The Entry of New Oncological Medicinal Products in Colombia Concerning Patient, Government and Industry Interests and How the Quality of the Regulatory Affairs Environment Can Be Used as a Tool for Ensuring Access to the Market of Innovative Medicines.

Wissenschaftliche Prüfungsarbeit
Scientific Thesis

zur Erlangung des Titels
to Obtain the Degree

“Master of Drug Regulatory Affairs”

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn
at the Faculty of Mathematics and Natural Sciences,
Rhenish Friedrich-Wilhelms-University Bonn (Germany)

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Bonn 2015

So eine Arbeit wird eigentlich nie fertig, man muß sie für fertig erklären, wenn man nach Zeit und Umständen das Mögliche getan hat

A Work as this is never finished, one must simply declare it finished when one has within limits of time and circumstances done what is possible.

Johann Wolfgang von Goethe

(1749 – 1832)

Erster Referent: Dr. Josef Hofer
Zweiter Referent: Dr. Santiago Figueroa-Perez

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LIST OF ABBREVIATIONS

ATPA	Andean Trade Preference Act
ATPDEA	Andean Trade Promotion and Drug Eradication Act
CHMP	Committee for Medicinal Products for Human Use
CNPMDM	Comision Nacional de precios de medicamentos y dispositivos medicos (National Commission for Medicinal products and Medical Devices Pricing)
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
EDQM	European Directorate for the Quality of Medicines
EFS	Event-Free Survival
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPS	Entidades prestadores de salud (Health Insurance Companies)
EU	European Union
FDA	Food and Drug Administration
FOSYGA	Fondo de solidaridad y garantia (Resources of Solidarity and Guarantee)
GMP	Good Manufacturing Practices
IETS	Instituto de evaluación tecnologica en salud (Institute of technological evaluation in health
INVIMA	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (National Institute for the Vigilance of Medicinal Products and Food)
INN	International Nonproprietary Name
IPS	Instituciones prestadoras de salud (Health Provider Institutions)
LoA	Letter of Authorization
MAA	Marketing Authorization Application
MSPS	Area de financiamiento del Ministerio de Salud y Protección Social (Financing area from the health ministry)
NCE	New Chemical Entities
NME	New Molecular Entities
ORR	Overall Response Rate
OS	Overall Survival
PFN	Politica Farmaceutica Nacional (National Pharmaceutical politic)
PFS	Progression-Free Survival
POS	Plan obligatorio de salud (Obligatory Health Plan)
SEMPB	Sala especializada de medicamentos y productos biologicos. (Revising Commision of Pharmaceutical Products)
SGP	Generalized Preferences System
TLC	Tratado de libre comercio (Free Trade Agreement)
UPC	Unidad de Pago por Capitación (Unit of Payment by Capitación)
US	United States of America
UPC	Unidad de pago por capacitación (Unit of payment by qualification)

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1. INTRODUCTION

The aim of this Master Thesis is to evaluate how oncological medicinal products are introduced in the market in Colombia, explaining the general considerations for registration of them and the relevant laws influencing this process, how the approval behavior of oncological medicinal products has been from 2010 to 2014 (establishing a comparison with the decisions taken in two of the most important Health authorities worldwide, EMA from Europa and FDA from the United States) and to evaluate how the quality in the local Regulatory Affairs Environment can be used as a tool for ensuring the entry of innovative and necessary medicinal products with a good benefit/risk relationship, taking into account the interest of patients, government and pharmaceutical industry.

Other topics influencing indirectly the entry of oncological medicinal products will also be analyzed, within Health System, Health Reforms and Free Trade agreements with The United States are included.

Furthermore, there is a need to discuss the conflict of interests between pharmaceutical companies, Government who act as public payer, physicians and patients in Colombia. Pharmaceutical companies aim to maximize profit and cover development costs in order to be able to investigate in other innovative developments. Public players are involved with a need to protect their budgets while providing access to medicines to as many people as possible. Last but not least, physicians must also be considered. Their objective is to provide the best healthcare possible, regardless of the associated cost, which also corresponds to the patients' expectation.

As political, economic and scientific aspects are influencing the entry of medicinal products in Colombia, the complexity of the topic is very high and all three aspects are connected, The main goal is to analyze from the scientific point of view, how the quality of the Regulatory Affairs Environment can be used as an effective tool for guaranteeing the access of innovative safe, effective and cost-effective oncological medicinal products to patients without creating unnecessary barriers while considering the fairest solution for the parties involved.

It is, of course, considered to be a difficult task to find "the fairest solution", as what can be seen as fair from the government's point of view may not match the expectations of the industry or the physicians' or patients' opinions and vice versa.

Aspects like resource availability are an important factor. "A government has the duty to ensure Health as a fundamental right but as the resources are limited, a good process has to be implemented to ensure that everything what is excluded is accepted and legitimate for the society" (Ronderos, 2009).

"No country in the world can provide their citizens with the best medicinal alternative existent in the world at the moment but the best possible within that, that according to the economic and human resources is available". (Ronderos, 2009)

2. SCOPE

The scope of this thesis includes the Colombian population, the Colombian government and the Industry. Involved parties that play a role with respect to oncological medicinal products.

3. COLOMBIA: AN OVERVIEW OF THE CURRENT HEALTH SYSTEM AND RELATED TOPICS FOCUSSING ON THE ENTRY OF ONCOLOGICAL MEDICINAL PRODUCTS

Clarifying how the health system is set up in Colombia will ultimately help to understand its influence on the entry of oncological medicinal products in the market. The problems faced by the Colombian health system regard the need to provide access of innovative medicinal products to patients while at the same time considering the budget available and the interest of the industry.

3.1. Background: Current Healthcare System in Colombia and Access to Medicines

The Health System in Colombia is regulated by the State through the support of the "Ministry of Health and Social Protection" (Ministerio de la Salud y Protección Social).

It is necessary to provide some historical background in order to be able to understand the changes through time and the reasons for that: the National Constitution of Colombia was reformed in 1991, which led to the reform of the general system of Social Security, through the implementation of the Law 100.

The Colombians' Health System depends on the article 48 from the National Constitution, which states that Social Security is a public service of mandatory character that will be provided by the State to their citizens in accordance with the principles of efficiency, universality and solidarity. (ConstitucionPolitica, 1991)

The general system of the Social Security is regulated by the Law 100, dated 23 Dec 1993. (Ley 100 de 1993) and the Health System is specifically regulated in the

second book (Segundo libro) of the same law. (Ley100, 23.12.1993) (ConstitucionPolitica, 1991)

This last reform of the Health System mentioned above aimed to avoid the monopoly of the State over the Health System and to allow competition by including health insurance companies (EPS "Empresas prestadoras de salud") as a decentralized model.

Additionally, the law 100 established fundamental rules governing the public Health System such as fairness, obligatory nature, integral protection, free choice, autonomy of the institutions, administrative decentralization, social participation and quality. (ConstitucionPolitica, 1991)

The health system is integrated as follows: the state, the health insurance companies (entidades promotoras de salud EPS) and the health providers' institutions (Instituciones prestadoras de salud IPS). (ConstitucionPolitica, 1991)

The state acts by coordinating, directing and controlling the health system. The health insurance companies (EPS) are private and public entities that act as intermediaries and administrators of the resources that the state provides. The health providers institutions (IPS) are the hospitals, clinics, laboratories, and so on that directly provide the services to the users for health recovery or prevention of illness.

There are two types of affiliation with the health system, through the contributing regime and through the subsidized one. In the contributing regime all the people affiliated have a job contract and are public workers or independent workers with possibility of payment or pensioners. They pay monthly health care insurance (EPS) and these contracts, as well with the IPS to provide the services or give it directly. The monthly amount paid is equal to 12.5 % of a person's base salary**.** (Wikipedia, 2014)

In the case of the subsidized regime, people without work or the capacity to contribute to the system (earning less than two minimal salaries) receive total or partial subsidies with transferences from the government and from the Solidarity and guaranty institution (Fondo de Solidaridad y garantia FOSYGA). (Wikipedia, 2014).

Futher,it is to be taken into account that in the law 100 is the concept of listing essential medicinal products has been incorporated as a part of the obligatory health plan (POS "Plan obligatorio de Salud"). The POS states the minimal services (activities, procedures, health interventions, hospital services, medicinal products) that must be offered according to the rights of the users to protect, prevent and be cured in case of illness. Additionally the National Commission for Medicinal Products prices (CNPM "Comision Nacional de precios de medicamentos") together with the national institute for evaluation of medicinal products and food (INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos) where created. (PFN, 2012) (Gaviria Uribe, 2014)

Before 01 July 2012, the benefit plans (POS) for the subsidized regime and the contributing one were unfortunately different, having that citizens affiliated to the

contributing regime acquired better quality and quantity of services which included of course access to the oncological medicinal products. As this was generating an unequal situation depending on the social class, a measure to unify the POS for both regime took place starting on 01 July 2012. By now, independent of the regime citizens belong to, they are supposed to receive the same quality and quantity of services included in the POS. (Minsalud, 2012). The reality shows that unfortunately, still efforts should be made in this regard as the aim to offer the same quality for both regime has not been achieved and the citizens affiliated to the subsidized regime suffer under the inefficacy of the system.

Moving on to the alternatives that patients have in order to get access to services (medicinal products) not included in the POS, is necessary to understand that after a no POS service has been prescribed by the physician, the physician should submit a formal request to the EPS in order to get the authorization for the provision of it to the patient. Such a request should justify the need of the no POS service based on the fact that it is authorized or approved for its use, that the manual for assessing of the prescription has been consulted and that there is an imminent health risk for the patient. This request is further sent for evaluation to a committee called technic-scientific committee by the EPS, who will decide on the authorization or not of the service. In case that the no POS service get denied by the technic scientific committee, or that the decision is delayed, the patients have the alternative of applying for Judgments of defense (Tutelas) in order to obtain access legally. This Tutela is a protection mechanism for the right health that has been widely used to request immediate protection of the constitutional rights when those have been harmed or threatened by the action of omission from any public authority. This alternative option is heavily criticized by the government as additional budget has to be provided for covering the No POS services and a health collapse can take place from having to provide resources and services not included in the POS therefore diminishing the general cover. (Londoño Soto, 2012) (Palacio Betancourt, 2008) (Betancourt, 2008)The problem mentioned above includes the additional scenario, where the physicians aim is to have a free exercise of the profession based on their criteria of what is the best for the patient which include also No POS services, this puts in doubt the existence of a conflict of interest, due to the fact that the pharmaceutical industry can have an influence on the decisions that physicians do.

Finally, it should be mentioned that regarding the price and reimbursement situation in Colombia, the situation is described as follows:

Prices of all medicines in Colombia are controlled by the National Pricing Commission for Medicines and Medical Devices (CNPMDM), established in 1993 and further enforced by law in 2011 . Medicines are thus classified into the following two pricing schemes depending on the level of market competition and the difference between the national proposed wholesaler selling price, and the national reference prices defined by the CNPMDM:

- free price system: All medicines are in principle in this scheme as long as they belong to a homogeneous group, in which at least 3 suppliers exist for the products within the group, and the retailer price is equal or less than the reference price of the corresponding homogeneous group. The manufacturer of the medicines, as well as all participants in the supply chain can freely set the prices for these medicines but must report the selling price at each level of the supply chain quarterly to the Information System for Medicines pricing (SISMED).

- Direct pricing control: Medicines with limited level of market competition and / or higher price than the reference prices are subject to direct pricing control and their maximum selling price is defined by the CNPMDM without exceeding the reference price. (Amaya Rodriguez, 2015) (CNPMDM, 2013)

Theoretically, a drug product entering the free price system remains in this system for one year, until the Commission determines whether an abuse in pricing exists, in which case it is transferred to a direct control system. If no abuse is detected, the drug shall remain on the free price system. (CNPMDM, 2013)

Reality shows even though that pricing control is having deficiencies in Colombia. It becomes evident when Colombia appears as one of the countries with higher prices in Latin America of Medicinal Products. (Semana, 2015)

Regarding reimbursement is to be mentioned that as mentioned previously there is a obligatory health plan POS which is a positive list including the services that are to be covered by the national health system, which means, are to be covered by the EPSs with the resources provided by the state in the form of UPC (Unit of Payment by Capitación), which corresponds to the quantity of resources that EPSs receive per each afiliated by the goverment. Medicines or procedures not included in the POS can be reimbursed by the Fund of Solidarity and Assurance FOSYGA to the Health Institutions upon a formal request to the Ministry of Health, which is assessed by Technical Scientific Committee as previously explained. (Amaya Rodriguez, 2015)

All of the above will have a direct influence on the access to patients of medicinal products which may in turn be extrapolated to the aim of this thesis which is the specific evaluation of the access to oncological medicinal products.

The original idea of the explained last reform (with the inclusion of the law 100) was to create a health system where the health being decentralized through the EPSs could avoid the establishment of monopoly and get more efficient through the decentralization, even though reality demonstrates that the mentioned Health system doesn't necessarily give a solution to the problem of the deficiency of the health system. It creates barriers for the access between the users and the IPS and due to corruption has conducted to lose in the budget destined to health in the country. The corruption aspect can be mainly explained by the fact, that EPSs receive a specific amount of money from the government for each affiliated citizen. This amount of money should be aimed to cover the Health services required by the affiliated and is expressed as UPC as previously explained. The fact is, that in most cases EPSs were refusing to cover all the established needs of the affiliated and in this way

health resources got lost. The aim to achieve the universality in the access to health services has unfortunately not been reached until now, due to the many problems with the system operation as such.

Additionally the price control based on the free pricing that should get auto regulated by the competition and the free game of market did not achieve its goal, which can be reflected on the fact that Colombia is one of the countries with the most expensive medicinal products in Latin America and is one of the countries with less efficacy on the price policy as explained above. In 2006, during the government of Alvaro Uribe Velez (2002-2010) authorities gave free way to companies for the establishment of the prices of medicinal products, which used this advantage to get the maximal profit possible. The medicinal product Novoseven for hemophilia had as a median price in 21 countries of approximately 1000 dolars while in Colombia it achieved 5600 dollars (Semana, 2015)

Even the medicinal products that should be under direct price control due to the lack of competition are not being controlled properly.

What is especially critical are the medicinal products for the treatment of cancer as due to their high prices there is a risk that the patients cannot get access to them as they have a big impact on the financial sustainability of the health system and costs are untenable. One example of it can be reflected in the case of imatinib, a medicinal product for the treatment of LMC that due to the lack of competency and price control has generated in the last 6 years costs for 392.962 millions pesos (Silva Numa, 2015)

3.2. Agreements With The United States of America; A Challenge for the Adaptation of Regulatory Environment

In the last decade, Colombia's foreign trade policy was based on expanding trade relations with the Andean community and the efforts to obtain unilateral access to certain markets, especially through the United States, using schemes such as ATPA/ATPDEA and SGP scheme via the European Union. (MINCOMERCIO)

Due to the increasing diversity between exports and imports, imports being the majority for Colombia, it became evident that there is a need to promote important changes in commercial policy. For example to find new markets and free trade agreements such as one negotiated with the USA (TLC) which was a bilateral agreement. After the last extension of the ATPDEA in 2010, which finalized the 15 of February of 2011 the TLC was established to promote the long term investment, increasing the productive capacity for exports and, in time, stability and increased conditions. (MINCOMERCIO)

The TLC is an agreement with the aim to create Jobs and to improve the performance of the national economy. The topics negotiated were considered as

general and included: access to the market, in their two slopes (industrialist and agriculturist); intellectual property, regime of the investment, purchases of the state, competition, electronic commerce, services, ambient and labor.

To understand the aim of this Thesis, the comprehension of these agreements is especially important. It is imperative to take into account that intellectual property and competition are some of the main points included in the negotiation between Colombia and the United States of America and will have a direct influence on the entry of medicinal products to the Colombian market.

Intellectual property includes the rules for suitable and effective protection of the rights of the innovation and the purpose is the facilitating of the commerce from intangible goods. The objective of intellectual property is to stimulate and to protect intellectual creativity, the generation of knowledge and investigation as well as the development of the arts and the letters, promoting the scientific and cultural advances at the same time as it maintains a balance in front of the access to the technology and the new knowledge on the part of the users. The protection to the intellectual property is a right of constitutional rank in Colombia. (MINCOMERCIO)

In regard to the TLC many different opinions arise. Some entities are of the opinion that several dispositions (PI rights for example) included in the free trade agreement (TLC) have a negative impact on the public health which can be understood if taking into account that the PI rights increase the average price of medicinal products in Colombia. Specifically, the chapters of intellectual property are very sensitive as they help to maintain the monopoly of the pharmaceutical industry and can increase the prices of medicinal products between 12% and 68% according to the determinations of the United Program Nations for the Development (PNUD). This needs to be considered in a health system like the Colombian one, which is facing a financial crisis. Higher prices of medicinal products result in a barrier for the equitable access to medicines and, therefore, for the effective exercise of the right to the health. (Ernesto Cortés, et al., 2012) (Silva Numa, 2014)

The TLC increases the monopoly in the market when incorporating in its dispositions the figure of the protection with data exclusivity that proves the security and effectiveness of a medicine. In Colombia, this protection is 5 years and exists from year 2002 under the figure of decree 2085 (Ernesto Cortés, et al., 2012).

The TLC with the United States incorporates IP rights to the obligations of Colombia, obligations that when being in a TLC and not in a decree will not be easily modified.

The particular interests of the multinational pharmaceutical industry with presence in Colombia and its will to press the Colombian Government so that it is adapted to his will, can be observed year after year. An example of this pressure is reflected for example in the letter that the U.S. Vice-president Sr Joseph R.Biden sent to the Colombia president Sr Juan Manuel Santos, who in favor of the interest of the industry emphasized the opposition to the adoption of a regulation pro-competitive for medicines of biological origin. (Biden, 2014) (Gomez-Maser, 2014)

The PI disciplines already incorporated in the commercial agenda with the USA are aimed to be implemented being alleged that they are necessary to stimulate the innovation and to protect the investment in future research. It turns companies into closed dominant groups that operate beyond the borders of their countries of origin to control the production and the pharmaceutical market. (Drahos, et al., 2004) (Restrepo, et al., 2014)

The decisions on such agreements should always be carefully evaluated. The high interference of the multinational pharmaceutical industry in technical standards, in the fixation of the commercial agendas and in the negotiation of agreements constitutes a conflict of interest that should be managed with precaution without putting in danger the capacity of the states to protect and comply with the right to the health of the people.

Regarding the first biological legislation signed on October 2014, a big polemic arose. The entry of competitors was being facilitated via one of the pathways of registration. This pathway was deeply criticized, especially for the pharmaceutical industry, but in the chapter 3.5.1 this conflict of interest will be further explained. Even the USA government showed concerns, alleging it could hurt the base of the TLC. (Biden, 2014)

The convenience or not of fortifying the rights of intellectual property must be clearly defined and must consider the economic and social differences between the countries. For Colombia, there is high-priority to stimulate the development of local industry in order to increase the budget investigation and to prioritize the universal access to all services and products related to the health of its inhabitants. Required measures should be implemented so that some PI Rights dispositions of the TLC do not hit the price and the access to medicines for the people who need them. (Cortes, Miguel Ernesto. Sanchez, Edna. Lopez, Julian, 11)

According to the paper of questions and answers signed by the ex-president of Colombia Alvaro Uribe Velez, the TLC does not affect the supply of generics and it does not increase the prices of medicine. With the TLC, Colombia continues protecting the intellectual medicine property to as it has been doing. Colombia grants patents from 1994 for pharmaceuticals and provides data exclusivity from 2002. During this period, the participation of generic products grew in the Colombian market. (Uribe Vélez, Alvaro, 2006)

A study of Fedesarrollo found that after eleven years of existence of patents on pharmaceuticals today only 17 commercialized active principles count on that protection, equivalent to 1.3% of products of the market. (Uribe Vélez, Alvaro, 2006)

The agreements in the TLC do not have incidence of prices, therefore medicines will not get more expensive. On the contrary, generic medicines from the United States will not have tariffs, which contribute to reducing the prices for the consumer. Furthermore, Colombia preserves the capacity to use instruments as the control of prices, the licenses obligatory and the parallel importations to avoid or correct abuses of intellectual property right from its holders. (Uribe Vélez, Alvaro, 2006)

3.3. How New Oncological Medicinal Products Obtain Access to the Colombian Market

In Colombia the registration process of medicinal products is regulated by the Decree 677 from 1995. This decree partially regulates the Conditions of Registration and Licensing, Quality Control and the Health Surveillance System for Pharmaceuticals, Cosmetics, Pharmaceutical Preparations of Natural Resources, Grooming Products, Household Care and other products of “domestic use" (Decreto677, 1995).

All products included in the Decree N° 677/95 require a Marketing Authorization (Registro Sanitario) in order to be manufactured, imported, exported, processed, packed, sold and marketed (Art. 13). Such authorization can be issued by the Instituto Nacional de Vigilancia de Medicamentos y Alimentos - INVIMA (National Institute of Food and Drug Monitoring) if in compliance with the technical scientific sanitary and quality requirements established by the decree. (Decreto677, 1995) (Reuters, 2015)

As seen before, this decree considers a big spectrum of products; however the registration of medicinal products is specifically regulated starting from the article 19 to the article 31 (Decreto677, 1995).Taking into account that oncological Medicinal Products are within the scope of Decree 677 as belonging to the category: Medicinal Products following is to be considered.

Before explaining in detail the different articles, an important concept has to be understood first; the “Pharmacological Norm”. The pharmacological norms are defined as: The set of conditions and restrictions established by the health authority as a requisite for considering the therapeutic use of a drug and its associations allowed in the country, as safe, effective and risk / benefit balanced in circumstances of rational use. It includes the minimum information to be printed on labels, packaging and pharmaceutical leaflets and information to be communicated to the prescriber. It may include among others, the accepted indications, the dose form, warnings, precautions and contraindications, as well as any other information that in the opinion of the authority is considered appropriate ". Is to be mentioned that the pharmacological norms have not been updated since 2008 and that efforts have to be done to keep it up-to-date. (Decreto677, 1995).

