Needs*, Boston University School of Public Health, Department of Health Statistics and Informatics, WHO, Geneva, 2011.
59. Balczar E,Tomiwa AF, Kovacs N, Varga O, *Analysis of how research funding is allocated to a wide variety of projects on rare diseases* - a case study. Affiliation: Department of Preventive Medicine, Faculty of Public Health, University of Debrecen. http://www.rare-diseases.eu/wp-content/uploads/2013/08/232_t3.pdf (accessed 22 July 2015).
60. WHO, Geneva. The rational use of drugs. *Report of the Conference of Experts, Nairobi, WHO, Nov 1985*. http://apps.who.int/medicinedocs/documents/s17054e/s17054e.pdf (accessed 3 July 2015).
61. WHO, Geneva, Hai Global, *Measuring medicine prices, availability, affordability and price components,* Second Edition, WHO/PSM/PAR/2008 (accessed 3 July 2015).
62. Congreso de la República de Guatemala. Decreto Legislativo 90-97, Código de Salud 1997. http://webcache.googleusercontent.com/search?q=cache:http://www.ccad.ws/documentos/legislacion/GT/DL-90-97.pdf (accessed 3 July 2015).
63. Cameron A, Margaret E, Martin A, Dele A, *The World Medicines Situation 2011, Medicines prices, availability and affordability*. 3rd Edition. WHO, Geneva, HAI; 2011.
64. Cohen JP, Felix A , Are payers treating orphan drugs differently, Journal *of Market Access and Health Policy. 2014. Vol 2.* Tufts center for the study of drug development, Boston, MA, USA. http://www.jmahp.net/index.php/jmahp/article/view/23513 (accessed 20 July 2015).
65. Hadjivasiliou Andreas, EvaluatePharma, Orphan Drug Report 2014. EvaluatePharma.com (accessed 3 July 2015).
66. Ford Nathan, Patents, Access to Medicines and the Role of Non-Governmental Organisations. *Journal of Generic Medicines:* The Business Journal for the Generic Medicines Sector January 2004 1: 137-145, doi:10.1057/palgrave.jgm.4940005 (accessed 18 July 2015).
67. Central America Data.com. *Bill on Medicines and Prices*, Tuesday, May 6, 2014. http://en.centralamericadata.com/en/article/home/Guatemala_Bill_on_Medicines_and_Prices (accessed 18 July 2015)
68. Picavet E, Morel T et al, Shining a light in the black box of orphan drug pricing, *Orphanet Journal of Rare Diseases*, 2014, 9:62. http://www.ojrd.com/content/9/1/62 (accessed 3 July 2015).
69. Critchley Wayne, CORD Board of Directors, Canadian Organization for Rare Disorders (CORD), *A Strategy for Rare Disease in Canada. Where are we now and What else is needed?* , Powerpoint presentation. http://www.slideshare.net/raredisorders/wayne-critchley-strategy-for-rare-diseases-in-canada-present?next_slideshow=1 (accessed 22 July 2015).
70. Central AmericaData.com. *Guatemala: Free Competition on Medicines.* http://en.centralamericadata.com/en/article/home/Guatemala_Free_Competition_in_Medicines (accessed 18 July 2015).