All medicinal products have to be included in the pharmacological norm as one of the requisites for further evaluation. If not included there, they have to request the health authority (INVIMA) to be included, if not included there already they can be considered as medicinal products containing new molecular entities (NME), also known as a new drug. Is it to be considered that NME include new chemical entities (NCE) or new biological entities (NBE).

After the concept above has been clarified it is easier to understand how the registration process will work depending on if the medicinal product is included in the

pharmacological norm or not (new drug). This master thesis will focus in the entry of new medicinal products containing new entities for the treatment of cancer.

Further is important to understand that the evaluation of applications aiming to obtain a Marketing Authorization by the INVIMA will go this following 3 evaluations depending if they are new molecular entities or not.

a) **Pharmacological Evaluation:** Includes the procedure by which health authorities form an opinion on the usefulness, convenience, and safety of a drug. This evaluation is performed exclusively by the Revising Commission of Pharmaceutical Products (Art. 8 of Decree 2078/12 (IDRAC 151564)). Applies for new molecular entities or new drugs not included in Pharmacological Norms. (Reuters, 2015)
b) **Pharmaceutical Evaluation**: It has the purpose of assessing the manufacturer's technical capability, manufacturing process, and quality of the product. (Reuters, 2015)
c) **Legal Evaluation**: Includes legal study of the documents provided by the interested party supporting the marketing authorization approval, and the compliance with laws governing such matters. (Reuters, 2015)

Marketing authorization procedures for all products, either included in Official Pharmacological Norms, or for new molecular entities, must be submitted under a unique process involving both pharmaceutical and legal evaluation . For the new products, the pharmacological evaluation should be first by passed. (Reuters, 2015)

The articles defining the Marketing authorization are following described:

a) **General Articles.**

Article 19 of Decree 677 of 1995 establishes that every medicinal product, whether included in pharmacological norms or a new drug, requires a sanitary registration issued by the Competent Sanitary Authority for the production, importation, exportation, processing, bottling, packaging, sale and commercialization thereof. (Decreto677, 1995).

b) **Articles applicable for medicinal products already included in the pharmacological norm:**

Article 20 of Decree 677 of 1995 establishes the technical (pharmaceutical evaluation) and legal requirements for granting sanitary registration of medical drugs contained in pharmacological norms. Article 21 and 22 explain briefly the aim and documents required in order to perform the pharmaceutical evaluation. Article 23 explains the procedure for the pharmaceutical evaluation (Validation of completeness, if not complete 30 days to provide missing information, after completion, 30 work days of review). If not approved, the holder should perform the recommended actions and after it request a new review. Article 24 explains the aim of the legal evaluation and the information to be presented. Article 25 of Decree 677

of 1995 establishes the process of sanitary registration of medical drugs contained in pharmacological norms or so called procedure of registration. (Decreto677, 1995)

c) Articles applicable for medicinal products not yet included in the pharmacological norm:

Article 26 of the said decree establishes the requirements for granting the sanitary registration of new medical drugs. (Pharmacological evaluation, pharmaceutical evaluation, and legal evaluation). The article 27 explains in detail how the pharmacological evaluation is performed: requirements and Article 28 explains the procedure for the evaluation. Finally, Article 29 summarized the procedure for the registration of medicinal products classified as new (containing new molecular entity and therefore not yet included in the pharmacological norms). (Decreto677, 1995)

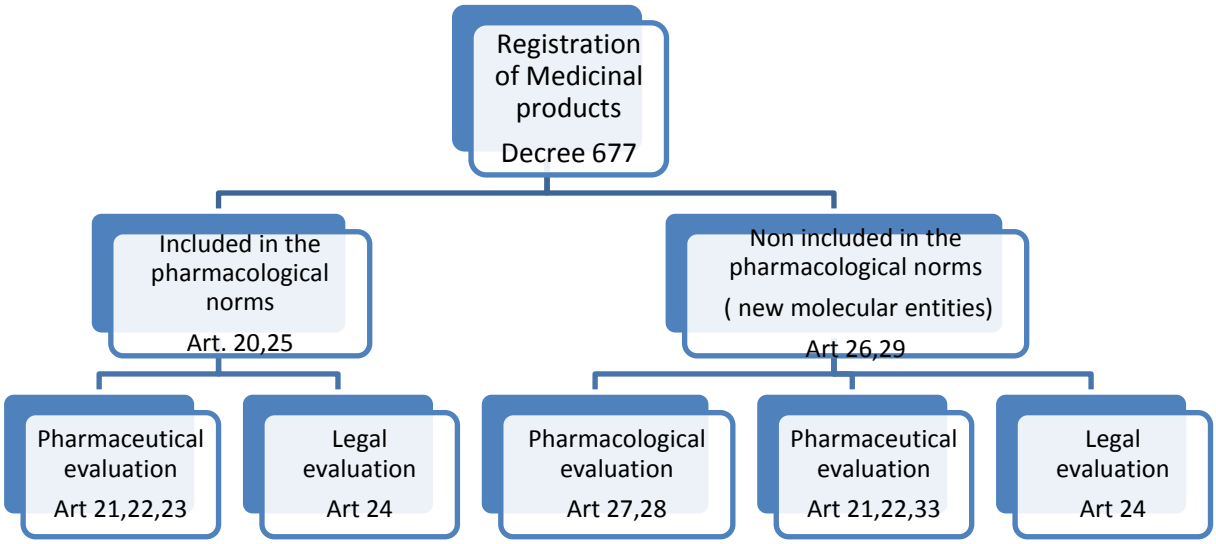


Figure 1. Registration of Medicinal Products in Colombia

The articles 30 and 31 explain how for medicinal products to be imported into the country, additional to the mentioned above (included or not included in the pharmacological norms) the following should be provided:

- CPP (Certificate of Pharmaceutical Product) from country of origin: CPP provides declaration of the marketing status and GMP compliance in the country of Origin of the product aimed to be registered.
- GMP Certificate

- Certificate that manufacturers are regularly inspected by health authorities.
- LoA from the manufacturer to the importer to request the register in his name, use the trade name or introduce the product to the market

Additionally is to be considered that when the product for which registration is soughtis registered in at least two (2) reference countries and was not rejected in any another reference country, a summary of clinical information with the relevant literature, in format defined by the INVIMA is required for the pharmacological evaluation. The reference countries are: the United States, Canada, Germany, Switzerland, France, England, Denmark, Netherlands, Sweden, Japan and Norway 677 (1995).

The Pharmaceutical Review Commission may request additional information about the product, when there is any doubt about the same.

The procedure is also explained:

a) Pharmacological evaluation

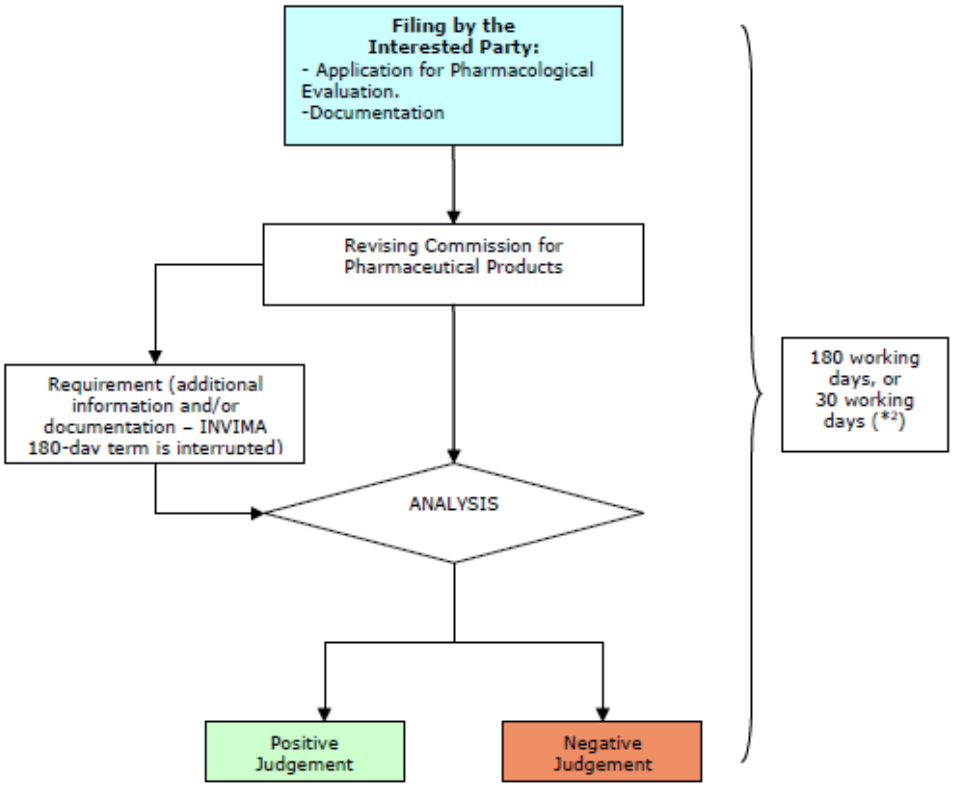
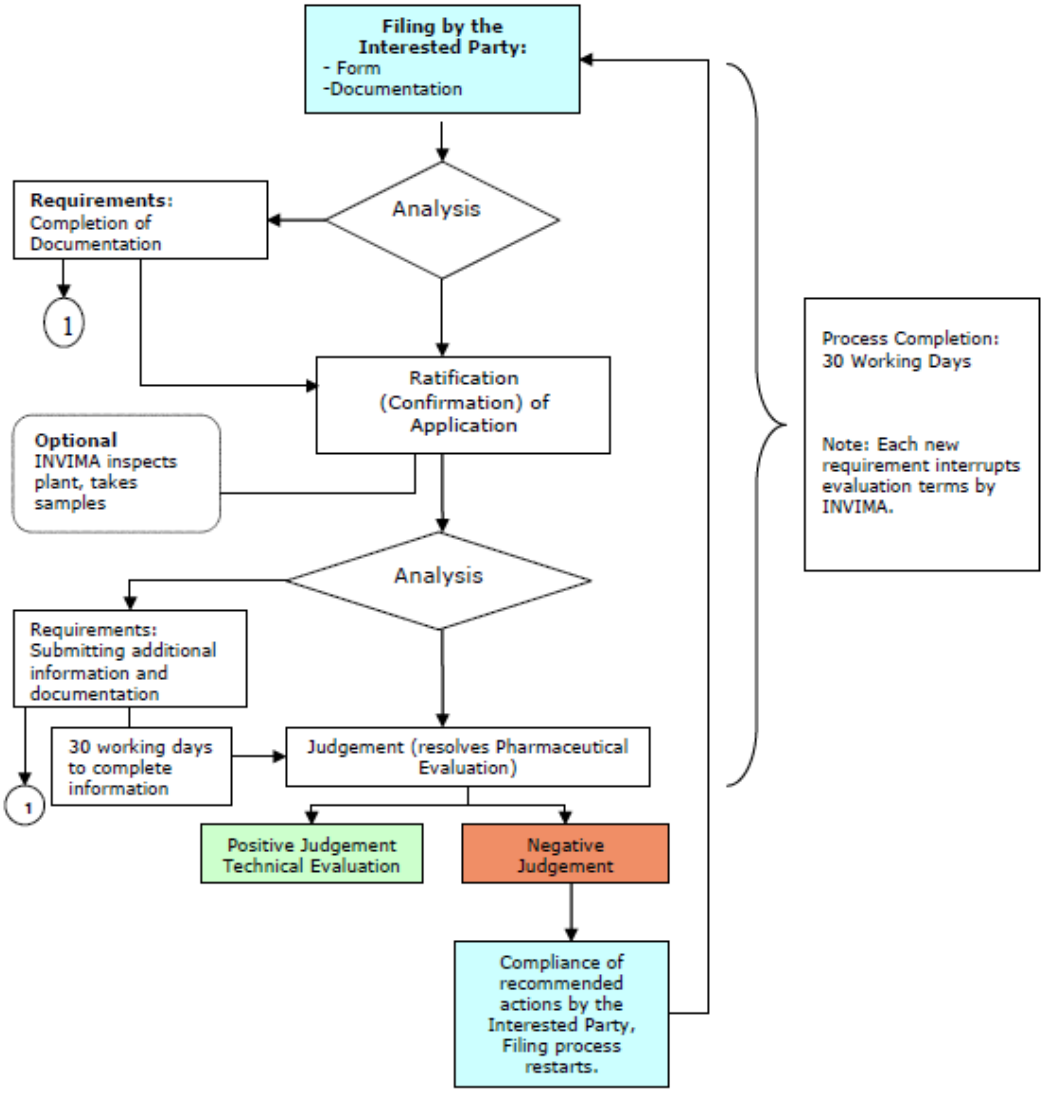


Figure 2. Pharmacological evaluation procedure**.** Adapted from Cortellis Database (Reuters, 2015)

(*2): Evaluation period by the Revising Commission for Pharmaceutical Products may become shorter if the product is already registered in at least two (2) countries of reference and not rejected in any country of reference .

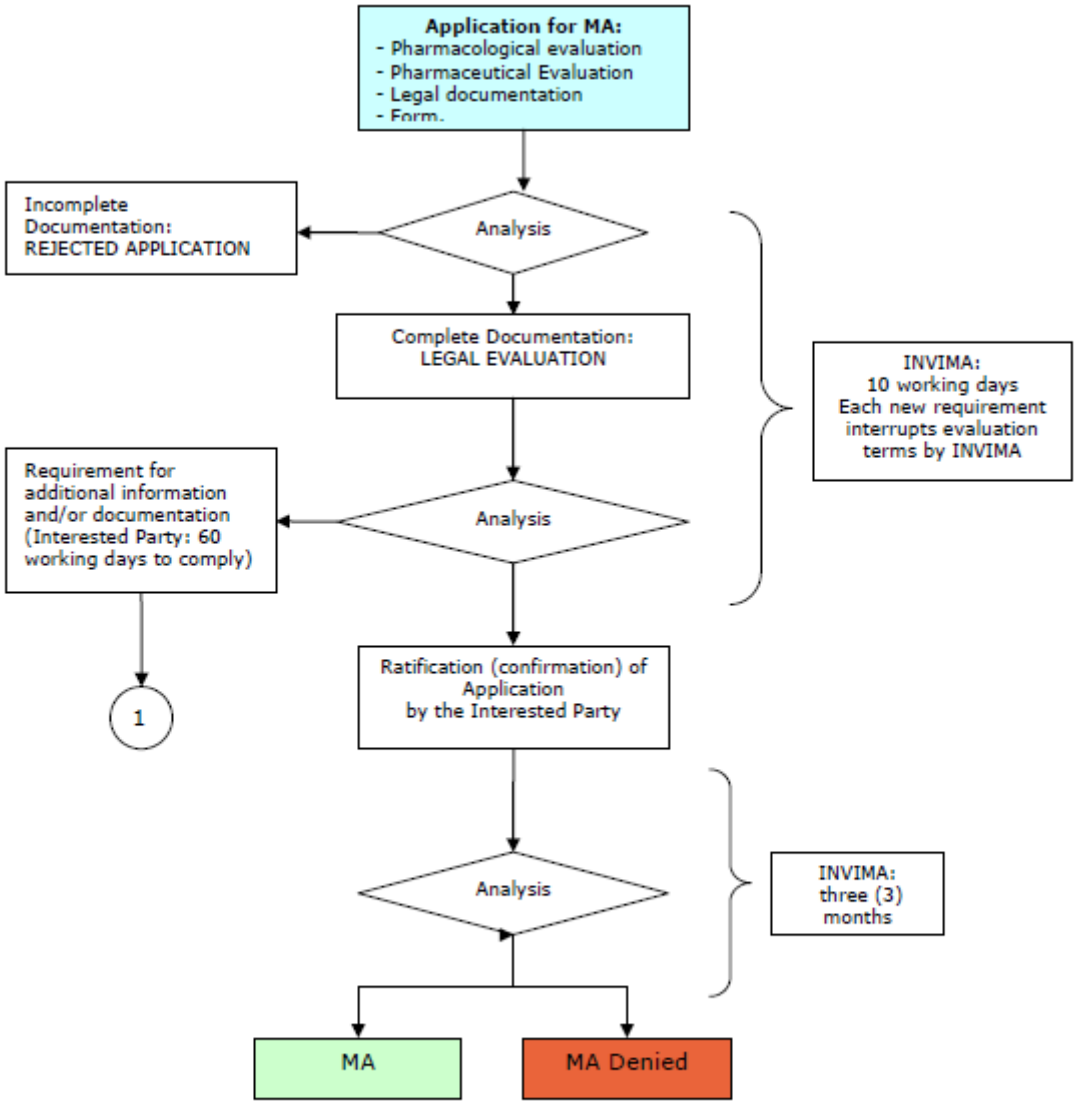
b) Pharmaceutical evaluation



1= TACIT WITHDRAWAL: Should the interested party fail to comply with one or more requirements, the process will be considered as dismissed.

Figure 3. Pharmaceutical evaluation procedure. Adapted from Cortellis Database (Reuters, 2015)

c) Total evaluation: Marketing Authorization Procedure for New Products (not yet included in the pharmacological Norm)



1= TACIT WITHDRAWAL: Should the interested party fail to comply with one or more requirements, the process will be acknowledged as dismissed.

Figure 4. Marketing Authorization procedure for New Products. Adapted from Cortellis Database (Reuters, 2015)

For the products already included in the pharmacological norm (no new molecular entities), the procedure explained above is the same with the only two exceptions that no pharmacological evaluation has to be performed and additionally regarding of timelines, once the pharmaceutical evaluation is submitted, it takes 20 additional working days to get a decision instead to 10. The process after it is the same as illustrated above.

The documents not available in Spanish should be officially translated and the expiry date of such documents should not be of more than 1 year to the time of the registration request. (Decreto677, 1995) (Guaia, 2014)

The validity of the license after approval has been granted is of 5 years, period after which is necessary to renew the license by providing technical and legal information and following the same procedure as the registration procedure. The renewal of a request to the INVIMA should be done within the year before to the expiry of the register and at least 3 months before the expiry. (Decreto677, 1995)

It is important to also take into account that biological medicinal products have within its area of application, the oncology, the decree number 1782 from 2014 is also important to be considered. Its recently signature and publication create a new polemic that will be explained in more detail in the chapter 3.5.1. (Decreto1782, 2014)

Additionally, this thesis is mainly focused on the entry of new molecular entities to the market. The decree 2085 from 2012 is also relevant, as it regulates aspects related to the information provided for registration of medicinal products containing new molecular entities. In this decree, the data protection establishes a period of 5 years, period in which the undisclosed information may not be used directly or indirectly as support for another request for the same chemical entity. New molecular entities should be understood as the active substance that has not been yet included in the pharmacological norm in Colombia. (Decreto2085, 2002) (MoellerIPAdvisors, 2008)

Annexes 1 and 2 offer a more detailed list that can be found in regard to the requirements for registration of medicinal products in Colombia. This detailed lists shows the requirements in a way that allows for comparison with the CTD dossier structure used in Regions such as Europe or The United States.

3.4. Involved Fields and their Perspective Stances on Medicinal Products

3.4.1. Industry

Innovation in the pharmaceutical field is a complex process result of the knowledge applied for the discovering, developing and bringing to clinical use new medicinal products that extend or improve the lives of patients. A successful pharmaceutical R&D process is one that minimizes the time and cost needed to bring a compound from the scientific ‘idea’, through discovery and clinical development, to final regulatory approval and delivery to the patient.

Pharmaceutical companies generate innovation in healthcare by inventing and developing new treatments for previously untreated health problems (radical

innovation) and also developing improved versions of existing medicines or new indications for them e.g. to treat diseases other than those for which the medicines were originally invented (incremental innovation). Often underestimated, these incremental innovations significantly improve health and quality of life, by providing patients with more choice, better risk tolerance, easier dosing and administration, as well as fewer side effects. An example of this can been seen when comparing how the life expectation has increased in time showing that in 1950 the life expectancy in more developed regions was 65.9 years of age and in less developed regions of 42.3 years of age.In 2005 the life expectancy in more developed regions was 77 years of age and in less developed regions it was 66 years of age. It continues to increase in time making it evident the benefit that innovation has generated. (IFPMA, 2012)

However, today pharmaceutical R&D is characterized by increasing magnitude, complexity and scale. The pharmaceutical industry is one of the most highly regulated industries in the world across all of its activities in order to protect public health. Development of medicinal products generally requires the conduction of extensive studies in animals and humans, i.e. the generation of pharmacological-toxicological and clinical data. This data shall ensure that medicinal products have the appropriate safety and efficacy for its intended use and is therefore necessary to protect public health. Strictly controlled studies, some with thousands of patients worldwide, are used to prove whether a drug is effective and is truly safe. This is why pharmaceutical research is complex and expensive. On this basis, the medicinal product shall be approved by the competent authority for placing on the market. Legislation and regulation covers the full lifecycle of pharmaceutical products, including marketing authorization, clinical trials, competition law and intellectual property rights. (vfa, 2012) (Berntgen, 2003)

As explained above, researchers face an increasingly demanding clinical and regulatory environment. They are confronting complex diseases (such as Alzheimer's, cancer and HIV/AIDS) that require much more basic research to identify novel treatment targets. Moreover, recent advances in science and technology have contributed to the emergence of powerful new research tools such as nanotechnology, pharmacogenomics, high-throughput screening and combinatorial chemistry, which make pharmaceutical innovation both more promising and more challenging than before. Because of the increased complexity and expensiveness, it requires more extensive collaboration. (IFPMA, 2012) (Berntgen, 2003)

From initial concept to approval, the process takes on average over 13 years. From an original 5,000 to 10,000 active substances under consideration, only one active ingredient achieves approval in the end, costing an average of $1.2 billion, based on a study from 2007. The few successes must make up for the many failures. In fact, only two out of every 10 medicines will recoup the money spent on their development. (Pharma, 2014) (vfa-Research, 2014)

The cost of bringing a new medicine to market is rising, not falling. Since 2000, US pharmaceutical manufacturers have increased their R&D budgets by roughly 55 percent, from $26 billion to almost $40 billion in 2005, of which they invested more

than $10 million in preclinical studies (25% of total R&D spending) and $17.2 billion in clinical trials (43% of R&D spending). It should be noted that R&D costs vary widely from one new medicine to the next. Those costs depend on the type of medicine being developed, the likelihood of failure, and whether the medicine is based on a molecule not used before in any pharmaceutical product (a new molecular entity, or NME), rather than an incremental modification of an existing medicine. (IFPMA, 2012)

As the generation of the data collected in extensive studies in animals and humans increases, new technologies become costly and take more time and resources. This has caused the approach of intellectual property to be introduced into legislation for medicinal products. The PI is a key enabling factor for the industry's research and development efforts.

It is important to understand that without the enabling conditions of the PI, industry could neither provide innovative medicines nor be able to support partnering initiatives in developing countries. The PI systems include protection of patents, trademarks and data protection, all of which are critical for stimulating R&D. They provide some assurance that companies that have invested in life-saving medicines have an opportunity to justify their investments. If a new medicine is to be successfully approved, the innovator has a chance to generate revenues sufficient to justify the investments in R&D and to ensure sustainable innovation into the future giving hope to patients who await tomorrow's innovative medicines. The vast majority of medicines available today would not exist without the incentive provided by intellectual property rights. (IFPMA-IP, 2014) (Pharma, 2014)

Data protection means the temporary prohibition on direct or indirect use of the safety and efficacy data, which has been used for registration purpose, by another applicant. It has to be clearly distinguished from patent protection, which is an important tool for granting exclusivity rights but is not relevant for the regulatory approval process. Data protection generally requires that a generic product relying on the clinical data supporting approval for an innovator reference product not be approved for a defined period of time. Without intellectual property rights, competitors could simply copy innovations as soon as they were proven safe and effective, offering their own versions without investing the time and money to develop the medicines. (Pharma, 2014)

Is to be noted that the changes in the demographic and epidemiologists conditions in the world-wide population appear as an opportunity of business for the pharmaceutical industry by the increase of the amount of people requiring different therapeutic alternatives to live or to improve their quality of life. However, the model of business based on the intellectual property, on which this sector has bloomed, is in crisis due to several factors that are effecting their return on equity, as they are the expiration of patents, the advance in the availability of scientific knowledge, the technological advances, the appearance and use of effective services more cost effective, and the management of the governments in the attempt to control the

increase in the pharmaceutical cost via regulation of prices of medicines and the impulse to the competition. (Restrepo, et al., 2014)

The limited duration of the patents force the pharmaceutical companies to reduce the prices after their expiry. This is due to the competition generated by generics. Additionally, it is a big challenge for companies to launch medicinal products that really represent important therapeutic advances for great population groups. To evidence an additional improvement it is even more difficult, especially from the regulatory point of view of approval.

The strategies that the great pharmaceutical companies are unfolding to achieve their goals include cuts of internal expenses, fusion of companies, investigation and development of products that can sell monopolistically high prices, effort to obtain the approval of commercialization in a smaller time frame and the maximization of the use of the privileges of intellectual property. The tactics include the increase of the prices to the maximum that resist the markets, the perpetuation of the patents (ever greening), the launching of new pharmaceutical forms, the incursion in emergent markets, the blockade of the entrance of competitors and the participation in the generic markets (Restrepo, et al., 2014) (ResearchandMarkets, 2009).

The background explained above derives in the interests of the industry to support the strengthening of intellectual property rights in both industrialized and emerging developing countries in order to encourage and manage further innovation. Pharmaceutical companies have a humanitarian engagement for contribution to medical progress and public health. However, considering the required investments, strong regulations in regard to the PI will always be wished as in this way the entry of competitors will be delayed allowing for the maintenance of the monopoly. Having no competitors for a certain time allows companies to establish higher prices of medicinal products. Patent and data protection are incentives that help the industry to recover the inversion and to obtain profit. (Berntgen, 2003)

All around the word there are institutions taking the lead for the interests of the pharmaceutical industry. Examples of these institutions are the following:

At an international level: The IFPMA International Federation of Pharmaceutical Manufacturers & Associations: http://www.ifpma.org/#sthash.rtty62tp.dpuf

In the USA: PHRMA http://www.phrma.org/about

In Europe: EFPIA (European Federation of Pharmaceutical Industries and Associations) http://www.efpia.eu/

In the UK: ABPI (The association of the British Pharmaceutical industry) http://www.abpi.org.uk/Pages/default.aspx

In Germany: VFA (Die forschenden Pharma- Unternehmen) http://www.vfa.de/de/home.html

In Colombia: AFIDRO) (Asociacion de laboratiorios farmaceuticos de investigacion y desarrollo) http://www.afidro.org/

3.4.2. Government

In regard to the health system and specifically to the resources destined for the covering of medicinal products, there is a big problem that all of the governments all over the world will have to face. It is the increasing health costs arising mainly by the fact that new technologies employed are very expensive because of the height of biotechnology and also as a result that the strong regulation to protect health may make more challenges for the development of innovations, which is lately reflected in the prices. Additionally the cost of development that companies have to pay should be recovered in some way. As the intellectual property has been implemented as a tool for the promotion of the innovation, the entry of competitors becomes limited during the protection times (patent, data protection) and therefore prices increase.

Given the finite character of resources from the government and the impact of the administration on the access to the services in health, the government's aim is to protect their budget by paying as little as possible while still giving access to medicine to the largest number of people. These include government implement strategies such as price control, promotion of competition and rational use of medicinal products. Regarding the rational use of medicinal products, is important to mention that according to a study about health in the world, the proportion of health resources that get lost due to inadequate health practices is about 40%. For this reason is urgent to find systematic solutions in order to reduce the waste of resources and promote the rational use of health services (Policy reforms, implementation of national essential medicines, list standard treatment guidelines, rational prescription, education and training of prescribers, dispensers and patients, etc). (WHA, 2014)

These mechanisms have demonstrated to be the most effective to lower the price of medicine and in general improve the health of the people and the cover at national and international levels.

The biological products are specifically concerned in this regard because of their high costs when compared to other technologies. In the United States for example only six biological medicines consume 43% of the budget in "Medicare" Part B (S.A., 2010). The Federal Commission of Commerce of the United States reports that at the moment the biologicals approximately consume 25% of the $320 trillion spent annually in this country for pharmaceutical treatments (Federal Trade Commission, 2013). (Restrepo, et al., 2014)

This situation is economically unsustainable, since it places the national system of health in difficult situations, due to the drainage of resources and the cost of opportunity. Additionally, it causes the access of treatment with biological products to become unattainable for patients who require them. (Restrepo, et al., 2014)

In addition, it must be considered that while in the 2007 market of these products was of only a half-trillion dollars, 2012 registered 2.4 trillion dollars and in 2020 it is

projected to ascend between 10 and 25 trillion dollars following the number of products that enter the market, especially in the United States, where half of the biological medicinal products produced in the world are consumed. (Rickwood S, 2013) (Restrepo, et al., 2014)

Unfortunately, Colombia is not an exception to the health crisis because of the high prices of biotechnological. In the country, the rise of costs in biotechnological medicinal products is alarming. In the present conjuncture, there are serious indications that the high cost which the health system incurs can be mainly explained by the costs of recoveries and high prices of biotechnological medicinal products. Thus, the recoveries, that in the 2005 were around $207 billion, reached in the 2010 the $2.4 trillion. In those six years the total of recoveries surpassed the $6 trillion and in both last years (2009 and 2010) they surpassed the $4,1 trillion (Zapata, et al., 2012) (Restrepo, et al., 2014)

Additionally, according to Salazar (2011), in 2009, 87% of the total cost of recoveries by the FOSYGA corresponded to medicinal products. By then, it was considered that a 80% of the value of the concepts of the Scientific Committees Technical (CTC) corresponded to medicinal products not included in the obligatory health plan (POS). In agreement with the Colombian Association of Companies of Medicina Integral (ACEMI), this increase was mainly due to the reclamation via Judgments of defense (Tutela) and as a consequence, that the majority of those medicinal products were biotechnological medicinal products.Of the 10 main medicinal products recovered in value to the FOSYGA in the last three years, 8 were biotechnological. (Zapata, et al., 2012) (Restrepo, et al., 2014) (RedaccionSalud, 2014) (PFN, 2012)

In further detail, Colombia in the period from 2008 to 2013, had only 10 medicinal products to treat diseases as cancer, arthritis and diabetes registered sales by more than 3 trillion Pesos, which located them in top ten of medicinal products of the invoicing of the sector in the country. These products, manufactured by eight multinational companies, are at the forefront of biotechnological medicines and for its monopolistic characteristics have relatively high prices (PORTAFOLIO, 2014).

The prices of these products, as stated, are extremely high, and in the Colombian case, many of them are not in the obligatory Health Plan (POS) and are recovered by the EPS to the FOSYGA, which led to a financial collapse in the health system. (PORTAFOLIO, 2014)

The promotion of competition is oriented to reduce powerful asymmetries of agents in the market, these generating benefits for the consumer and the system of health. (PFN, 2012)

The increase in total expenditure of non-POS medicines, during the last decade, is opposed to the insufficient provision of medicinal products of the POS. The institutional weaknesses for the update of obligatory health plans, the problems of information for the calculation of the sufficiency of the Unit of Payment by Capitación (UPC), at the same time as an inoperative prices policy and weaknesses in the monitoring of the prices, generate inequity in the access; then they privilege the

destination of an increasing proportion of the resources in specialized benefits of high complexity and, on the use of essential medicinal products or the accomplishment of non-pharmacological interventions of promotion and prevention. These practices create inefficiency in the medical provisional model and generate risks of sustainability to the health system. The solution of those problems is the aim of the government. (PFN, 2012)

For this purpose, a new reform to the health system is in preparation and will be further explained in greater detail (please refer to section 3.5) which is looking to create a more efficient system and to reduce the barriers to access.

Additionally, a control prices strategy aims to avoid multinational pharmaceutical industry establishes irrational prices that conduct to the insolvency of the health system.

Further but not least, the establishment of the recently approved biological law has as an aim the promotion of the competition; the competition has been shown to be one of the most effective alternatives for the price reduction of medicinal product, this is also explained in more detail in the chapter 3.5.1. This will be relevant if considering that many oncological medicinal products are in the scope of the biologicals.

Finally, the aim of the government is to achieve a rational use for medicinal products as an inadequate use of them generate also unnecessary lost in the resources to the system. (RedaccionSalud1, 2014)

3.4.3. Patients

All over the world there are many patient associations acting as leading voices by sharing the opinions of the patients. Patients expect to get the best healthcare possible regardless of cost. (Espectador, 2013)

In Colombia, patients should have free access to what is included in the (obligatory health plan) POS. Despite deficiencies in the health system which fail to meet its responsibility of ensuring access to services which patients are entitled to by law, people use the Judgments of defense (Tutela) when they feel their well-being and life is at risk due to limited or no medical care access. This instrument for protection of fundamental rights was created in 1992 and is being employed for both, the services included in the POS and services not included in the POS. The entities that receive the most quantity of complaints via Judgments of defense are the EPSs. Nearly eight of ten judicial fights are filed against these entities.

70.93 percent of fights using this Judgments of defense method in health are conducted by people that are claiming procedures, medications and treatments that are contained in the POS. The rest corresponds to services not included in the POS (RedacionSalud, 2013).

In Colombia between 2003 and 2009, the annual growth average in the value of the reimbursements by medicines not included in the obligatory health plan POS was 68% and reached a number of nearly 1.317 million dollars. This expansion is explained by the increase of Judgments of defense or opinions of the Scientific Technical Committees (CTC). (PFN, 2012)

In the case of medicinal products that have not been approved or that are not covered by the POS, patients have the possibility to obtain access through the Judgments of defense mentioned above. These are examples of services not covered by the POS.

Furthermore, it is necessary to state that for medicinal products not covered by the POS and in some cases even if included in the POS, a very bureaucratic process, with many steps (Technic-scientific evaluation, Tutela) and institutions is required (detailed described in chapter 3.1), Patients have to go through this process if they want to get access to the medicinal products they require. This complicated process produces a delay to the access to the medicinal products and therefore big barriers to health services.

Patients aim is to get the best quality of health services, without bureaucracy and unnecessary steps that induce a delay on the health services access. For this reason, patients expect government to have good health policy in place that allow them to have access to the best healthcare possible independent on the kind of regime that the patient is being affiliated(either contributive or subsidized).

Finally, but no less important, it is in the interest of the patient that health corruption doesn't exist at all. Corruption creates a lack in the access and quality of health.

Concerning oncology specifically, patients are often close to death and are rooted to any hope. Hope that can be reflected in experimentation medicinal products, which even if not yet being approved can have a benefit. The possibility to get access to those experimental medicinal products is also desired by the patient population.

For patients with cancer, each single benefit is wished, especially if it implicates improvement in the quality of life, no progression of the illness or improvement in the global survival rate. An increase of just 2 months of life is worth it for them.

The fact that medicinal products are not approved as "no significant improvement is being shown" or because in order to get the medicinal product approved is necessary to have more data available on global survival is not in the interest of the patients. Especially if taking into account that in order to have global survival data, more time has to pass, and more people have to die.

In the case a patient would want to get access to an oncological medicinal product not approved in Colombia but in other states, they can go the approach of vital no available, where a patient or a public or private legal entity request it to the INVIMA in order to get it imported (Medicamento vital no disponible), for doing this approach 3 conditions should be fulfilled which are established in the Decree No 677/95. (Uribe Velez, 2004) (Decreto677, 1995)

1) The product is not under investigation in clinical trials;
2) The product is not marketed in Colombia, or if so, the quantities are not enough to meet the needs
3) The product does not have any substitutes available on the market.

Due to the fact that this process can delay the access to the required medicinal products, some patients take the decision to cover it with their own resources. The problem is that most of the time, these medicinal products are costly, especially if being biological and therefore only patients with high resource availability are able to access to them. In the health reform in Colombia, there has been a discussion the last few years regarding the defense of the rights of patients. Goals like equality independent of the affiliation system and the fight to keep the Judgments of defense (Tutela) as an opportunity to access medicinal products are aimed to be protected.

It is to be mentioned that for the defense of the rights of patients, patient associations have been created. Even though due to the fact that investition of the pharmaceutical industry to support the patient associations takes place, those patient associations are sometimes heavily criticized because of the opinion that due to the support obtained by the industry, the patient associations act in favor of the interest of the industry, which means that industry would be using patient associations to defend its interest. One example of that is the transparency measure that wants to obligate industry to publish all the information available on clinical data (by now only approximately 50 % of the information is public). The patient associations are of the opinion that this puts at risk the patient privacy, can be conducive to misunderstanding of the information and therefore conducive to public health problems due to a decrease on the number of new medicinal products available to the patients for the maintenance, cure and improvement of health. (CIMUN, 2013)

3.5. Summary of New Health Reform Proposals

In Colombia, a restructuring of the health system is taking place over the last years for improving and finding solutions to the problems to access medicinal products, combat inequality of access to health care and bad quality of it. Those characteristics have been the common of the health system since the implementation of the Law 100 in 1991.

The following summarizes the initiatives aiming to address the issues mentioned above.

A national pharmaceutical policy (PFN) has been created, which is a plan for 10 years starting in 2012 basically seeking to improve aspects like the rational medicinal product use, the equitable access to effective medicinal products and to quality pharmaceutical services and to correct defects of surveillance system and quality control. The PNF contains 10 strategies for the achievement of established goals and an investment of 250 billion dollars is planned. (PFN, 2012)

Under consideration of this national pharmaceutical policy, two laws are under discussion. These are the statutory and the ordinary law. In other words, the national pharmaceutical policy and the national health system are closely related by having the goal of health reform using two distinct laws: The statutory law and the ordinary one.

The Congress approved the Statutory Health law by Minister Alejandro Gaviria Uribe which establishes the basic structure of what will be the Ordinary law that redefines the health care system in Colombia. (MinSalud-Estatutaria, 2013)

Regarding the statutory law, it has to be noted that this counts with a constitutional character having as main function the establishment of the health right as a fundamental right. This fundamental right has to be evaluated from a technical-scientific point of view, with public character, collective and transparent. (Justicia, 2014)

The mechanism of this law has as a goal to avoid that the resources from the health system finance services or technologies that:

1) Have a primarily cosmetic purpose or sumptuary
2) Have a lack of evidence of safety, efficacy and clinical effectiveness
3) Are not authorized for use in the country
4) Are experimental or have to be rendered abroad

In any case it can be seen that what will change is that instead of having a POS (including a list of essential services and technologies) we will have is an exclusion list indicating the exceptions of what will not be covered by the health system. This means that the limits to the protection of the health right are established through these exclusions. A progression to the exclusions instead of inclusions. The policy of price control is also aimed to be strengthened. The mechanism for the exclusions should be defined in that way that it fulfills the constitutional requisites and is respected by the public, the judicial authorities and the agents of the sector. (Min, 2014)

Summarizing; the statutory law becomes the first of its kind issued in 22 years of operation of the Constitution of 1991, which regulates a fundamental right to social and economic character of the health. Stand out as most important points, that health is ensured as a fundamental right, does not remove the Judgments of defense reclamation complaint, sets strict controls on drug prices and prohibits denying services to the patients arguing economic reasons.

In regards to the ordinary law, in June 4, 2013, the discussions for the implementation of this law started and have been in discussion until now. (Minsalud-ordinaria, 2013)

It has been a goal of the General System of Social Security in Health to set system principles, the framework from which the health benefits are regulated, operated, managed and administrated. The provision of services, the unified management of health resources through the creation of a financial management unit of special

nature, some inspection procedures, monitoring and control, the system of social company -ESE- State and a transitional regime for the implementation of the provisions of this law are also aimed to be redefined. (Uribe Gaviria, 2013 p. 1)

This law regulates the manner in which the State organizes, directs, coordinates and controls the provision of public health services and the roles of the actors involved. (Uribe Gaviria, 2013)

The known POS will take the form of Mi plan (my plan) where the exclusion principle will be used so that what is not included will be excluded and those exclusions will be following:

1) Have a primarily cosmetic purpose or sumptuary
2) Have a lack of evidence of safety, efficacy and clinical effectiveness
3) Are not authorized for use in the country
4) Are experimental or have to be rendered abroad

EPS only changes their name to health service managers supervised by the national Health superintendence (Uribe Gaviria, 2013) (Huertas Vega, 2014)

Additionally a new approach to support the decisions on health is taking place. This proposal is looking to integrate a new entity called IETS (institute of technological evaluation in health) in the decision process that will advise and contribute to the development of better policies for the decisions on health, this, based on the information available from effectiveness, safety, economic evaluation and economic impact. All those above should conduce to final recommendations on which technologies should be covered by the public resources. (Vacca, et al., 2012) (IETS, 2015)

3.5.1. Biotechnologics as a Key Point Including Implementing New Laws and their Conflicts of Interest

Biotech drugs are the drugs of tomorrow. Their characteristics give them the ability to act, almost specifically and personalized on catastrophic illnesses like cancer. Attributed to them, in some cases, there is an efficiency of up to 50 percent higher than traditional synthetic chemical drugs. Biologics are able to achieve results where other treatments have failed, but since most of them are protected by patents, the costs cause them to become almost inaccessible therapeutic tools.

The reason is that there is no competition in the market and therefore monopolies sell them for high prices. High prices result in a barrier to equitable access to medicines and therefore to the effective exercise of the right to health .In Colombia they are not covered by the health system and the patients get access to them only via the Judgments of defense.

In Colombia between 2003 and 2009, the annual average of growth in the value of the reimbursements by medicinal products not included in the obligatory health plan POS was 68% and reached a number near 1.317 million dollars. This expansion is explained by the increase of Judgments of defense claims or by the opinions of the Scientific Technical Committees (CTC). The value of medicine is the main component of the total reimbursement (around 82% in both last years). On the other side, in 2010, half of the medicines of greater participation in the total value of the recovery, that altogether concentrated 60% of the total recovery, agreed with medicines of greater sale in the world-wide market, all of them of recent biological or biotechnological origin and innovations of recent introduction. (PFN, 2012)

The explosion of the reimbursement claims through the Judgments of defense(Tutela) , went from 60 thousand at the beginning of the decade, to almost a million administrative processes per year, therefore exceeded the administrative capacity of control. (PFN, 2012)

As a consequence, the first law for Biologicals were aimed to provide a solution to the significant increase of costs and at the same time to regulate the entry of medicinal products with good profile in regard to safety, efficacy and quality. The decree takes particular care not to set up "unnecessary barriers" that would "directly affect the speed of entry of biologic medicines as more efficient alternatives to treat patients and alleviate the financial burden for the health system" (Restrepo, et al., 2014)

After 3 years and 5 drafts, which were exposed to consultation, the final version of the first regulation on biological products and biosimilars has been approved in Colombia and was published in the Colombian official journal on September 18th 2014. It corresponds to the decree No. 1782 of 2014 (Decreto No 1782 de 2014). The 5th and last draft for discussion was published on July 10th, 2014. The regulatory body IINVIMA now has a year in which to draft and publish three guidelines implementing the decree, on immunogenicity, stability, and the risk management plan.