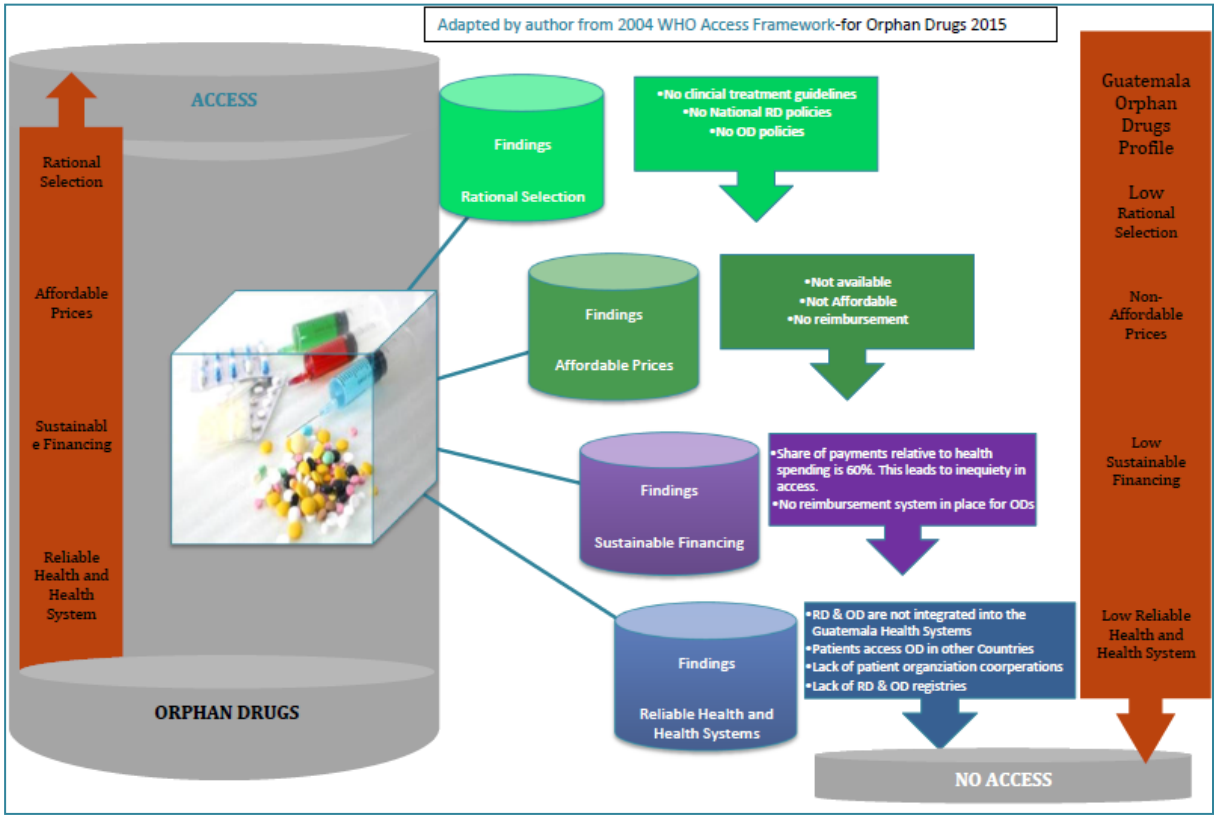
71. WHO, Geneva. Guatemala: Country Cooperation Strategy at a Glance. http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_gtm_en.pdf (accessed 18 July 2015).
72. Harvard School of Public Health. *Health Financing in Guatemala: A Situation Analysis and Lessons from Four Developing Countries.* Final Report, June 30, 2009. https://www.hsph.harvard.edu/ihsg/publications/pdf/GuatemalaFinancingAnalysisLessons7.23.09.pdf (accessed 18 July 2015).
73. USAID, *Health System Report:* https://www.hfgproject.org/resources/health-systems-database/country-profiles/guatemala/ (accessed 18 July 2015).
74. Anson A, Ramay R, Ruiz de Esparza A, and Bero L: *Availability, prices and affordability of the World Health Organization's essential medicines for children in Guatemala*, Globalization and Health July 2012, 8:22 .
75. Bastias G et al*, "Policy Brief, Financing Options for the treatment of rare diseases in Chile",* Santiago, Chile: EVIPNET-Chile, June 30, 2011. http://www.who.int/evidence/resources/policy_briefs/PBChileFinancing.pdf (accessed 5 August 2015).
76. Gobierno de Guatemala Ministerio De Salud Pública y Asistencia Social MSPAS, http://www.mspas.gob.gt/index.php/en/(accessed 18 July 2015).
77. WHO Resolution WHA58.33, *Sustainable health financing, universal coverage and social health insurance*, Geneva, World Health Organization, may 2005.
78. Bethesda, Abt Associates Inc. Health Systems DatabaseHealth Finance and Governance Project 2013. *Health Systems Report: Guatemala.* https://www.hfgproject.org/resources/health-systems-database/country-profiles/guatemala/: (accessed 3 July 2015).
79. Deloitte Touche Tohmatsu Limited, 2015 *Global life sciences outlook Adapting in an era of transformation.* www.deloitte.com/lifesciences. (accessed 05 August 2015).
80. International Federation of Pharmaceutical Manufacturers & Associations (IFPMA): *THE PHARMACEUTICAL INDUSTRY AND GLOBAL HEALTH; FACTS AND FIGURES 2014*, http://www.ifpma.org/fileadmin/content/Publication/2014/IFPMA_-_Facts_And_Figures_2014.pdf (accessed 18 July 2015).
81. WHO, Geneva, *WHO Model List of Essential Medicines, 19th List* (April 2015, Amended June 2015). http://www.who.int/medicines/publications/essentialmedicines/en/, Assessed on 25 July 2015 (accessed 22 July 2015).
82. WHO, Geneva. Global *Health Expenditure Database, National Health Account NHA indicators Guatemala*, Geneva, http://apps.who.int/nha/database/ViewData/Indicators/en (accessed 01 August 2015).
83. Orphanet, Rare Disease Registries in Europe. *Orphanet Report Series, Rare Diseases Collection, January 2015.* http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf (accessed 01 August 2015).
84. WHO, Geneva. *The world health report 2010. Health systems financing: the path to universal coverage*. Geneva, World Health Organization; 2010.
85. Christina Lao Pena, *Improving Access to health Care Services through the Expansion of Coverage Program (PEC): The Case of Guatemala*, World Bank, Washington DC, January 2013.
86. Stolk P, Willemen Marjolein JC, Leufkens Hubert GM, *'Rare Essentials': Drugs for rare diseases as essential medicines*, Bulletin of WHO September 2006; 84:745-751.
87. Ye Lu, Hernandez P, Abegunde D, Edejer T. WHO, Medicines Expenditure. *The World Medicines Situation 2011.* 3rd Edition. WHO, Geneva 2011. http://www.who.int/health-accounts/documentation/world_medicine_situation.pdf (accessed 18 July 2015).
88. Parker Samantha, *Global registries for rare diseases: challenges and solutions*. Power point presentation Orphan Europe Recordati Group, EUCERD, International Rare Disease Consortium (IRDiRC) member http://www.slideshare.net/KidneyOrgRu/103-rare-disease-registries-samantha-parker-eng?from_action=save. (accessed 29 July 2015).
89. Department for International Development (DFID). *Increasing access to essential medicines in the developing world*: United Kingdom Government Policy and Plans, London. Department for International Development; June 2004.