The new decree includes three pathways to support demonstratively that a biologic medication is of the necessary quality, safety, and efficacy to be afforded market access. (Decreto1782, 2014)

Article 6 lays out nine sets of data that are required for all products, whatever route they take, including a description of the manufacturing process and site, the expression system, evaluation of biological activity, immunogenicity, risk management plan, and so on. There are also some specific data requirements for each pathway. (Decreto1782, 2014)

The first Pathway is the complete dossier. This path appears mostly to closely align with the U.S. FDA 351(a) BLA of the PHS act approach, where a sponsor can submit a biological license application (BLA) for a “stand alone” biological product. In which case could contain a full complement (complete dossier) of data and information. In Europe the equivalent would be the application for a marketing authorization in the

community on the basis of a complete dossier in accordance with the provisions of article 8 of directive 2001/83. (U.S.Government, 2014) (Directive2001/83, 2001)

The second pathway is the Path of Comparability. Through this pathway, a comparability exercise versus the reference drug must be performed. This exercise should be a "phased and sequential comparison" of the quality, safety and efficacy of the attributes of the (similar) product under evaluation compared with the reference drug showing that the former is "highly similar" to the latter. Any differences should be explained and justified by the applicant, and the regulatory agency will evaluate their clinical relevance. This pathway appears to most closely align with the U.S. FDA 351 (k) BLA of the PHS, which is applicable for a bio-similar or interchangeable data product. This would contain an abbreviated package of data and information. In Europe a company may choose to develop a new medicinal product claimed to be “similar” to a referenced medicinal product, which has been granted a marketing authorization in the community on the basis of a complete dossier. For this scenario, the legal basis of Article 10 (4) of directive 2001/83/EC and section 4, part II, Annex I to the said directive should apply. It is based on the demonstration of the similar nature of the two biological medicinal products by comparability studies that generate evidence substantiating the similar nature in terms of quality, safety and efficacy. (U.S.Government, 2014) (Directive2001/83, 2001)

The third Pathway is the Abbreviated Pathway. According to article 9 of the decree, an applicant can take this route if the active substance of the product submitted for approval is “sufficiently characterized” and has a “well documented safety and efficacy profile”. It must also have “considerable clinical experience” and “robust pharmacovigilance data”. All this data must come from “reference countries and health authorities”. With this abbreviated pathway, waivers in the requirements can be granted in the case that an element in the comparability is considered as unnecessary. What can be waived is: only pre-clinical and clinical information, not allowing waivers of analytical studies. The European Medicines Agency (EMA) and U.S. FDA do not have such a pathway. Comparable pathways in these regulatory regions include the complete dossier route and comparability route. (U.S.Government, 2014) (Directive2001/83, 2001)

Behind this new decree, a great polemic is involved.

From one side it is noticeable that the position of the government is to establish requirements and procedures to ensure the quality, safety and efficacy of biotherapeutics without creating unnecessary barriers to the competition and promoting their availability. This strategy is basically based in the introduction of the second and third pathway where the biosimilars entry to the market is regulated. A third pathway of the Colombia regulation doesn’t exist in the European Medicines Agency (EMA) and U.S. FDA as such. But to this concern the Colombian health minister explain that the third pathway could be comparable to the U.S. FDA 351(k)(2)(A)(ii) BLA of the PHS act approach, where it says that “the secretary may determine, in the secretary´s discretion, than an element described in clause (i)(l)

(comparability route) is unnecessary in an application submitted under this subsection. (Gaviria, 2014) (ResponsetoFDA, 2014)

Additionally, this regulation gives the opportunity to increase the competition, as after the patent period of the innovator product expires, biosimilars can enter the market and in this way promote the price reduction. Government consider that the decree regulation facilitate entry of competitors into the market through the short route, which will result in a benefit to the consumer (Decreto1782, 2014)

Even though this strategy also considers the efficacy and safety of the products entering to the market, these aspects cannot be sacrificed in order to ensure decent prices of biological medicinal products. By 2020, 89 of the 93 innovator biotechnological medicinal products existing in the world will lose their patents and biosimilars will be able to enter the market if getting approval according to the recently signed decree. It is expected that with this measure in approximately one year, biosimilars will start entering the market having a price even 60 % less than the innovator medicinal product. This will represent annual savings estimated between 300.000 and 600.000 million pesos, conducting to the increased access to biological medicinal products. (Autor-Eltiempo, 2014)

On the other side, the point of view of the industry and entities such as the FDA and EDQM pioneers respectively in USA and Europe regard the following:

The FDA, for example, is concerned that under the Abbreviated Pathway that until now doesn't exist somewhere else in the world, it is still unclear how the safety, purity, and potency of products would be assured. Their opinion is that it is unclear if this abbreviated pathway is intended to describe the approval of a product based on comparison to a reference standard, rather than a reference product. And that in the case that with reference standard is meant a pharmacopeia monograph, it is unlikely that a pharmacopeia monograph will be extensive enough to cover all aspects of characterization, testing, release and stability. Additionally in the U.S., a sponsor must demonstrate that they are biosimilar to a licensed product, not similar to a monograph. (U.S.Government, 2014)

The EDQM is concerned regarding the third pathway as it is stated that an applicant may use an abbreviated route if the active pharmaceutical ingredient in the medicines is "adequately characterized" in terms of its identity, biological activity, physicochemical properties and purity. It further explains that an active pharmaceutical ingredient will be considered to be "adequately characterized" if it has a compendial monograph. The EDQM appreciates that monographs provide public standards for the quality of medicinal products and their constituents but they clarify that these monographs are not sufficient to assess identity and similarity of medicinal products that are required to establish comparability of a biosimilar with an original biological product in the context of a marketing authorization application. (EDQMResponse, 2014)

In Colombia, in representation of the industry, it is the institution AFIDRO who leads the transmission of the opinions and concerns regarding the new biological regulation to the health ministry in Colombia. (AFIDRO, 2014)

In their opinion, in the topics mentioned above, a risk for the patients using medicinal products approved via this abbreviated way can arise. (Gomez, et al., 2014)

Biotherapeutic medicines ("biologics") are substances, generally proteins, produced by living organisms (such as mammalian cells and bacteria), that are intended to be used for the diagnosis or treatment of human diseases. Because of their origin, these medicines are uniquely sensitive to changes in their environmental conditions. Thus, even seemingly small changes in manufacturing can alter the final quality and most importantly, clinical characteristics of biotherapeutic medicines. The high complexity of this manufacturing process requires precision, conformance to the most current good manufacturing practices and defined specifications in order to maintain the safety and efficacy of the product over time. Producing a biosimilar is far more complicated than producing a generic version of a small-molecule drug. Unlike chemically-synthesized medicines, it is impossible for biosimilars to be exact copies of the reference innovative biotherapeutic. In light of this, it has been recognized that distinct regulatory approaches are necessary to assess efficacy and ensure patient safety with respect to biosimilars. (BIO, 2013)

Regulatory authorities are increasingly aware of the need for specialized pathways and specific development and evaluation standards to address the unique nature of biosimilars. These standards require a thorough and directly comparative "head-to-head" analytical characterization and quality studies, followed by more or less abbreviated pre-clinical and clinical development programs to show high similarity to the reference innovative biotherapeutic medicine in terms of quality, safety and efficacy. The use of similarity exercises is the core of the unique pathway needed to appropriately assess biosimilars and to ensure they are comparable to the innovative reference product. This risk-benefit assessment process should ensure that there are no clinically meaningful differences with the reference product before the biosimilar candidate receives marketing authorization, thus minimizing risks to patients. (BIO, 2013)

The question that follows is: Which is the main role playing in the discussion between the government and the industry: is it in reality a scientific issue or is it more a political one? Of course the easy entry of biosimilars (only if those are really products with efficacy, safety and quality) would benefit the access to innovative therapies for many patients, having a mayor quantity of them could obtain profit, this especially if considering that economically speaking, the government could cover a bigger population with therapies after the considerable reduction of costs generated by the entry of biosimilars to the market.

However, even if being valid the concerns of the industry in regard to the uncertainness that through the third pathway, the efficacy, security and quality of the medicinal products being approved and entering the market would be ensured and

that the third pathway creates public health concerns and confusion among patients and physicians with inadequate benefit-risk profile for the Colombian population. It is also understandable that the entry without many barriers of the biosimilars would dismiss the profitability of the innovators that during the patent time were having the maximal profitability in the absence of competitors and after the expiry of the patent will have in a faster way competition. Is this the real reason behind the concern with the third way or keep it really being a public health one?

Data protection generally requires that a biosimilar product relying on the clinical data supporting approval for an innovator reference product not be approved for a defined period of time. This type of protection is essential for innovators to recoup their investment in research and development costs and thereby provides incentives for companies to develop innovative new therapies. But if this protection is enough incentive for the industry is also a question. Strong regulation for the entry of biosimilars could be an additional incentive willed to have by the industry.

In summary the important thing is that reduction of prices should never be an excuse for preventing the provision of medicinal products thereby putting in risk the health of millions of people.

Independent of those political issues and moving on to the scientific role, it is to be considered that the next step to be done after the signature of the new regulation is the fortification of the Regulatory Affairs Environment. A correct approach in this area will ensure that only what counts with efficacy, safety and quality can enter the market.

The Regulatory Affairs Environment should not create unnecessary barriers to the access while at the same time it must be rigorous enough to let the entry only of what fulfills the standards of efficacy, safety and quality that the citizens of Colombia deserve. In order to achieve those objectives some measures have to be evaluated to make the system more efficient, consistent and fair. Alternative to achieve this goal will be discussed in chapter 4.

3.6. Overview of Approvals and Rejections from New Molecular Entities of Oncological Medicinal Products from 2010 to 2014

36 New molecular entities (NME) within the therapeutic area of Oncology were filled between 2010 and 2014 for Health registration to the Colombian National Institute of Surveillance for Medicines and Foodstuffs (abbreviated as INVIMA in Spanish). As described below in Table 1, 23 (63.9%) of those 36 NME successfully received a Health registration (Colombian equivalent to Marketing Authorization), while the remaining 13 applications were rejected. Except from MEPACT (local approval in 2012) and CIMAvax-EGF (local approval in 2014), all other 34 NCEs have been previously submitted and approved by well-known High Surveillance Health Authorities (HA) like EMA or US FDA. MEPACT's NDA was found to be rejected by

the US FDA, while for CIMAvax-EGF no NDA/MA/Health submission for registration was found in High-Surveillance Health Agencies.

Table 1. Approvals and Rejections from New Molecular Entities of Oncological Medicinal Products from 2010 to 2014 in Colombia.

Year	Number of oncological medicinal products evaluated byINVIMA (Colombian HA)			Approved Product Name in colombia/INN	Rejected Product Name/INN
	Approved	Rejected	Total		
2010	3	0	3	TORISEL temsirolimus IRESSA Gefitinib VOTRIENT pazopanib	
2011	3	0	3	YERVOY ipilimumab JEVTANA cabazitaxel ZYTIGA abiraerona	
2012	5	2	7	ZELBORAF vemurafenib RIBOMUSTIN bendamustine hydrochloride INLYTA Axitinib TEMOZOLOMIDA temozolomida	STIVARGA regorafenib XALKORI crizotinib
2013	8	3	11	MOZOBIL Plerixafor PERJETA pertuzumab KADCYLA trastuzumab emtansina – T-DM1 MEPACT mifamurtida	JENZYL ridaforolimus XALKORI crizotinib GIOTRIF Afatinib

				XOFIGO cloruro de radio-223 FOLOTYN Pralatrexato ADCETRIS brentuximab vedotin AZEC PACLITAXEL paclitaxel	
2014	4	8	12	GAZYVA obinutuzumab CIMAvax-EGF rhEGF-rP64K IMBRUVICA ibrutinib XALKORI Crizotinib	ISTODAX romidepsin GIOTRIF Afatinib VARGATEF nintedanib XTANDI enzalutamida ZYKADIA ceritinib STIVARGA regorafenib CYRAMZA ramucirumab FARYDAK panobinostat
TOTAL	23	13	36		

(ActasInvima)

The regulatory approval dates in the EMA, FDA and INVIMA are listed below in Table 2. From this table it can be clearly observed that in some cases Colombian registrations are getting approval short after approval in Europa or the United States. The fact that a CPP (Certificate of Pharmaceutical Product) is required doesn't necessary delay the approval too much due to the fact that it can also be provided during the review process and is not mandatory at the time of the submission but it confirms that INVIMA grant its local approval based on the verification of the Marketing authorization status in the country of Origin and GMP compliance of the manufacturer, which are both declared in the CPP.

The implications of that are, that the applications for MA are most of the times first being filled in the US and Europe, and only after, they are filled in Colombia. Although an exception could be found regarding the product CIMAvax-EGF, were no submission evidence in the EMA or FDA was found.

In some other cases there was a big difference between the time when approval in the EMA and the FDA was granted in comparison with Colombia. This can be associated, either that pharmaceutical companies did not submit the applications in

Colombia in parallel or short after MA approval in CoO countries, or due to the stricter requirements of the INVIMA which leaded to the delayed final approval.

Table 2. Dates of approvals of Oncological Medicinal Products by INVIMA, EMA and FDA.

Product	Approval Date INVIMA	Approval Date EMA	Approval Date FDA
TORISEL temsirolimus	23/03/2010	19/11/2007	30/05/2007
IRESSA Gefitinib	23/03/2010	22/07/2009	05/05/2003
VOTRIENT pazopanib	23/08/2010	14/06/2010	19/10/2009
YERVOY® ipilimumab	18/10/2011	13/07/2011	25/03/2011
JEVTANA cabazitaxel	24/08/2011	17/03/2011	17/06/2010
ZELBORAF vemurafenib	25/04/2012	17/02/2012	17/08/2011
RIBOMUSTIN Bendamustine hydrochloride	29/02/2012	07/07/2012	20/03/2008
INLYTA Axitinib	24/09/2012	03/09/2012	27/01/2012
TEMOZOLOMIDA temozolomida	24/09/2012	28/01/2010	01/03/2010
MOZOBIL Plerixafor	25/02/2013	31/07/2009	15/12/2008
PERJETA pertuzumab	14/05/2013	04/03/2013	08/06/2012
KADCYLA trastuzumab emtansina – T-DM1	15/04/13	15/03/2013	22/02/2013
MEPACT mifamurtida	14/05/2013	06/03/2009	denied
XOFIGO cloruro de radio-223	12/06/2013	13/11/2013	15/05/2013
FOLOTYN Pralatrexato	10/10/13	21/06/2012	24/09/2009

ADCETRIS brentuximab vedotin	07/11/13	25/10/2012	19/08/2011
AZEC PACLITAXEL paclitaxel	18/03/2013	11/01/2008	29/12/1992
GAZYVA Obinutuzumab	27/02/2014	23/07/2014	01/11/2013
CIMAvax-EGF rhEGF-rP64K	05/02/2014	-	-
IMBRUVICA Ibrutinib	03/12/2014	21/10/2014	12/02/2014
XALKORI Crizotinib	03/12/2014	23/10/2012	26/08/2011

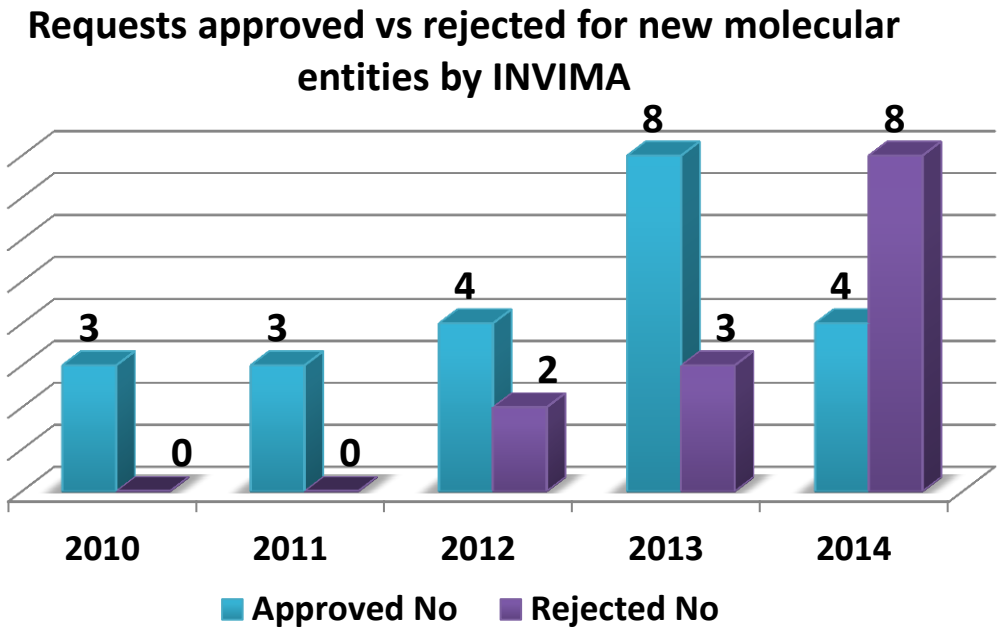


Figure 5. Number of applications for Marketing Authorization of new molecular entities in oncology indications approved and rejected from 2010 to 2014 in Colombia

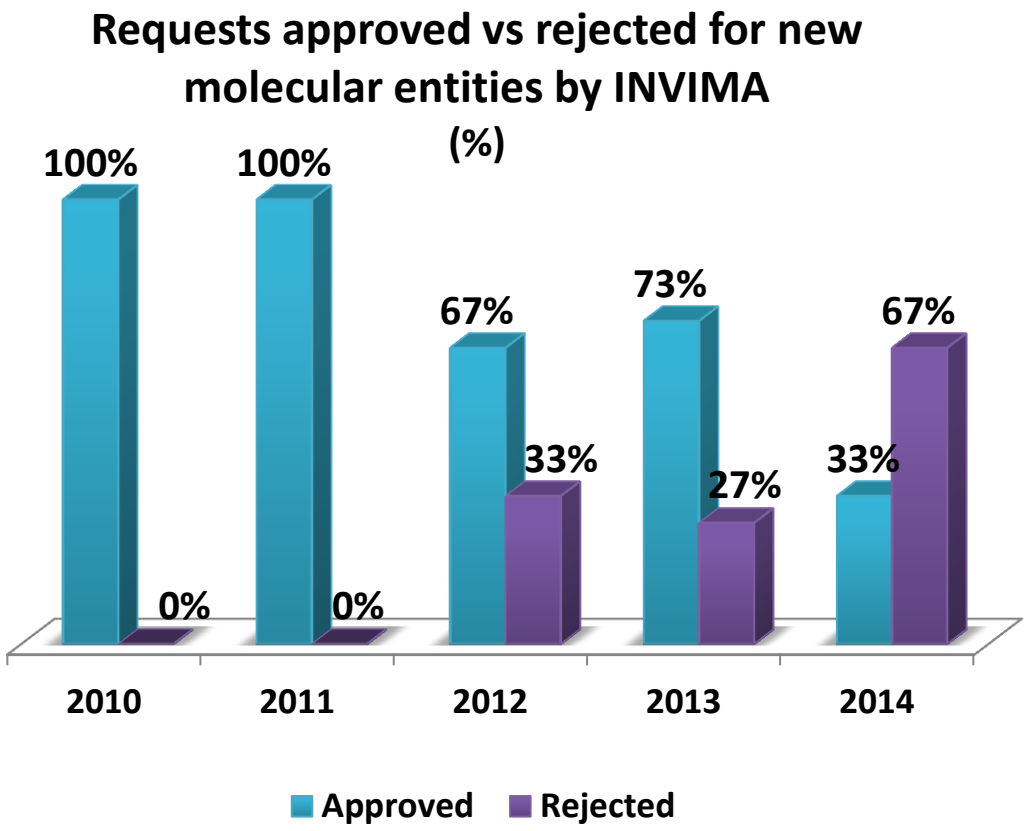


Figure 6. Percentage of applications for Marketing Authorization of new molecular entities in oncology approved and rejected from 2010 to 2014 in Colombia

Figure 5 shows an increase on the total number of applications within the analyzed 5-year period: 3 in 2010 versus 12 in 2014. Additionally, in Figure 6 it is also observed that the percentage of approvals in relation to the total number of applications per year has decreased from 100% to 33% within the same period and consequently a higher percentage of rejections is observed in the local market.

Oncological medicinal products that have not been approved until the end of 2014 (either rejected, additional data required or negative opinion) in Colombia are shown in table 3. A comparison between the decision taken by the HA in Europa (EMA) and the HA in the United States of America (FDA) for the same service are also included there. The Medicinal product Xalcori has been included in this table even though it has been approved by INVIMA at the end of 2014. Xalcori is included in the analysis because Xalcory was repeatedly rejected since 2011 and only received local approval at the end of 2014, which was only reflected in the first INVIMA´s report from 2015.

Table 3. Comparison on the decisions taken by the EMA and the FDA on the until end of 2014 rejected oncological medicinal products in Colombia

Product/INN	EMA Assessment/Date	FDA Assessment/Date	INVIMA Assessment/Date
STIVARGA regorafenib	Approved (EPARStivarga, 2014) 26/08/2013	Approved (FDARegorafenib, 2012) 27/09/2012	Not approved Act 40 11/09/2012 Act 66 31/12/2012 Act 5 14/05/2014 Act 9 08/07/2014 Act 18 21/10/2014
XALKORI crizotinib	Approved (EPARXalcori, 2014) 23/10/2012	Approved (FDACrizotinib, 2013) 20/11/2013	Not approved Act 61 13/12/2011 Act 34 23/07/2012 Act 40 21/08/2012 Act 12 10/04/2013 Act 3 13/03/2014 Act 5 15/05/2014 **Approved dec 2014** Act 27 20/01/2015
JENZYL ridaforolimus	Application has been withdrawn by the applicant (EPARJenzyl, 2013) 27/11/2012	No public information found.	Not approved Act 3 21/02/2013
GIOTRIF afatinib base	Approved (EPARGiotrif, 2013) 25/09/2013	Approved (FDAAfatinib, 2013) 12/07/2013	Not approved Act 23 05/06/2013 Act 47 22/11/2013 Act 11 04/07/2014
XTANDI enzalutamide	Approved (EPARXtandi, 2013) 21/06/2013	Approved (FDAEnzalutamide, 2012) 31/08/2012	Not approved Act 7 06/06/2014
VARGATEF nintedanib	Approved (EPARVargatef, 2015) 21/11/2014	No information on submission in cancer indication has been found.	Not approved Act 3 13/03/2014 Act 5 14/05/2014 Act 16 19/09/2014
ZYKADIA ceritinib	Is now under evaluation in the EMA. (EMACeritinib, 2014)	Approved (FDACeritinib, 2014) 29/04/2014	Not approved Act 14 03/09/2014 Act 27 20/01/2015
ISTODAX romidepsin	Refused (EPARIstodax, 2012) 12/02/2013	Approved (FDARomidepsin, 2010) 05/11/2009	Not approved Act 7 06/06/2014
CYRAMZA ramucirumab	Approved (EPARCyramza, 2015) 19/12/2014	Approved (FDARamucirumab, 2014) 12/12/2014	Not approved Act 27 20/01/2015

FARYDAK panobinostat	Orphan designation granted 02/02/2010 Application has been withdrawn by the applicant 04/2012 (RDDPanobinostat, 2010)	Approved (FDAPanobinostat, 2015)	Not approved Act 24 19/12/2014

A closer look at the reasons why 10 oncological medicinal products were rejected or not approved upon evaluation by INVIMA shows that INVIMA considered that either the presented data on efficacy or safety were incomplete, inadequate and/or insufficient. Despite the fact that the EMA and the FDA have reviewed most of these NMEs 10 with a positive outcome by both health authorities in 5 cases, namely, STIVARGA (regorafenib), XALKORI (crizotinib), GIOTRIF (afatinib base), XTANDI (enzalutamide) and CYRAMZA (ramucirumab), the INVIMA still decided not to approve them (at least until the last report emitted by INVIMA at the end of 2014), thus preventing the introduction of these innovative medicines in the Colombian market.

One of the applications mentioned in the table above (JENZYL, ridaforolimus) was withdrawn by the applicant from the evaluation after the applicant perceived a low likelihood of approval by the EMA. No public information is available regarding a submission of the same application to the FDA.

The application of VARGATEF (nintedanib) was approved by the EMA. At the FDA it is approved for a non-oncological indication, but the cancer indication has not been submitted.

ZYKADIA (ceritinib) which is approved by the FDA, is under evaluation by the EMA at the end of 2014.

ISTODAX (romidepsin) has been refused by the EMA but approved by the FDA.

Finally, the application of FARYDAK (panobinostat) has been withdrawn from the EMA, whereby the FDA granted its approval.

It is to be noted that since 2012, the INVIMA started becoming stricter on the clinical endpoints accepted to prove the efficacy of the medicinal products, giving for example a big weight to the endpoint overall survival (OS) and being less flexible with other endpoints usually evaluated in cancer such as progression-free survival (PFS), Quality of life (QoL), etc. Although INVIMAS´s competence is the scientific evaluation of medicinal products and not its price or eligibility for reimbursement, this shift toward more strict clinical endpoints have coincidentally occur while the health crisis in Colombia reached a critical point, in part due to the high costs of medicinal products, where oncological products play an important role.

Strengthening of the clinical requirements can be tentatively observed as a protective government measure to ensure sustainability and coverage of the Colombian Health system.

Some of the factors leading to the current health crisis in Colombia, included the high prices of new medicinal products that were either directly covered by Public and Private founds (POS – Obligatory Health Plan) or reimbursed to the patients after claiming on the case by case basis at the Colombian Law Courts based on the individual´s right to Health and Medicinal treatment (Individual class action, so called Tutela). Taking this into consideration, it becomes easier to understand the reluctancy of the INVIMA to approve new medicinal products.

Although FDA and EMA the two most important HA worldwide approved medicinal products, INVIMA is not granting approval until end of 2014 in 5 of the cases, which can be seen as a measure for cost containment, that is necessary for helping the health system to recover from the crisis of the last years. This holds true especially if taking into account that these new medicinal products, although bringing innovative treatment options to many Colombian patients, generate additional high costs to the ailing health system.

INVIMA's increasing rejection-trend can also be analyzed from a different perspective. In the case of Xalcory (crizotinib), which was rejected for at least 6 opportunities during the pharmacological evaluation until its final approval in December 2014, the INVIMA might have been safeguarding by awaiting the outcome of the assessment on efficacy and safety of these new medicinal products provided by the experienced High Surveillance Health Authorities (i.e. FDA and EMA) before deciding its local approval. A clear consequence of this "conservative approach" is the delayed access of Colombian patients to new medicinal products when comparing with other countries.

Finally, this can also be seen as a sign of lack of expertise for the evaluation of complex applications at the INVIMA which is maybe a consequence among others of low resources; since the INVIMA is waiting for the evaluation of other Health Authorities before issuing an approval. This is a valid approach that also other HAs in the world follow as an option when due to the low resources they base their scientific assessment on the evaluation of High Surveillance HAs. This can be reiterated by the fact that Certificate of Pharmaceutical Product (CPP) is one of the requirements for approval in Colombia and that in none of the analyzed cases, a case could be found, where submitted application to the EMA or the FDA and still under evaluation there, were first approved in Colombia. What call the attention is, that in some cases INVIMA doesn't base its decision on EMA and FDA positive outcome on applications as reflected in the 5 mentioned cases denied in Colombia but approved in the EMA and the FDA.

In the following subsections 3.6.1 - 3.6.10 a detailed comparison can be appreciated between the final decisions that the EMA, FDA and INVIMA took in regard to the 10 medicinal products not approved until now in the period from 2010 – 2014 in

Colombia. It helps to understand how are those 3 HA taking decisions, what is guiding the decisions for granting or not approval.

3.6.1. STIVARGA (regorafenib)

Table 4. EMA Decision, FDA Decision, INVIMA Decision on STIVARGA

Agency	Decision in detail
EMA Approved	The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that Stivarga's benefits are greater than its risks and recommended that it be approved for use in the EU. The Committee noted that in colorectal cancer the benefits in terms of extending patient survival were modest, but considered that they outweighed the risks in patients for whom there are no other remaining treatment options. However, given the side effects, the CHMP considered it important to find ways to identify any subgroups of patients who are more likely to respond to Stivarga. With regard to GIST, the Committee noted that the outlook is poor for patients whose disease gets worse despite treatment with imatinib and sunitinib. Stivarga had been shown to delay the worsening of the disease in these patients and its side effects are manageable. (EPARStivarga, 2014)
FDA Approved	In September 27, 2012, the U. S. Food and Drug Administration approved regorafenib (Stivarga tablets, Bayer HealthCare Pharmaceuticals, Inc.), for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. The approval was based on the results of an international, randomized (2:1), double-blind, placebo-controlled trial (Study 14387) enrolling 760 patients with previously treated mCRC. A statistically significant prolongation in overall survival was observed in patients randomized to receive regorafenib [hazard ratio (HR) 0.77 (95% CI: 0.64, 0.94); p=0.0102]. The median survival time was 6.4 months (95% CI: 5.8, 7.3) in the regorafenib arm and 5.0 months (95% CI: 4.4, 5.8) in the placebo arm. The trial also demonstrated a statistically significant improvement in progression-free survival [HR 0.49 (95% CI: 0.42, 0.58); p<0.0001]. The median progression-free survival was 2.0 months (95% CI: 1.9, 2.3) in the regorafenib arm and 1.7 months (95% CI: 1.7, 1.8) in the placebo arm. No difference in overall response rate was observed. Five patients (1%) in the regorafenib arm and one patient (0.4%) in the placebo arm experienced partial responses. The safety population in Study 14387 comprised 500 patients who received regorafenib and 253 patients who received placebo. The most frequently observed adverse drug reactions (≥30%) in patients receiving regorafenib are asthenia/fatigue, decreased appetite and food intake, hand-foot skin reaction, diarrhea, mucositis, weight loss, infection, hypertension and dysphonia. The most serious adverse drug reactions in patients receiving regorafenib are hepatotoxicity, hemorrhage, and gastrointestinal perforation. Regorafenib is approved with a boxed warning describing the risk of hepatotoxicity. (FDARegorafenib, 2012)
INVIMA Not approved	The Revising Commission of Pharmaceutical Products (Sala especializada de medicamentos y productos biologicos de la comision revisora) considers clinical studies presented are not conclusive because the margins of overall survival and progression-free survival are clinically insignificant which means results from clinical studies show no

	clinical relevance in terms of effectiveness and improvement of the quality of life of patients. Additionally they consider that it failed to properly set the security balance / risk of the product this as a consequence that the RAM frequency is high and may generate severe problems such as hepatotoxicity, bleeding and cardiac disorders. (ActasInvima)

In the case of the product STIVAGRA (regorafenib), in the indication of colorectal cancer; the INVIMA was of the opinion that the small improvements in overall survival and progression-free survival are not seen as acceptable for granting approval. Greater results are looked for. The EMA and the FDA serious adverse reactions are very common, the EMA and the FDA were of the opinion that the benefits outweighed the risks, since it was acknowledged that for these patients no other remaining treatment options are available and granted therefore the approval.

3.6.2. XALKORI (crizotinib)

Table 5. EMA Decision, FDA Decision, INVIMA Decision on XALKORI

Agency	Decision in detail
EMA Approved	The CHMP concluded that the available study results showed that treatment with Xalkori has a beneficial effect, and noted that this was supported by updated data on the survival of patients and the preliminary results of a larger study. Therefore the CHMP decided that Xalkori's benefits are greater than its risks and recommended that it be given marketing authorisation. Xalkori has been given 'conditional approval'. This means that there is more evidence to come about the medicine, in particular data from a larger study and the longer term outcomes of patients included in the studies already considered. Every year, the European Medicines Agency will review any new information that may become available and this summary will be updated as necessary. (EPARXalcori, 2014)
FDA Approved	On November 20, 2013, the U. S. Food and Drug Administration granted regular approval for crizotinib (Xalkori, Pfizer, Inc.) capsules for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. Today's approval was based on demonstration of superior progression-free survival (PFS) and overall response rate (ORR) for crizotinib-treated patients compared to chemotherapy in patients with ALK-positive NSCLC with disease progression after platinum-based doublet chemotherapy. The trial demonstrated significantly prolonged progression-free survival (PFS) for crizotinib treatment compared to chemotherapy [HR=0.49, (95% CI: 0.37, 0.64), p<0.0001]. Median PFS was 7.7 and 3.0 months on the crizotinib and chemotherapy arms, respectively. The ORR was significantly higher for the crizotinib arm (65% vs. 20%) with median response durations of 7.4 and 5.6 months in the crizotinib and chemotherapy arms, respectively. No difference in overall survival was noted between the two arms [HR= 1.02 (95% CI: 0.68, 1.54)] in a planned interim analysis. Common adverse reactions in clinical trials with crizotinib, occurring at an incidence of 25% or higher, included visual disorders, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue.

	Safety data from this trial was evaluated in 172 crizotinib-treated patients. Serious adverse events were reported in 37% of crizotinib-treated patients. The most common serious adverse reactions of crizotinib were pneumonia, pulmonary embolism, dyspnea, and interstitial lung disease. Fatal adverse reactions occurred in 9 crizotinib-treated patients and included acute respiratory distress syndrome, arrhythmia, dyspnea, pneumonia, pneumonitis, pulmonary embolism, interstitial lung disease, respiratory failure, and sepsis. Crizotinib was previously granted accelerated approval in August, 2011 based on durable, objective response rates (ORR) of 50% and 61% in two single-arm, open-label studies. (FDACrizotinib, 2013)
INVIMA Not approved	The Revising Commission of Pharmaceutical Products (Sala especializada de medicamentos y productos biologicos de la comision revisora) considers that current studies are insufficient as only Phase I and Phase II studies are available and to evaluate efficacy and safety, well-controlled phase III comparative studies are needed in order to demonstrate what is the difference in overall survival time and progression free survival when comparing with the standard treatment. Additionally it was reconfirmed that the information is insufficient to determine the risk / benefit in patients with ALK-positive advanced non-small cell lung cancer, in regard to the overall survival and quality of life. Further they informed that because of the extent of the information and the way how it was presented it was not easy to perform the evaluation of the application. That the information has to be provided organized, clear, legible and in a number of rational folios that not unreasonably increase the evaluation time and additional administrative wear. In the last concept, the Revising Commission of Pharmaceutical Products considers that although the reference product shows differences versus conventional chemotherapy in patients with subtype variant ALK (+) in outcomes such as disease-free time, risk reduction and response speed, no differences demonstrated in overall survival times and considering that the chromosomal mutation ALK (+) is a poor indicator in the proposed indication, the Chamber finds no evidence that allows to recommend approval of the product. The Revising Commission of Pharmaceutical Products (Sala especializada de medicamentos y productos biologicos de la comision revisora) recommend to approve the product of the reference. Act 27 20114. (ActasInvima)

In case of XALKORI (crizotinib) in the indication of ALK-positive NSCLC, the INVIMA was of the opinion that results of a well-controlled phase III comparative trial is necessary to evaluate the benefit in OS and PFS compared to standard treatment. As the OS endpoint did not show differences and more data should be generated, approval was not granted. The first negative opinion arose in 2011 and only in Dec 2014 the approval for Xalcori was granted.

EMA provided conditional approval, an option which is not available in Colombia. Through this option (conditional approval), approval and access to this medicine is granted but confirmatory trial with additional supportive data should be provided later in order to convert to a full approval. The FDA approved based on demonstration of superior progression-free survival (PFS) and overall response rate (ORR)

3.6.3. JENZYL (ridaforolimus)

Table 6. EMA Decision, FDA Decision, INVIMA Decision on JENZYL

Agency	Decision in detail
EMA Withdrawn	Based on the review of the data and the company's response to the CHMP list of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Jenzyl could not have been approved for the treatment of patients with metastatic soft-tissue sarcoma or bone sarcoma as maintenance therapy. The CHMP was concerned that taking Jenzyl only led to a small increase in the time patients lived until their disease got worse compared with placebo (18 versus 15 weeks in patients who had one or more regimens of previous chemotherapy, and 16 versus 10 weeks in patients who had received two or three previous regimens of chemotherapy). The CHMP considered this benefit to be modest, when taking into account that patients usually survived for a long time after their disease had progressed. The CHMP also considered that the somewhat larger effect seen in patients who had received two or three previous regimens of chemotherapy compared with those who received one or more regimens might not reflect the medicine's true effect size, as the reason the medicine would work better at later stages of the disease was unclear. In terms of safety, the CHMP was concerned by the high frequency of side effects interfering with the patient's wellbeing as well as some uncommon but potentially lifethreatening side effects. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Jenzyl did not outweigh its risks. (EPARJenzyl, 2013)
FDA No Information	
INVIMA Not approved	The Revising Commission of Pharmaceutical Products considers that the information is insufficient to support the efficacy and safety of the product in the proposed indication, therefore the application of pharmacological evaluation for the product has been refused. (ActasInvima)

In case of Jenzyl (ridaforolimus) for the indication of metastatic soft-tissue sarcoma or bone sarcoma as maintenance therapy, the INVIMA was of the opinion that the benefit is modest and as there is a high frequency of side effects, therefore the approval should not be granted. EMA was of the opinion that the benefits of Jenzyl did not outweigh its risks and gave a negative opinion therefore the applicant decided to withdraw the application. The negative opinion was based on the small increase of PFS relative to the side effects. In the FDA no information on submission could be found.

3.6.4. GIOTRIF (afatinib base)

Table 7. EMA Decision, FDA Decision, INVIMA Decision on GIOTRIF

Agency	Decision in detail
EMA Approved	The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that the benefits of Giotrif outweigh its risks and recommended that it be granted marketing

	authorisation in the EU. The CHMP considered that in patients treated with Giotrif the improvement in progression-free survival (how long they lived without the disease getting worse) was a meaningful benefit for patients. In addition, the side effects of the medicine were considered to be manageable and similar to those seen with medicines of the same class. (EPARGiotrif, 2013)
FDA Approved	On July 12, 2013, the U. S. Food and Drug Administration approved afatinib (Gilotrif tablets, Boehringer Ingelheim Pharmaceuticals, Inc.), for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. The safety and efficacy of afatinib have not been established in patients whose tumors have other EGFR mutations. Concurrent with this action, FDA approved the therascreen EGFR RGQ PCR Kit (QIAGEN) for detection of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. The approval of afatinib was based on the demonstration of improved progression-free survival (PFS) in a multi-center, international, open-label, randomized (2:1) trial. The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). A statistically significant prolongation of PFS determined by the IRC was demonstrated for patients assigned to the afatinib treatment arm [HR 0.58 (95% CI: 0.43, 0.78); p < 0.001, stratified log-rank test]. The median PFS was 11.1 months in the afatinib arm and 6.9 months in the chemotherapy arm. Objective response rates were 50.4% and 19.1% in the afatinib and chemotherapy arms, respectively. No statistically significant difference in overall survival between the two arms was demonstrated. In patients whose tumors have exon 19 deletions or exon 21 (L858R) substitution mutations, the median PFS was 13.6 months in the afatinib arm and 6.9 months in the chemotherapy arm. The most frequent (≥20% incidence) adverse reactions from afatinib were diarrhea, rash/dermatitis acneiform, stomatitis, paronychia, dry skin, decreased appetite and pruritus. Serious adverse reactions were reported in 29% of patients treated with afatinib. The most frequent serious adverse reactions were diarrhea (6.6%), vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in afatinib-treated patients included pulmonary toxicity/ interstitial lung disease (ILD)-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%). (FDAAfatinib, 2013)
INVIMA Not approved	The Revising Commission of Pharmaceutical Products considers that the information provided by the applicant is insufficient regarding safety and effectiveness, conducting to the non-approval of the product. The Revising Commission of Pharmaceutical Products considers that the applicant must bring comparative studies with medicinal products inhibitors of epidermal growth factor to evidence clinical utility. Additionally, the Board notes that the overall survival does not have the sufficient sample size to be considered "mature" and therefore recommends to complete the study. (ActasInvima)

In case of (afatinib base) for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC), the INVIMA did not grant approval even if statistically significant prolongation of PFS was demonstrated but for the fact that no statistical significant difference in the overall survival was demonstrated when comparing with placebo. The INVIMA gives mostly importance to the OS as endpoint

for evaluation of the additional benefit. The EMA and FDA conversely accepted PFS when approving this medicinal product. As not conditional approval is possible in Colombia, there is a delay in the access to medicinal products.

3.6.5. XTANDI (enzalutamide)

Table 8. EMA Decision, FDA Decision, INVIMA Decision on XTANDI

Agency	Decision in detail
EMA Approved	The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that Xtandi's benefits are greater than its risks and recommended that it be approved for use in the EU. The CHMP considered that the anticancer effects of Xtandi had been clearly demonstrated and that its benefit in terms of prolonging life is important for patients. Regarding its safety, the Committee concluded that the side effects with Xtandi were generally mild and could be managed appropriately. (EPARXtandi, 2013)
FDA Approved	On August 31, 2012, the U. S. Food and Drug Administration approved enzalutamide (XTANDI Capsules, Medivation, Inc. and Astellas Pharma US, Inc.), for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel. The primary efficacy endpoint was overall survival (OS). At the pre-specified interim analysis after 520 events, a statistically significant improvement in OS [HR 0.63 (95% CI: 0.53, 0.75), p < 0.0001, log rank test] was observed. The median OS was 18.4 and 13.6 months in the enzalutamide and placebo arms, respectively. The most common (≥5%) grade 1-4 adverse reactions included asthenia or fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3-4 adverse reactions were reported in 47% of patients treated with enzalutamide and in 53% of those on placebo. Seizures occurred in 0.9% of patients on enzalutamide. No patients on the placebo arm experienced seizures. In the clinical trial, patients experiencing a seizure were permanently discontinued from therapy. All seizures resolved. Patients with a history of seizure, taking medications known to decrease the seizure threshold, or with other risk factors for seizures were excluded from the clinical trial. The safety of enzalutamide in patients with predisposing factors for seizures is unknown. (FDAEnzalutamide, 2012)
INVIMA Not approved	The Revising Commission of Pharmaceutical Products recommended denying the reference product, as it does not lead to the conclusion about the actual effectiveness and safety. (ActasInvima)

In case of XTANDI (enzalutamide) for metastatic castration-resistant prostate cancer, the INVIMA did not grant approval without much information available on the reasons, except only that it does not lead to the conclusion about the actual effectiveness and safety. The EMA and the FDA granted approval based on the consideration that the benefits are greater than the risks demonstrated by the end point OS (Statistical significant improvement). INVIMA's result is not comprehensible and also inconsistent, since here the OS is shown to be significant different.

3.6.6. VARGATEF (nintedanib)

Table 9. EMA Decision, FDA Decision, INVIMA Decision on VARGATEF

Agency	Decision in detail
EMA Approved	The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that Vargatef's benefits are greater than its risks and recommended that it be approved for use in the EU. The CHMP noted that Vargatef was effective at slowing down disease progression and prolonging life in the subgroup of patients with non-small cell lung cancer of the adenocarcinoma type. Regarding its safety, although more side effects were reported in patients treated with Vargatef plus docetaxel than in those treated with docetaxel alone, the side effects were considered manageable with dose reductions, supportive treatments and treatment interruptions. The benefits with the addition of nintedanib to docetaxel were in terms of an improvement in progression – free survival and Overall survival as compared to docetaxel plus placebo. The most common side effects are: neutropenia (including febrile neutropenia), decreased appetite, electrolyte imbalance, peripheral neuropathy, bleeding, diarrhoea, vomiting, nausea, alanine aminotransferase increased, aspartase aminotransferase increased, blood alkaline phosphatyase increased, mucositis (including stomatitis), rash. (EPARVargatef, 2015)
FDA No information	
INVIMA Not approved	The Revising Commission of Pharmaceutical Products informed that becuase of the extend of the imnformation and the way how it was presented it was not easy to perform the evaluation of the application. That the information has to be provided organized, clear, legible and in a number of rational folios that not unreasonably increase the evaluation time and additional administrative wear. Additionally after the evaluation of the information the review committee considers that one of the two Phase III studies was inconclusive, little difference was also evident in the results of progression-free survival and overall survival versus comparators, and a considerable number of adverse events, some serious and fatal. Therefore, the Special Branch of Drugs and Biologicals Review Commission considers that further phase III studies to assess and determine with greater certainty the efficacy and safety profile of the product in the proposed indication are needed. They consider that the results of the evaluation parameters of the disease (progression-free survival and overall survival) don't show an impact of great magnitude against adverse effects, some serious and fatal, which establishes a negative risk-benefit ratio. Additionally, for the application of new indication for the treatment of Idiopathic Pulmonary Fibrosis, the Board recommended denying presented because it corresponds to a phase II study. (ActasInvima)

In case of VARGATEF (nintedanib) for the non-small cell lung cancer, the INVIMA consider that the results of the evaluation parameters of the disease (progression-free survival and overall survival) don't show an impact of great magnitude against adverse effects, some serious and fatal, which establishes a negative risk-benefit ratio.