90. Emmanuelle Lecomte, *Development of International Orphan Drug Policies*, VP, Head International Regulatory Strategy, Powerpoint presentation. 8 May 2014. http://www.rare-diseases.eu/wp-content/uploads/2014/05/0401_Emmanuelle_LECOMTE-BRISSET.pdf . (accessed 15 August 2015).
91. Canadian Organization for Rare Disorders, *Canada's Orphan Drug Policy: Learning from the Best*.http://www.raredisorders.ca/documents/CanadaOrphanDPFinal.pdf, (accessed 15 August 2015).
92. Henkel J, *"Orphan Drug Law Matures into Medical Mainstay"*. FDA Consumer. U.S. Food and Drug Administration; 1999.
93. Gayatri R. Rao, Orphan Drug Designation 101 (Rao Presentation), Director, FDA Office of Orphan Products Development; Oct.12, 2012. athttp://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/OOPDNewsArchive/UCM324031.ppt (accessed 22 July 2015).
94. Forrest Christopher B, Bartek Ronald J, Rubinstein Y, Groft Stephen C. *The case for a global rare-diseases registry*, The Lancet, 26 March 2011, Volume 377, No. 9771, p1057-1059.
95. Ministerio De Salud Pública y Asistencia Social MSPAS. Acuerdo Gubernativo 744-99. Reglamento para el Registro y Control de Productos Farmacéuticos y Afines.1999. http://www.who.int/medicines/areas/coordination/pscp_guatemala_sp.pdf (accessed 3 July 2015).
96. WHO, Geneva. *Guatemala Health Financing,* WHO 2010, http://apps.who.int/nha/atlasfinal.pdf (accessed on 3 July 2015).
97. WHO, Geneva. Millennium Development Goals (MDGs). http://www.who.int/topics/millennium_development_goals/about/en/ (accessed 18 July 2015).
98. Alvarez W. Country presentation. *Presented at the WHO workshop on traditional and indigenous medicine in the Americas*, Guatemala City, Guatemala, 18–23 March 2001.
99. Cam, Y.Le and Tejada P. European Organisation for Rare Diseases (EURORDIS). Rare diseases: A hidden priority - *OECD Observer,* October 2010. No. 281. http://www.oecdobserver.org/news/fullstory.php/aid/3337/Rare_diseases_:_A_hidden_priority.html (accessed 3 July 2015)
100. Arnold RJG, Bighash L, Bryón Nieto A, *et al. The role of globalization in drug development and access to orphan drugs: orphan drug legislation in the US/EU and in Latin America* [v1; ref status: indexed, http://f1000r.es/3ix] *F1000Research* 2015, 4:57, doi: 10.12688/f1000research.4268.1 (accessed 18 July 2015)
101. Ellen R. Shaffer and Joseph E. Brenner. *A Trade Agreement's Impact on Access to Generic Drugs. Health Affairs* , 28, no. 5 (2009): w957-w968. (published online August 25, 2009; 10.1377/hlthaff.28.5.w957). http://content.healthaffairs.org/content/28/5/w957.full.pdf+html (accessed 18 July 2015).
102. WHO, Continuity and Change: *Implementing the third WHO Medicines Strategy*, 2008-2013. WHO, Geneva, 2011. WHO/EMP/2009.1.