The EMA considers that benefits are greater than its risks based on the results on PFS and OS and that the side effects were considered manageable with dose reductions, supportive treatments and treatment interruptions. In the FDA no information could be found on submission.

Stricter evaluation appreciated by the INVIMA without possibility of conditional approval.

3.6.7. ZYKADIA (ceritinib)

Table 10. EMA Decision, FDA Decision, INVIMA Decision on ZYKADIA

Agency	Decision in detail
EMA **In still under evaluation**	By December 2014 this product is under evaluation by the CHMP (Committee for Medicinal Products for Human Use) (EMACeritinib, 2014)
FDA **Approved**	On April 29, 2014, the U. S. Food and Drug Administration granted accelerated approval to ceritinib (ZYKADIA, Novartis Pharmaceuticals Corporation) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) with disease progression on or who are intolerant to crizotinib. On March 6, 2013, FDA granted ceritinib breakthrough therapy designation based on preliminary evidence of clinical activity in patients with metastatic ALK-positive NSCLC previously treated with crizotinib. The approval of ceritinib was based on the results of a multicenter, single-arm, open-label clinical trial enrolling a total of 163 patients with metastatic, ALK-positive, NSCLC who had progressed on or were intolerant to crizotinib. All patients received ceritinib at a dose of 750 mg once daily. The primary endpoint supporting approval was objective response rate (ORR) according to RECIST v1.0 as evaluated by both investigator and a Blinded Independent Central Review Committee (BIRC). Duration of response (DOR) was also assessed. The trial results demonstrated durable responses of large magnitude with an ORR of 44% (95% CI: 36, 52) and DOR of 7.1 months based on BIRC-determined tumor assessments. The analysis by investigator assessment showed similar results with an ORR of 55% (95% CI: 47, 62) and DOR of 7.4 months. The safety evaluation of ceritinib was based on 255 patients with ALK-positive tumors (246 patients with NSCLC and 9 patients with other cancers) who received ceritinib at a dose of 750 mg once daily. The most common adverse reactions (greater than or equal to 25%) were diarrhea, nausea, transaminitis, vomiting, abdominal pain, fatigue, decreased appetite and constipation. The most common CTCAE Grade 3-4 adverse reactions (greater than or equal to 5%) were diarrhea, fatigue, transaminitis, hyperglycemia, hypophosphatemia, increased lipase levels, and anemia. Additional serious adverse reactions include interstitial lung disease and QT prolongation. (FDACeritinib, 2014)
INVIMA **Not approved**	The Revising Commission of Pharmaceutical Products considers that the information provided is insufficient considering that the clinical evaluation of the product is incipient and no comparative phase III studies that adequately evaluate the usefulness and safety product in the claimed indication have been provided. (ActasInvima)

In case of Zycadia (ceritinib), the INVIMA did not consider the information provided sufficient as no comparative phase III study is available and request for confirmation

on benefit-risks relationship, therefore no approval has been achieved until now. The FDA provided approval based on the preliminary evidence of clinical activity in patients with metastatic ALK-positive NSCLC previously treated with crizotinib. In the EMA the application has been submitted but is still under evaluation.

3.6.8. ISTODAX (romidepsin)

Table 11. EMA Decision, FDA Decision, INVIMA Decision on ISTODAX

Agency	Decision in detail
EMA Refused	In July 2012, the CHMP noted that the main study showed that Istodax had anti-tumour activity in terms of patients' response to treatment. However, the fact that Istodax was not compared with any other treatment did not allow the Committee to conclude on the clinical benefit of the medicine in terms of overall survival (how long the patients lived) or progression-free survival (how long the patients lived without their disease getting worse). The CHMP also noted that, due to an oversight, the company failed to provide an adequate certificate of Good Manufacturing Practice for the site where the medicine is manufactured, which is legally required. In November 2012, following the re-examination, the CHMP removed its concern over the certificate of Good Manufacturing Practice, but retained its other concerns. In particular, the Committee could not conclude on the clinical benefit of the medicine. As it was not compared with any other treatment, it was not possible to establish whether the observed effects were due to the medicine or due to the disease characteristics of patients in the main study. Therefore it was not possible to conclude that the benefits of the medicine outweigh the risks and the CHMP confirmed its initial negative opinion. (EPARIstodax, 2012)
FDA Approved	On November 5, 2009, the U.S. Food and Drug Administration granted approval to romidepsin for injection (ISTODAX, Gloucester Pharmaceuticals Inc.) for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. The efficacy and safety of romidepsin were evaluated in two single-arm, multicenter, open label trials. Efficacy was assessed in 167 patients with CTCL treated in the United States, Europe, and Australia. Study 1 included 96 patients with CTCL who had received at least 1 prior systemic therapy. Study 2 included 71 patients with CTCL who received a median of 2 prior systemic therapies. In both trials, patients could be treated until disease progression. Overall response was evaluated according to a composite endpoint that included assessments of skin involvement, lymph node and visceral involvement, and Sézary cells.The primary efficacy endpoint for both trials was the overall response rate (ORR) based on the investigator assessments, and defined as the proportion of patients with confirmed complete response (CR) or partial response (PR). The ORRs in these two trials were similar (34 and 35% in Study 1 and Study 2, respectively) and CR rates were the same (6%). The median response duration was 15 months in Study 1 and 11 months in Study 2. Safety data was available and evaluated in 185 patients with CTCL. The most common adverse reactions in Study 1 were nausea, fatigue, infections, vomiting and anorexia. The most common adverse reactions in Study 2 were nausea, fatigue, anemia, thrombocytopenia, ECG T-wave changes, neutropenia and lymphopenia. Serious adverse reactions reported in > 2% of the patients in Study 1 were infection, sepsis, and pyrexia. Serious adverse reactions reported in > 2% of the patients in Study 2 were infection, supraventricular arrhythmia, neutropenia, fatigue, edema, central line infection, ventricular arrhythmia, nausea, pyrexia, leukopenia, and thrombocytopenia. (FDARomidepsin, 2010)
INVIMA Not	The Revising Commission of Pharmaceutical Products considers that there is insufficient evidence to demonstrate the true clinical utility of the product of reference in the

approved	treatment of cutaneous T-cell lymphoma and Hodgkin's cells peripheral T, considering that the results of clinical trials are given in objective and not overall survival or progression-free survival responses. Also, there is not enough clarity in areas such as cardiac toxicity and possible responses due to pharmacogenetic patient characteristics. (ActasInvima)

In case of ISTODAX (romidepsin), for the treatment of cutaneous T-cell lymphoma (CTCL), the INVIMA considered the clinical utility of the product insufficient when considering the primary endpoints was ORR and not OS or PFS. The EMA did not approve based on the fact that no comparison with any other treatment allowed to conclude on the benefits of this medicinal products. Finally and opposite to the EMA and the INVIMA, the FDA granted approval based on the overall response rate in two single arm trials, which showed similar results (confirming one another). The fact no comparator was used, was not considered as a problem.

3.6.9. CYRAMZA (ramucirumab)

Table 12. EMA Decision, FDA Decision, INVIMA Decision on CYRAMZA

Agency	Decision in detail
EMA Approved	The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that Cyramza's benefits are greater than its risks and recommended that it be approved for use in the EU. The CHMP noted that the benefit of Cyramza in prolonging the lives of gastric and gastro-oesophageal junction cancer patients was clearly demonstrated when Cyramza was given with paclitaxel. The benefit was smaller when Cyramza was given on its own, but this could still be a therapeutic option when treatment with paclitaxel is not considered appropriate. The size of the benefit is considered clinically relevant given the normally poor prognosis in these patients. The safety profile of ramucirumab is in line with what is expected for other medicines blocking VEGFR activity and considered acceptable given the benefits of the medicine. (EPARCyramza, 2015)
FDA Approved	On December 12, 2014, the U. S. Food and Drug Administration approved ramucirumab (Cyramza Injection, Eli Lilly and Company) for use in combination with docetaxel for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab. Ramucirumab was previously approved as a single agent and for use in combination with paclitaxel for the treatment of patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma after disease progression on first line therapy. The approval of ramucirumab in combination with docetaxel in NSCLC was based on the demonstration of improved overall survival (OS) in a multicenter, double-blind, placebo-controlled study (I4T-MC-JVBA) that enrolled 1253 patients with previously treated metastatic NSCLC. Patients were randomized to receive either ramucirumab (10 mg/kg every three weeks) in combination with docetaxel (75 mg/m^2 every 3 weeks) on day 1 of a 21-day cycle (n=628) or matching placebo plus docetaxel (n=625). A statistically significant prolongation of OS was demonstrated [HR 0.86; (95% CI: 0.75, 0.98); p=0.024]; median OS was 10.5 months in the ramucirumab plus docetaxel arm and 9.1 months in the placebo plus docetaxel arm. Progression-free survival was also significantly longer for patients receiving ramucirumab plus docetaxel [HR=0.76 (95% CI: 0.68, 0.86); p<0.001)]. Safety data was evaluated in 1245 patients who received at least one dose of study drug.

	The most frequently reported adverse reactions with ramucirumab plus docetaxel (incidence greater than or equal to 30%) were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. The most common serious adverse reactions with ramucirumab plus docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). Recently CRC (Colorectac cancer) indication approved. (FDARamucirumab, 2014)
INVIMA Not approved	The Revising Commission of Pharmaceutical Products recommends to deny the product of the reference considering that the results presented in the three clinical studies phase III do not allow to favorably conclude on the balance risk benefit in the proposed indication, since in spite of the statistical significance, clinical relevance in the replaced one of the patients is not demonstrated and serious adverse effects appear especially hemorrhages, tromboembolicos phenomena and arterial hypertension. (ActasInvima)

In case of CYRAMZA (ramucirumab), the INVIMA denied the approval based on the consideration that the three phase III studies do not allow to favorably conclude on the balance risk benefit in the proposed indication because of serious adverse events .The EMA granted approval for in the indication in advanced gastric cancer by concluding the extent of the benefits is clinically relevant when considering the benefit of prolonging the lives of the patients.

The FDA approved in the indication for advanced or metastatic gastric cancer, NSCLC and recently in metastatic colorectal cancer based on the statistical significance of OS and PFS.

3.6.10. FARYDAK (panobinostat)

Table 13. EMA Decision, FDA Decision, INVIMA Decision on FARYDAK

Agency	Decision in detail
EMA Orphan designation granted Application withdrawn by the applicant	On 2 February 2010, orphan designation (EU/3/09/721) was granted by the European Commission to Novartis Europharm Limited, United Kingdom, for panobinostat for the treatment of Hodgkin's lymphoma. This product was withdrawn from the Community register of designated orphan medicinal products in April 2012 on request of the sponsor. (RDDPanobinostat, 2010)
FDA Approved	On February 23, 2015, the U.S. Food and Drug Administration (FDA) granted accelerated approval to panobinostat (FARYDAK capsules, Novartis Pharmaceuticals) in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. As a condition of this accelerated approval, FDA requires the sponsor to conduct a trial to verify and describe the clinical benefit of panobinostat for patients with multiple myeloma. The approval was based on the results of progression-free survival (PFS) in a subgroup of patients from a randomized, international, two-arm, placebo-controlled trial evaluating panobinostat (or placebo) in combination with bortezomib and dexamethasone. In this pre-specified subgroup of 193 patients who had received prior treatment with bortezomib and an immunomodulatory agent, the median age was 60 years (range 28-79). The primary efficacy endpoint was PFS determined by investigators. The median PFS values were 10.6 and 5.8 months in the panobinostat-containing arm (panobinostat-

	bortezomib-dexamethasone) and control (placebo-bortezomib-dexamethasone), respectively [HR 0.52 (95% CI: 0.36, 0.76)]. Overall response rates were 58.5% (95% CI:47.9, 68.6) in the panobinostat arm and 41.4% (95% CI:31.6, 51.8) in the placebo arm. Safety was evaluated in 758 patients with relapsed multiple myeloma who were treated with panobinostat-bortezomib-dexamethasone or placebo-bortezomib-dexamethasone. The most common adverse reactions (>20%) on the panobinostat-containing arm were diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting. Serious adverse reactions included pneumonia, diarrhea, thrombocytopenia, fatigue, and sepsis. There was an increased incidence in deaths not due to progressive disease (7% vs. 3.2%) on the panobinostat-containing arm. The most common hematologic abnormalities included thrombocytopenia and neutropenia; the most common chemistry abnormalities were hypophosphatemia and hypokalemia. ECG changes, including new T-wave changes and ST-segment depressions, occurred in 64% of patients in the panobinostat-containing arm and 42% in the control arm. Arrhythmias occurred more frequently in patients receiving panobinostat compared to the control arm (12% vs. 5%). Panobinostat is approved with a BOXED WARNING alerting patients and health care providers of severe and fatal cardiac toxicities and severe diarrhea. Hemorrhage and hepatotoxicity are other important safety concerns with panobinostat and are included in the WARNINGS and PRECAUTIONS section of the label. (FDAPanobinostat, 2015)
INVIMA Not approved	The Revising Commission of Pharmaceutical Products recommends to deny the product of the reference, considering that the information is insufficient to determine the true utility of the product, combined with Bortezomib and Dexametasona in the multiple myeloma, in as much as when analyzing the results of the studies phase I,II and III, although there are statistically significant differences, the clinical relevance of such findings is not demonstrated and has security risks as greater frequency of hematological adverse reactions and mortality, in the arm with the treatment that includes the product. (ActasInvima)

In case of FARYDAK (panobinostat) the INVIMA denied approval considering the information is insufficient to determine the utility even if statistically significant improvements in PFS are seen, which is due to the high risk associated to the product, and therefore the benefit does not outweigh the risk. The EMA granted an orphan designation but later the applicant withdraws the application for unknown reasons. In Case of the FDA, there were initially issued a negative opinion on November 2014 but an approval has been granted on February 2015 with the condition that clinical trials should continue in order to verify the clinical effect. (FDA, 2015)

3.7. Endpoints in Cancer and Health Economics

3.7.1. Endpoints, critical issue in evaluation of cancer

Due to the complexity of the development of cancer, the endpoints should be carefully evaluated which are relevant to prove a relevant additional benefit of innovative medicinal products. Detailed guidelines have been established by the EMA and the FDA to provide guidance on the selection of the endpoints depending

on tumor entity and tumor stage, this due to the fact that the expectations on results from the treatments are different depending on it.

One example of it can been seen for the case of Breast Cancer in early stage, where a cure is to be expected and overall survival would not be an adequate endpoint. This due to the long survival time for this condition, where an extension of OS could only be proven many years after the initial treatment. On the opposite, QoL endpoints and measure of the improvement of the morbidity would be more appropriated; additionally PFS could also be considered as the magnitude of PFS effect could help to predict OS.

For a cancer without cure expectation but palliative treatment like advanced metastatic non-small cell lung cancer (NSCLC) or metastatic renal cell carcinoma (RCC), where short survival is expected, OS would be an appropriated endpoint. In this regard the EMA, European HAs and the FDA have guidelines to support in the adequate selection taking into account this complexity. (vfa, 2012)

Specifically, assessment solely on the basis of the endpoint “overall survival” (OS), which has been mainly practiced recently, can lead to distorted results that put patients at a disadvantage, due to a delayed access to new treatment options. This delay to the access is due to the fact that the analysis of overall survival (OS) requires long follow-up monitoring periods, which delay the development of additional effective substances or make the implementation of clinical trials impossible, because in some cases the endpoint can only be reached after many years or decades. Therefore, for ethical reasons alone, overall survival (OS) must not be the sole valid endpoint for benefit assessments. (vfa, 2012)

Results on survival of patients without their disease getting worse, namely progression-free survival (PFS) is measurable on an earlier time point than overall survival and is not influenced by additional therapies after progression of the cancer disease. (vfa, 2012)

In summary, for proving a patient-relevant additional benefit in oncology, endpoints in terms of morbidity must be considered in addition to those regarding mortality and quality of life in order to do justice to the complexity of the situation of the individual patient and his or her treating physicians. (vfa, 2012)

The best possible oncological treatment often achieves an improvement in the state of health that is limited in time, but this improvement does not necessarily manifest itself in an extension of overall survival (OS). Insured patients are also entitled to treatment, if it provides relief from their suffering. (vfa, 2012)

It must be emphasized that a definition of the term *"patient relevance"* and a final weighting of endpoints have yet to be made. Specifically, it must be discussed how the relevance of endpoints for patients can be incorporated more strongly in a benefit assessment in the future. (vfa, 2012) (FDA, 2007)

LIVE LONGER ----------Effective

LIVE BETTER –QUALITY ------Effective

Therefore, as part of the (additional) benefit assessment, the aspects of clinical research and international marketing authorization experience must also be incorporated in order to avoid a “separate Colombian method.” (vfa, 2012)

3.7.2. Health Economics Considerations

Taking a look at the global panorama, the number of oncology-related investigational new drug applications has increased worldwide during the last years, with a growing financial effect on patients and society. Cancer care costs are escalating at a rate of 15% per year, which is nearly three times of the expenses in overall health care. Because of the incidence, severity, the unmet medical need and rising costs of cancer treatments, it is becoming increasingly important to deliver consistent, high-quality, cost-effective care (Chouaïd C, 2014)

The rising financial burden of cancer treatment on health-care systems worldwide has led to the increased demand for evidence-based research as ground for reimbursement decisions. Economic evaluations are an integral component of this necessary research. Ascertainment of reliable health-care cost and quality-of-life estimates to inform such studies has been historically challenging. (Mihajlović J, 2014)

It is to be considered if the decisions for the delay on granting approval in Colombia are aimed on the cost containment in the health system, there are other aspects which should also be studied. Health economics, as previously explained plays an important role. Delaying the access to adequate medical care can generate on the long term higher cost due to the worsening of the conditions which can be translated in decrease quality of life (QoL) of the patients. Patients with low QoL generate most costs and do not contribute much to the economic growth (taking into consideration that the health deficiency doesn’t allow them to develop a normal life, for example to work and in this way to help the economic growth by their contribution to the society), additionally the worsening of the conditions lead to additional measures to be taken which also increase the costs.

The cost of cancer treatment is much discussed and internationally of considerable relevance, given the rising health-care costs and financial constraint. The initial treatment period, rehabilitation and early follow-up after a new diagnosis of cancer incurs heavy resource demands on secondary care. The use of patient quality – adjusted life –years is an important endpoint in economic evaluations. QoL can be measured across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and is an important parameter in the economic evaluations (Mihajlović J, 2014)

The duty of the respective countries is to find the most appropriate way for the distribution of the health resources and, for this purpose, economic evaluations should be in place. Reliable analyses require robust estimation of costs and patient

quality-of-life. Data obtained in such analysis may then be used to best invest resources available. When linked with clinical care and outcome data, improved clinical ownership of resource decisions and evidence-based analysis also becomes possible. (Mihajlović J, 2014)

Additionally preventive measures should also be considered. Stratifying the population of patients according to future risks of suffering a given condition, and the treatments, can be understood as action to be taken in advance to avoid or delay the development of the disease. (F. Antonanzas, 2014)

One example of the application of health economics is one study on breast cancer called “the relationship between quality, spending and outcomes among women with breast cancer” form Hasset Mj et al, which analyzed the relationships between quality of clinical care provided in the treatment of cancer, cost, and survival. 15357 Women aged 65 to 70 years were enrolled for the study and the care provided, cost and outcomes were analyzed. Despite this analysis, some breast cancer patients fail to receive treatments known to be effective, such as radiation therapy and chemotherapy, and some experience inferior outcome results which has been defined as health outcomes achieved per dollar spent, most found that measures of quality were not associated with spending or outcomes, whereas a few demonstrated that appropriate use of recommended therapy was associated with greater expenses but improved outcomes. (Hassett MJ, 2014)

In the mentioned study it became clear that efforts have to be done to assess the relationship between quality of clinical care provided in the treatment of cancer and expenses or to determine whether either the measure of spending is associated with improved outcomes for breast cancer patients. It may take years to realize the savings associated with higher quality initial cancer care. The measure of overall quality included recommendations for proven treatments and against unnecessary treatments. (Hassett MJ, 2014)

In the mentioned study, it was particularly challenging to establish a link between quality of initial care and long-term outcomes for cancers that have a favorable prognosis or are curable (where outcomes occur years in the future and can be influenced by many other factors) and for cancers where treatments are predominantly palliative. (Hassett MJ, 2014)

No statistically significant association between total expenditure and overall survival has been found. This suggests that breast cancer patients, like those with other medical conditions, receive many clinical care treatments that do not impact overall survival. While some of these clinical care treatments could be integrated in achieving other relevant outcomes, such as quality of life, many are superfluous.

The challenge is distinguish between health care treatments that do or do not add value.

The findings of the mentioned study help to identify where improvement of efforts could impact health outcomes while considering expenditure of resources, but they also highlight the need for more and better tools to measure value of health care

services. Most importantly, efforts that identify the system, patient, and disease factors that impact the relationship between quality, cost, and outcomes are critical for developing effective improvement strategies. (Hassett MJ, 2014)

Finally it is necessary to say that in this study of breast cancer, the conclusion that has been achieved is that to optimize and maintain the health of cancer survivors and the quality of life, it is essential to deliver high quality care. Incorporating economic analysis into survivorship intervention research can inform the translation of effective interventions into practice. (de Moor JS1, 2015)

It is not an easy task, but more studies as the explained above should be performed, and not only globally but at the local level as well. Health resources should be invested in such a way that all variables are considered for an optimal outcome. Health economic decisions should not be randomized decisions but based on the needs of the country. It is of course the duty and the right of the respective countries to take decisions with autonomy how to invest in health, what to reimburse, etc. always taking into account the right to Health.

Due to the complexity and problematic explained above, a good approach has to be performed in regard to the Regulatory Affairs Environment, this in order to support from a scientific point of view the correct decision-making. This approach includes an improvement in transparency, knowledge, capacities, scientific advice, harmonization, quality on the evaluation process by the establishment of standardized procedures, etc. This will be discussed in the chapter 4.

Finally is important to say that scientific and economic evaluations should definitely be performed in regard with oncological medicinal products; however those two evaluations should be done separately, as scientific concepts on the benefit/risk relationship of medicinal products should not be influenced by political or economic reasons. Of course, after scientific decisions achieve a conclusion, which can be reflected on approvals or rejections of medicinal products, the health economics should join the game by providing its input on how the resources available will be best distributed, which preventive actions can help to safe future costs, etc. This should be accompanied by adequate reimbursement policies, price policies and rational use of medicinal products. Finally corruption is to be completely eliminated.

4. QUALITY OF REGULATORY ENVIRONMENT AS A WAY TO GUARANTEE ACCESS OF PATIENTS TO NEW SAFE/EFFECTIVE INNOVATIVE ONCOLOGICAL MEDICINAL PRODUCTS. (PROPOSAL)

The fortification of the quality of the Regulatory Affairs Environment should, from a scientific point of view, ensure the access of patients to the necessary oncological medicinal products but also ensure that each approved medicine fulfills the applicable standards regarding efficacy, safety and quality that patients deserve. This delicate balance should not create unnecessary barriers to accessibility but needs to be rigorous enough to ensure public health is safeguarded. This chapter will discuss a proposal of how to achieve a more efficient, consistent and fair system.

The primary objective of regulatory agencies is the predictable review of new medicines, permitting market entry of products with a positive benefit-risk profile while demonstrating value to national or regional healthcare systems in a timely manner. (Peterson, 2011). On the other hand, it is the duty of the Industry to provide adequate and organized information that allows for the correct evaluation of the medicinal products aiming to obtain a Marketing Authorization (MA) approval.

The key question therefore is, what are the underpinning components of good regulatory decision making and what are the regulatory scientific tools that can be used to ensure a timely, high-quality, predictable and transparent process whilst ensuring an efficient evaluation of new medicinal products. In other words the challenge is how to develop methods to ensure timely access of patients to new medicines as a consequence of an efficient benefit-risk decision making process. (McAuslane N., 2009)

Those components or aspects which are part of the Regulatory Affairs Environment will be analyzed, first by taking a look at each of them in the current situation, identifying the deficits, and second by providing proposals on how they could be improved. Those components are the following: time of evaluation of MA applications, scientific advice, transparency, knowledge, scientific competence, training , quality of the dossier submission and the dossier review and harmonization.

For purposes of performing the above mentioned evaluation, several sources have been consulted, like published documents, laws, decrees. Additionally, a questionnaire has been created to collect the input of employees from the pharmaceutical industry and from the Colombian Health Authority (INVIMA). Although the number of answers obtained was not sufficient to draw a significant conclusion, it provides a general overview of some aspects that will be discussed. 15 participants took part on the query, 11 of which had purely experience in the Pharmaceutical

Industry, 3 in both the Health Authority INVIMA and the Pharmaceutical Industry and 1 in other related area. The questionnaire can be found as annex 3

4.1. Time of evaluation of applications for Marketing Authorization (MA)

1) How it looks like: (Outcomes from the questionnaire and bibliographic search)

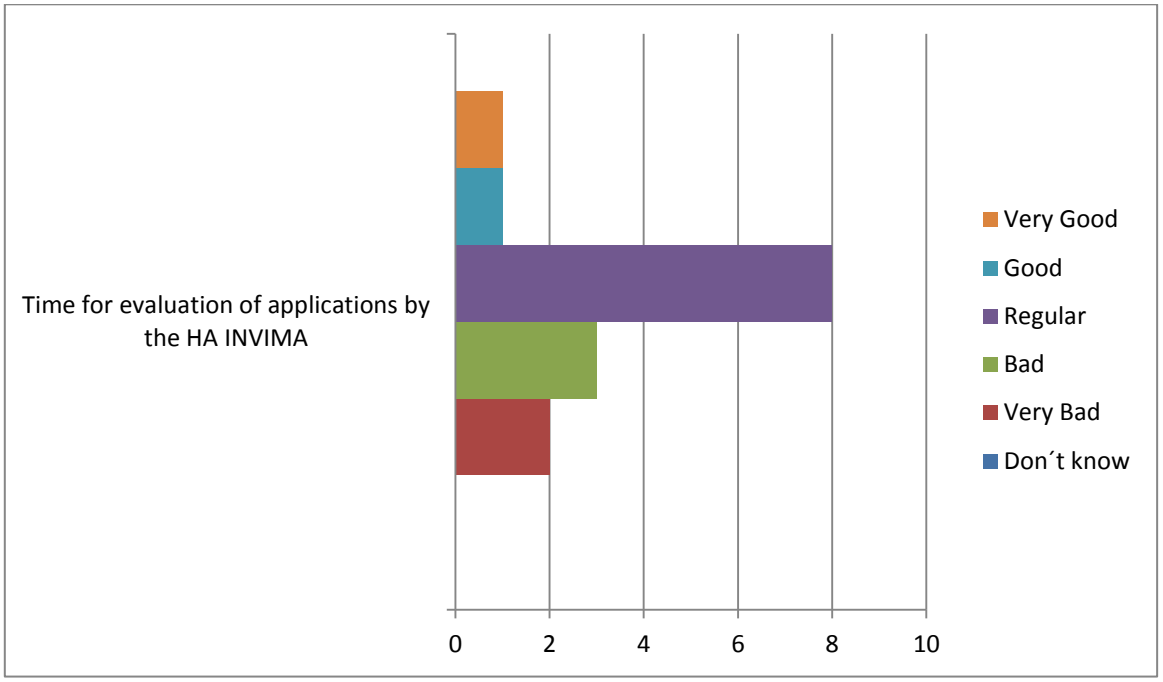


Figure 7. Opinions from employees from the pharmaceutical industry and the INVIMA in Colombia, regarding the time required for evaluation of applications aiming to get MA by the INVIMA

According to the decrees regulating the time of evaluation of applications for MA, it should be as follows:

a) Estimated time required to obtain a MA for a medicinal product included in the pharmacological regulations

- First, it takes 30 working days to obtain a favorable "pharmaceutical evaluation".
- Once the pharmaceutical evaluation is obtained, it takes 20 working days to get a decision. If this evaluation is favorable, the MA is granted; if the INVIMA requires further information and/or additional documentation, the response should be submitted within 10 working days. Upon receipt of the additional information INVIMA decides whether or not to grant the MA within 3 months.

b) Estimated time required to obtain a MA of a "new" product

- First, it takes 180 working days for the pharmacological evaluation to be decided (or 30 working days, if the product has been authorized in two reference countries and has not been rejected by any of these countries).
- Then, it takes 30 working days to obtain a favorable "pharmaceutical evaluation".
- Finally, once the pharmaceutical and pharmacological evaluations have been approved, it takes 10 working days to get a decision. If this decision is favorable, the MA is granted; if the INVIMA requires further information and/or additional documentation, another 10 working days must be added. Upon receipt of the additional information, the INVIMA decides whether or not to grant the MA within 3 months.

c) Priority review: For new drugs declared of public health interest by the Colombian Government (priority drugs), the pharmacological evaluation review time is reduced by half, i.e. it should take 90 working days or 15 working days if the drug has already been approved in at least 2 reference countries, and not been rejected by any reference country. Pharmaceutical and legal review should be conducted in less than 40 working days.

d) Compassionate Use: For essential not available (vital and not available) drugs, as an alternative to import medicinal products for unmet medical needs which have not yet been approved in Colombia. It can be compared with the compassionate use denomination used in Europe.

Conclusion:

Generally, the MA for a medicinal product included within the pharmacological regulations may take approximately 90 working days; however in practice INVIMA takes more time than the legally expected. (Reuters, 2015)

Generally, the MA for a new medicinal product may take approximately 200 working days, or 60 working days (in case a reduced pharmacological evaluation time is applicable). However in practice INVIMA takes more time than the legally expected. (Reuters, 2015)

In Colombia there is no possibility of granting Marketing authorizations with conditional approval. CPP from country of Origin is required and is to be provided during the review process.

2) Proposals for improvement: (Outcomes from the questionnaire and bibliographic search)

- The evaluation process should be revised and improved to ensure enough personal and resources are in place to allow an efficient review and the fulfillment of the established timelines for the evaluation of applications.
- The priority review for medicinal products for the treatment of life threatening diseases should be improved to ensure a faster access of the patients to such drugs.

- The time required for evaluation should be adjusted depending on the complexity of the product aiming to get a MA, i.e. products of less complexity should have a faster evaluation and more time should be spent on more complex applications.

4.2. Scientific advice

1) <u>How it looks like: (Outcomes from the questionnaire and bibliographic search)</u>

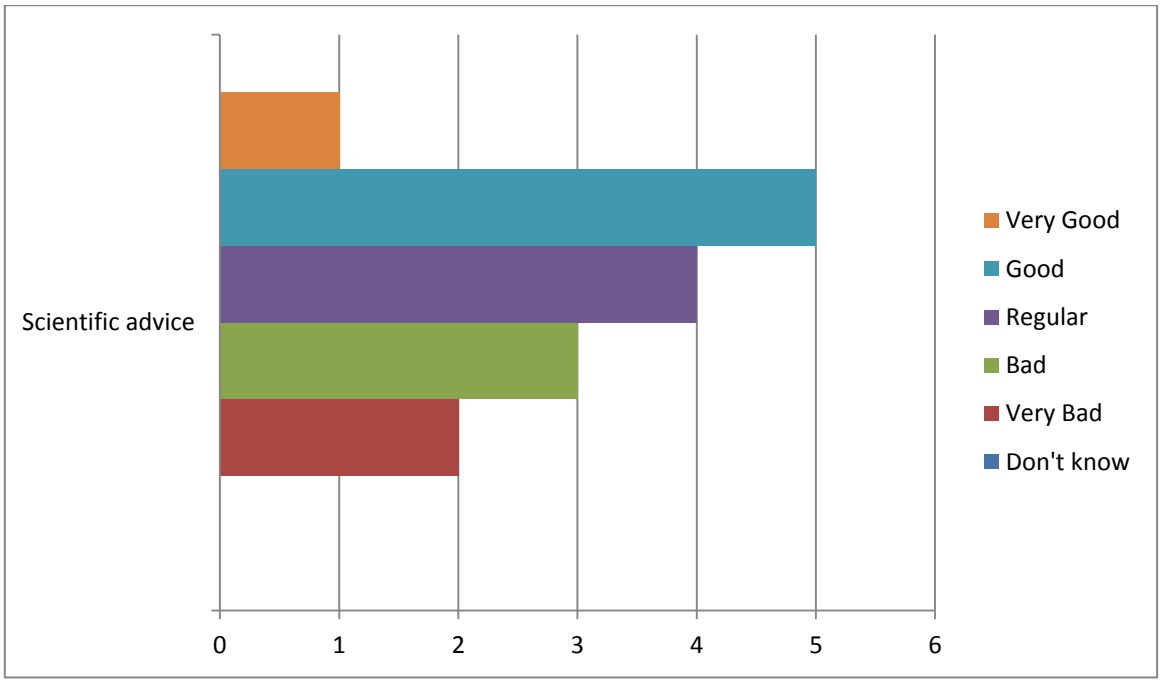


Figure 8. Opinions from employees from the pharmaceutical industry and the INVIMA in Colombia, regarding the scientific advice received by the INVIMA before the submission of applications aiming to get MA.

The question regarding scientific advice in Colombia has been probably misunderstood by the participants. In Colombia there is no scientific advice as such. For that reason it is not understandable why some of the participants evaluated as regular, good and very good this section. The reason of this outcome can be explained due to the fact that this figure of scientific advice is not known in Colombia and employees normally don't have international experience and therefore no comparison can be established.

- In Colombia there is not a scientific advice or pre-submission meeting as such.

- The INVIMA's website (Home) offers the possibility to request the following: a meeting with the Sub-Office of the Sanitary Registration, to be notified of the decisions of a submission, and answers to questions related to the registration of a product. (Reuters, 2015)
- It should also be noted that general questions related to the registration of medicinal products may also be made to CHAT, where a technical professional or a lawyer of the HA will provide advice. (Reuters, 2015)
- In practice, according to the study that evaluated the link between the process in Health Authorities and the reimbursement decisions from Vacca et al, the conclusion reached is that establishing contact with the INVIMA has to be improved as communication is not easy. Even for communication via email, answers are difficult to be received. (Vacca, et al., 2012)

2) Proposals for improvement: (Outcomes from the questionnaire and bibliographic search)

Establishment of a standardized procedure for the interaction between the industry and INVIMA, more specifically a Scientific Advice should be created and duly implemented. This is designed to facilitate the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients. Early, open and frequent dialogue between companies and agencies with continuity and consistency in regulatory advice, aligned to clinical and regulatory strategies helps the company to make sure that it performs the appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during the evaluation of the MA application. (Cone, et al., 2014).

Such major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal of the MA. Following the Agency's advice increases the probability of a positive outcome. The Agency gives scientific advice by answering questions posed by companies. The advice is given in the light of the current scientific knowledge, based on the documentation provided by the company (SCUBED, 2012). For example, at EMA and FDA, the company provides questions and proposes the answers which justify the path forward as well. It is asked whether EMA and FDA accept the proposed way. With the answers and explanations of the HAs there is given advice. So, it is not only about posing questions to the HA but rather a dynamic interaction with predefined proposals from the side of the industry. As a general observation, the quality of scientific advice can be improved by ensuring that the agency understands the company's development plans as early as possible. There should be open dialogue on the full plan as it goes forward. (Cone, 2004)

In general the panorama worldwide looks like this: Companies can request scientific advice or protocol assistance either during the initial development of a medicinal product before submission of a MA application or later on, during the

post-authorization phase. Scientific advice and protocol assistance are particularly useful to companies developing a medicinal product and it is paid by the requesters who are the pharmaceutical companies, in this was the scientific advice can get the resources.

a) There appears to be no or insufficient relevant detail in guidelines or guidance documents, or in monographs, including draft documents or monographs released for consultation;
b) When the company chooses to deviate from the available guidance in its development plan (SCUBED, 2012)

For the reasons mentioned above, it would be very useful to implement scientific advice in Colombia. Meetings of scientific advice should be frequent and should be a regular process adopted by the INVIMA. Such meetings typically address product-specific legal, regulatory and logistic issues in order to facilitate subsequent validation and assessment of the application. Aadditionally, the use of electronic communications measures should be implemented in order to help on the interaction with the evaluators.
For the specific problematic of endpoint selection in the evaluation of medicinal products for cancer, applicants should meet with the HA INVIMA before submitting protocols intended to support new MA applications. The HA should ensure that these meetings include a multidisciplinary team of oncologists, statisticians, clinical pharmacologists, and if possible external expert consultants. In this way the acceptability of endpoints could be evaluated in advance and efficiency with access achieved properly. Additionally, approaches for assessing patient-relevant benefit should build on comprehensive experience and on guidelines. It must be ensured that this clinical knowledge is continuously taken into account during the decision-making process.
Finally, the scientific advice should allow companies to ask about specific scientific issues concerning the development of a product, including:
a) Quality: chemistry and pharmaceutical development
b) Non-clinical: toxicity and pharmacology development
c) Clinical: study design, endpoints, choice of population, appropriate comparator, sample size, statistical plan
d) Pharmacovigilance and risk management plans, and post-authorization safety study protocols
e) Regulatory questions relating to eligibility for procedures, legal basis of applications

4.3. Transparency and communication

1) **How it looks like: (Outcomes from the questionnaire and bibliographic search)**

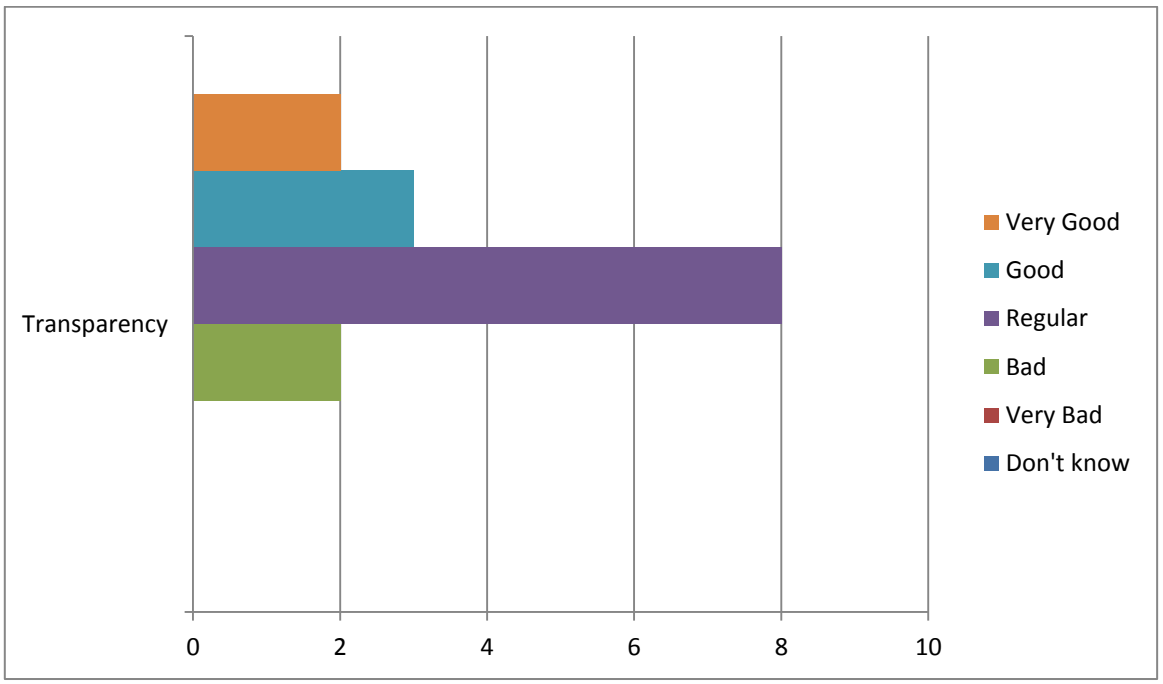


Figure 9. Opinions from employees from the pharmaceutical industry and the INVIMA in Colombia, regarding the Transparency and communication in the Regulatory Affairs Environment

- It is the general opinion that transparency has to be improved and that there are many deficiencies in this regard, were efforts should be put. Some applications are evaluated in record time; while for others it takes too long. transparency and diffusion of information should be in place in order to be able to understand those differences
- A recent study, which evaluated the relationship between processes of evaluation of efficacy and safety in several sanitary agencies (Colombian HA included) and the reimbursement decisions, provides a clear panorama of the current status of transparency in Colombia. It could be appreciated that there is impairment in obtaining Marketing Authorization, additionally different decisions on approval by INVIMA when comparing with decisions taken in other agencies in the world can be appreciated with a growing tendency in the last years. (Vacca, et al., 2012).