ANNEX 1. ACCESS TO MEDICINES FRAMEWORK REFERENCED

Figure 2.*WHO Equitable Access to Essential Medicines Framework*
Source: www.who.com
[Accessed on May 2015]

ANNEX 2. ACCESS TO ORPHAN DRUGS IN GUATEMALA–*Study Findings (Gaps)*



ANNEX 3. CURRENT LEGAL DECREE FOR THE TREATMENT OF RARE DISEASES IN GUATEMALA– REFERENCED

GENERAL OFFICE OF HEALTH REGULATION, SUPERVISION AND CONTROL
DEPARTMENT FOR THE REGULATION AND CONTROL OF PHARMACEUTICAL AND RELATED PRODUCTS
3era calle final 2-10 Colonia Valles de Vista Hermosa Zona 15. Tel: 23656255-60 Guatemala, C.A.

Ministry of Public Health and Social Assistance

Guatemala, January 20, 2008.

MINISTRY OF PUBLIC HEALTH AND SOCIAL ASSISTANCE, DEPARTMENT FOR THE REGULATION AND CONTROL OF PHARMACEUTICAL AND RELATED PRODUCTS

WHEREAS:

According to section 177 quinquies of the Intellectual Property Law and its amendment through Congressional Decree 11-2006 of the Republic of Guatemala, the corresponding administrative authority will apply measures directed to avoiding the commercialization of a Sanitary Registry for a patent protected product, without the patent holder's proper authorization;

WHEREAS:

It is necessary to have a database containing patents that are registered and currently in force in the country, made up of the patents object of protection; this database will consist of the information presented by the patent holders and may be consulted by the interested parties, providing information on patents that are currently in force in the chemical field that shall include pharmaceutical products or their approved uses and to provide the protection of intellectual property established by Law;

THEREFORE:

In exercise of the powers conferred by Section 35, literal a), of Government Agreement number 115-99, Internal Organic Regulation of the Ministry of Public Health and Social Assistance and according to that stated by Section 177 quinquies of the Intellectual Property Law;

THE MINISTRY AGREES:

To issue the following:

REGULATION No. 55-2008 Creation of an Invention Patent Database Covering Products Object of Intellectual Property Protection

Section 1. The Department for the Regulation and Control of Pharmaceutical and Related Products creates a database of patents currently in force in the country that covers pharmaceutical products or the approved use of such, which is made up of information presented by patent holders, their legal representatives or agents in the country.

Section 2. The Department calls for all patent holders requesting intellectual property protection to present the following written information, signed and sealed by the legal representative, in the case of legal entities, or the name of the owner:

a) Registration Certificate of the patent in the Intellectual Property Registry of Guatemala, issued within a maximum period of thirty calendar days as of its date of submittal;
b) Identification of the approved molecule, product or use;
c) International Common Denomination (DCI for its initials in Spanish);
d) Identification of the Trademark with which the approved product or products, if any, are or will be commercialized, and the corresponding Sanitary Registry numbers, if any;
e) Patent holder's full name;
f) Name of the patent holder's Legal Representative or Agent in Guatemala;
g) Indication of the address of service in the country; and
Special observations added due to their importance.

Section 3. Once the certificate has been received, the Department will update the database and provide the information to all users through physical or electronic means. The Department will establish the procedure to access the information.

Section 4. The Department will be responsible for the database management, guaranteeing its reliability, integrity and security.

Dr. Jorge Alejandro Villavicencio Álvarez
Head of the Department for the Regulation and Control
of Pharmaceutical and Related Products