- Additionally regarding the information that can be found in the website of the INVIMA, the transparency is reflected as follows:

a) The webpage provides general information about the organization, INVIMA related regulation, a data base with the health registries (MAs), links related to pharmacovigilance and information on the requests in course for the approval of health registries (MAs). (Vacca, et al., 2012)

b) The information found in the webpage of the INVIMA is very scarce, especially concerning the methods of evaluation of efficacy and safety of medicinal products. Additionally there is room for improvement in the processes of communication and possibility of the INVIMA to obtain consultation of information presented to other agencies as an additional mechanism to support the taken decisions. When comparing with other HAs in the world it could be identified that other agencies provide more information in their web sites that supports the evaluation of the efficacy, safety and monitoring post marketing. Existence of standardized methods and pre-established procedures were good examples of transparent agencies. Some agencies as the Australian TGA and Health Canada publish the general description of the process with an important degree of detail and others like the EMA or the FDA even provide information on the professionals and/or areas in charge of the evaluation. FDA is perhaps the only one agency that describes in a general way the process of evaluation of new medicinal products. (Vacca, et al., 2012)

c) In the case of the INVIMA, for obtaining information pre authorization is needed to contact people as this information is not available for public consultation on the web page and the information on approvals and decision taken requires of expertise on the web page, not very easy to find. In contrast, the consultation of approval, submitted studies, and taken decisions can be done easily through the webpages of agencies of reference like the FDA, EMA, TGA, Health Canada. FDA, TGA and EMA are of the ones who provide more information at the disposal of the users and professionals of the health, information which allow for the good understanding on how are decisions being made (Vacca, et al., 2012)

d) It is not possible to value the robustness of the decisions by difficulty of access to information on methods and processes of evaluation in the Web. (Vacca, et al., 2012)

e) The preoccupation increases when the divergences between the decisions of commercialization or restriction of the use between the different agencies are observed, taking into account that the evidence presented for the authorization does not differ in the majority of the cases between sanitary agencies. Possibly the divergences come also from the lack of communication that allows a flowed interchange of information or by weaknesses in the national capacities associated to the availability of suitable human resource or from ignorance and availability of methodologies standardized and validated to evaluate the evidence. The fact that medicinal products have not been approved in Colombia but in agencies like the FDA or the EMA can be the reflection of problems of standardization in the methods of evaluation, difficulties of communication and interaction with the homologous agencies or

HA and limitations in the number and profile of the evaluating experts. Those divergences in the decisions of the agencies and in particular between the INVIMA and some of the analyzed agencies, although the presented evidence is the same demonstrates the importance of establishing detailed processes (Vacca, et al., 2012)

f) In the case of the INVIMA although exigencies became on the presentation of new clinical studies, it is not clear the specific observations to them and it is not documented that the holder has presented this information. (Vacca, et al., 2012)

g) At the moment the INVIMA does not count on an own sanitary publication system of alert, discloses the information of medicinal security and biological products that consider apply in the local scope from the alert of agencies of international reference. (Vacca, et al., 2012)

h) In order to be able to obtain information in the mentioned study, emails were sent to different HA like the EMA,MHRA,TGA, Health Canada, FDA, ANVISA and INVIMA and the time response where between 24 hours and 5 days for most of the agencies, besides ANVISA and INVIMA, where the E mails were not answered at all. (Vacca, et al., 2012)

2) <u>Proposals for improvement: (Outcomes from the questionnaire and bibliographic search)</u>

- The promotion of the transparency fortifies the democracy and foments the responsibility and effectiveness in the government. HA are enforced to take suitable measures to disclose information to the public in fast, simple form and with easy access. In addition, transparency should be settled down as a fundamental and essential priority in the activities of the HAs. To include the spreading of information is a fundamental ingredient in the decision making. The availability of the information must allow the construction and traceability of the commercialization file of a medicinal product (pre and post commercialization) to facilitate the decision making by the part of professionals and organizations of health, as well as from citizens and users. The implementation of the recommendations for increasing the transparency should make possible that the actions, the decisions, and the underlying processes are more transparent for the public, without letting off-side the goal of the agency to protect the confidential information.
- The establishment of a transparency policy that is reflected in an integral information system and a website readily accessible is key element for the consolidation of the sanitary agency and its positioning before the citizenship as a central organization that protects the public health. The information availability is an important measurement of the transparency and friendliness of the websites of the agencies

- The transparency policy must transcend as much as possible to the operation of the Revising Commission of Pharmaceutical Products, as to the other levels of the organization and incorporate the adoption and spreading of the methods, instruments and tools of evaluation of the evidence as well as of the participants of the decisions as a mechanism to increase to the confidence and legitimacy of the agency.
- The HA INVIMA is called to extend the information on the tactically important points reviewed in the evaluation, to include of clear way the results of the voting, the justifications of approval or not, and in addition the evaluation results of other agencies. (Vacca, et al., 2012)
- There is a need to provide a friendly and structured access to the information in order to make it more accessible, it should be in an easy way, that include more informative descriptions of the results of the clinical trials, it could be through tables in which it is described, including the outcomes. Also to include clear summaries for the doctors; information for patients with the clear and direct benefits of the medicine as well as their adverse events.
- The update of the pharmacological norms for information to the public.
- In relation to the fortification of the sanitary agencies and its capacity to generate solid evidence in a transparent way, efforts should be made to facilitate processes of interchange with other decision makers (HA) and evaluators of technologies in health. In other parts of the world can be seen that such initiatives takes place, which are for example the recent initiatives of interactions between European Agency EMA and evaluators of technologies in health. These experiences explore opportunities of collaboration in relation to the evidence requirements; additionally, offer the opportunity of a mutual contribution to the construction of guidelines of clinical practice, alignment of requirements of medicinal products for accessing the market, and interchange of experiences from activities and investigation pos-commercialization. In order to include INVIMA in this approach, it is important to establish formal mechanisms of exchange of information where the national teams have access to direct consultations to experts from other agencies. For this purpose it is indispensable that institutional agreements and inter agreements are reached to protect the confidential information during the exchange with other agencies. Such mechanisms of communication and interaction between the committees of experts of the agencies help to improve and to multiply the capacities of evaluation and the exchange of information and therefore allow to develop adequate levels of performance (Vacca, et al., 2012)
- Another subject that can be related to the promotion of better practices than facilitates the evidence generation from the sanitary agencies constitute the policies of handling of conflicts of interest of the people in charge of the process of authorization of medicinal commercialization. The prevalence of the conflicts of financial interests between the doctors and the pharmaceutical has been a subject of preoccupation for more than two decades. The influence of conflict of interest in the medical research, the decision making of approval of commercialization that arise by regulatory organizations, the practice of “ghost

writing" for the article publication in scientific magazines or the elaboration of guides of clinical practice worries about the slants that can favor to third parties interested in these decisions. (Vacca, et al., 2012)

4.4. Knowledge/scientific competence/Training

1) How it looks like: (Outcomes from the questionnaire and bibliographic search)

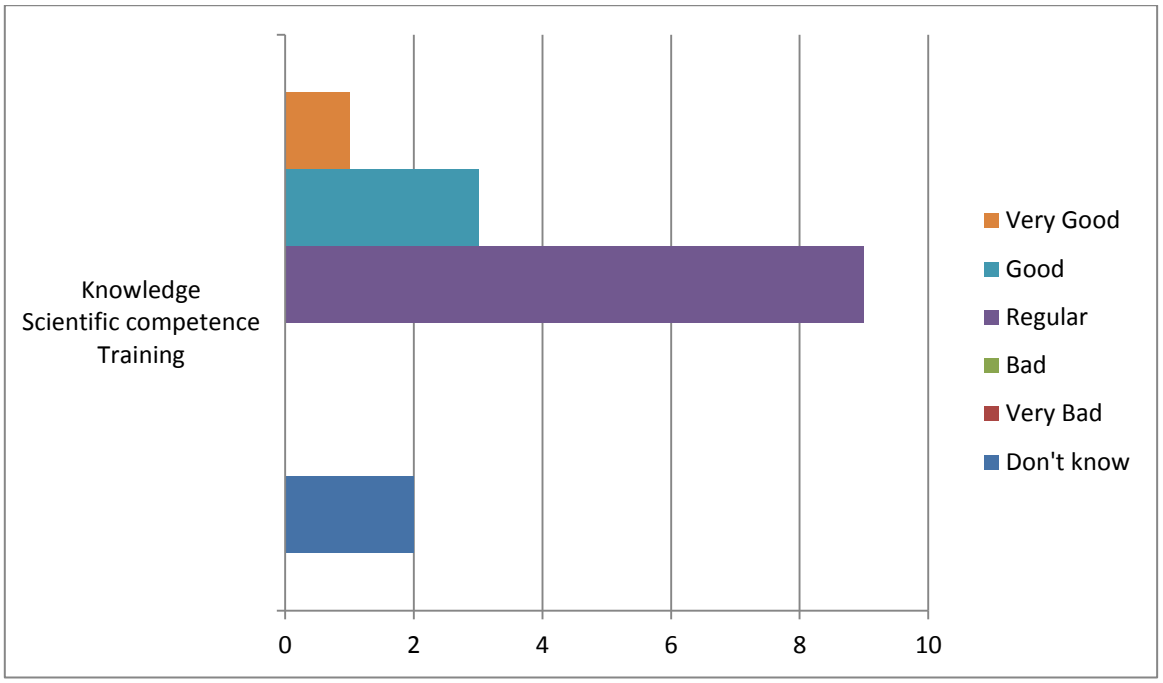


Figure 10. Opinions from employees from the pharmaceutical industry and the INVIMA in Colombia, regarding the knowledge, scientific competence and training of the evaluators of applications in the Health Authority INVIMA

- The Revising Commission of Pharmaceutical Products SEMPB from INVIMA is in charge of evaluating the application for Health Registrations (Marketing Authorization) and is Conformed by five professionals, four doctors (3 pharmacologists and one toxicologist) and a pharmaceutical pharmacologist.
- Sometimes the SEMPB requires technical and scientific support for the evaluation of specific cases, for these effects incurs in external hirings with Universities or Groups of Investigation (biotechnological medicinal products), as well as scientific associations. In the same way it counts on the not specialized technical support of 3 professionals of complete time for all the Revising Commission of Pharmaceutical Products. (Vacca, et al., 2012)

- The decisions are taken by the evaluating group, without explicit support of specialized professionals, if they had been consulted.
- Lack on the training of the evaluators to make them able to conduct adequate evaluations of the applications and to adjust to the reality the time that each specific case requires depending on the complexity. This lack on enough knowledge causes delays in the registration process.
- Criteria of the evaluators differ due to a deficiency and quality of the Training.
- The problems of standardization in the methods of evaluation, difficulties of communication and interaction with the homologous agencies can be within other aspects due to limitations in the number and profile of the evaluating experts. (Vacca, et al., 2012)
- The preoccupation increases when the divergences between the decisions of commercialization or restriction of the use are observed if the evidence presented for the authorization does not differ in the majority of the cases between sanitary agencies. Possibly the divergences come also from the lack of communication that allows a flowed interchange of information or by weaknesses in the national capacities associated to the availability of suitable human resource or from ignorance and availability of methodologies standardized and validated to evaluate the evidence.
- Lack of experienced reviewers and insufficient IT resource are also regarded as important factors. (Walker, et al., 2005)

2) <u>Proposals for improvement: (Outcomes from the questionnaire and bibliographic search)</u>

- The selection of staff with professional and ethical criteria, job security and wages, so that employees do not seek additional income.
- In the countries taken as reference, organizational structures of high complexity exist, in relation to the organization of the INVIMA, generally can be said that the agencies have structures, with personnel of plant supported in committees of expert advisers of the subjects of investigation, academic clinical areas and with knowledge in specific subjects. For that reason it is important the fortification of the base body of the INVIMA, generating a bank of experts and satellites bodies, in which people and specialized organizations of the national and international scope are included. The specialties of the technical bodies should be defined for example by:
  a) Clinical specialties
  b) Complexity of the medicinal product
- Fortification of the human resources by promoting the generation of evidence and the information dissemination, providing adequate capacitation and training and ensuring that suitable human resource fortifies the Branches of expert. Qualification in different subjects that go from regulation, correct medicinal products use, pharmacovigilance. (WHA, 2014)

- The capacitation of the professionals should be focused on the aims of the national pharmaceutical policy
- In a study evaluating the quality of regulatory quality in approval process there was consensus that one of the most important success factors for regulatory performance is good communications and the exchange of information between experts in companies and agencies. (Cone, 2004)

4.5. Quality of dossier submission and dossier review (compliance)

1) How it looks like: (Outcomes from the questionnaire and bibliographic search)

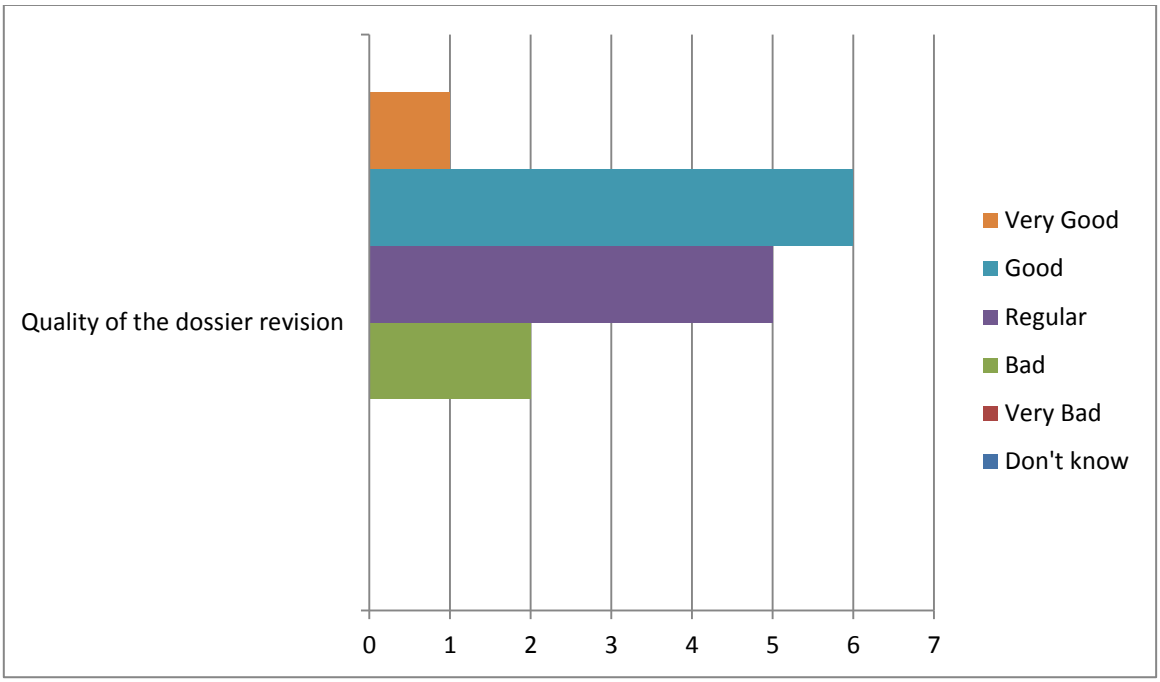


Figure 11. Opinions from employees from the pharmaceutical industry and the INVIMA in Colombia, regarding the quality of the dossier revision of the evaluators of applications in the Health Authority INVIMA

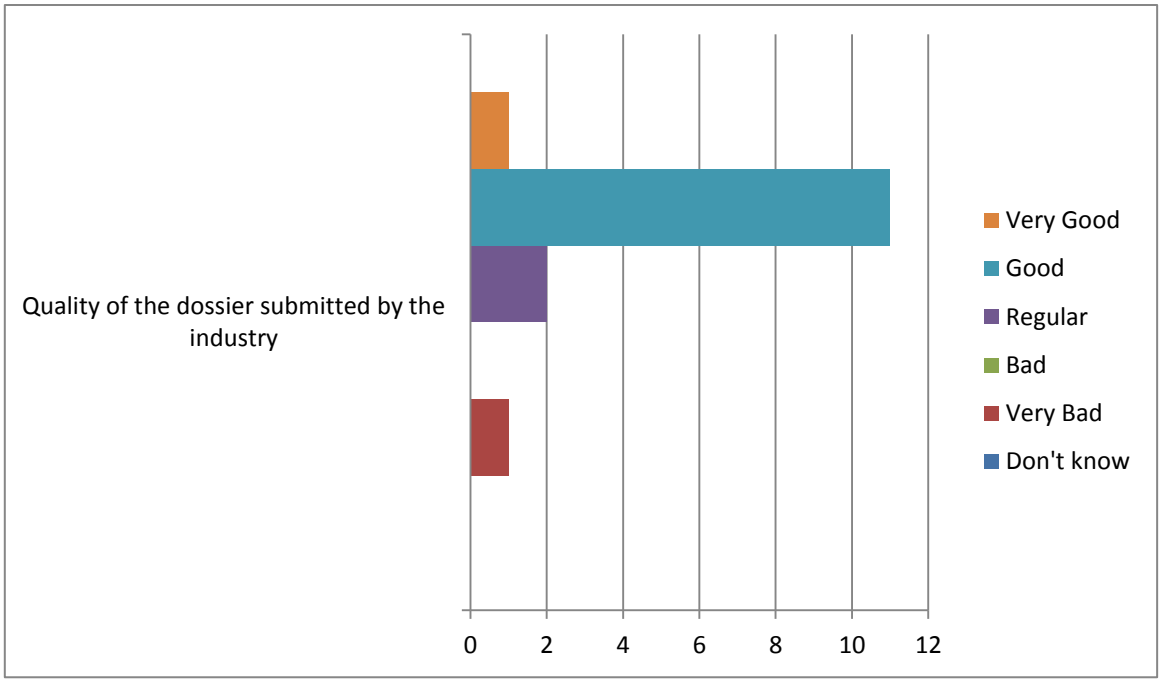


Figure 12. Opinions from employees from the pharmaceutical industry and the INVIMA in Colombia, regarding the quality of the dossier submitted by the industry

- There are bias as a consequence of the different criteria of the evaluators of applications and a lack in the capacitation and training of the evaluators.
- Is it not implemented in the regulation to submit technical information in CTD format. (Vacca, et al., 2012)
- It was not possible to identify methods on the evaluation of the evidence.
- Associations of patients, several sectors of the Pharma industry and international organisms, protest that the processes of medicinal products authorization can be limiting the access to new therapeutic technologies and acting as I discourage to the innovation and pharmaceutical investigation.
- There are no pre-established criteria, beyond those laid down in Decree No. 677/95 to be considered when submitting an application to the INVIMA. (Reuters, 2015)

2) <u>Proposals for improvement: (Outcomes from the questionnaire and bibliographic search)</u>

- The establishment of robust methods for evaluating the evidence for marketing approval and post-marketing surveillance and promoting transparency of information are valuable strategies to strengthen decision-making and make them more coherent and consistent. The transparency specially is a measure that helps to reduce the bias and the differences between the evaluators.

- At the global level and at the Colombian state level, efficient processes involve the attribute of traceability, for this reason it is important to develop and implement processes with these features in the INVIMA, based on the availability of information.
- The implementation of electronic submissions in CTD format could improve both, the quality review and the quality submission of the dossier. It could make easier the process and traceability in the review of the dossier. The ability to submit data and communicate electronically is becoming increasingly important in improving the speed and efficiency of interaction between authorities and companies. This is particularly important in relation to tracking the progress of applications and obtaining responses to questions. (Walker, et al., 2005)
- Requirements should be defined for the safe and effective therapeutic use of new medicines. This should be a risk-based approach to essential data and must avoid the growing tendency to include 'nice to have' information. (Cone, 2004)
- Strengthening of the registration process of innovations accompanied by an articulated monitoring that ensures the adherence to guidelines.
- The strengthening of the capacities and capacity of evaluation from INVIMA by incorporating appropriate and enough human resources to the Review commissions from INVIMA.
- Involvement of experts in the decision making.
- It is important that independence is kept regarding scientific decisions taken by the INVIMA on the approval of new medicinal products in relation with Reimbursement and Pricing decisions, even though a relationship should be constructed that while keeping the independency, establishes at the same time a good communications process that conduce to coherence in the decisions on approval and reimbursement. This need arise because the country is in a process of institutional adjustment of the Committee on Health Regulation, the INVIMA and INS, additionally due to the recent creation to the Technology assessment agency that will be supporting the decision-making of Reimbursement. The coordination of the link and communication mechanisms between INVIMA / IETS/ FOSYGA/ MSPS in the process of authorization to use no POS technologies has to be clearly and efficiently defined. Also communication mechanisms of approval decisions, warnings, restrictions on use and recalls of the market (Vacca, et al., 2012) (IETS)
- The use of validated methodologies for the critical evaluation of the evidence correctly linked to the evaluation of the add value of technologies (technology assessment) in future performed by the IETS will help to anticipate the impact of the use of innovative medicinal products on the cost in health. A close coherence and coordination between these two entities should be developed in assessing the pre/post marketing information. (Vacca, et al., 2012)
- The regulation of the report, assessment and monitoring of the use of technology in unapproved indications and updating of pharmacological norms for release to the public.

- The establishment and possible regulation of international benchmarking process to optimize coverage decisions and marketing authorization.
- The articulation of all the recommendations with the strategies and goals of national pharmaceutical policy.
- In Summary: Improvements in the methods used in evaluating the efficacy and safety (robustness, consistency, coherence and transparency), the public availability of information (completeness, traceability, availability and appropriate to the user), the existence of explicit links between health registration processes and the coverage decision (processes, information / evidence, capabilities and inter related agencies), the implementation of electronic submissions and the involvement of enough and expert personal in the evaluation of the applications will allow the improvement of quality dossier submission and dossier review and will at the same time will allow the prevention of future negative effects on health and on public expenditure.

4.6. Harmonization with international guidelines.

1) How it looks like: (Outcomes from the questionnaire and bibliographic search)

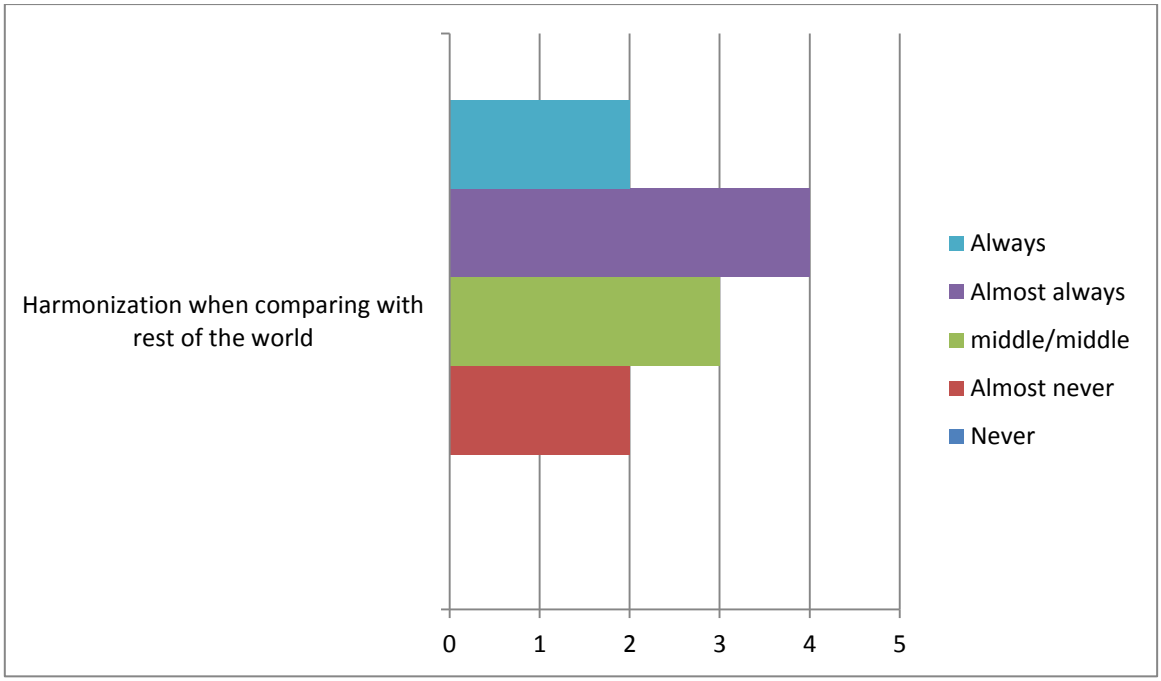


Figure 13 Perception from employees from the pharmaceutical industry and the INVIMA in Colombia on how harmonization in Colombia looks like when comparing with the rest of the world. If decision making in Colombia is consistent with decisions on the rest of the world, concretely.

- The current status of harmonization in Colombia leads to many concerns due to the increase on the differences between mark eting decisions or restriction observed if the evidence submitted for approval is not different in most cases among health agencies. Possibly differences arise from the lack of communication (communication and interaction with counterpart agencies) that allows a smooth exchange of information, weaknesses in national capacities associated with the availability of appropriate human resources (number and profile of expert evaluators) or ignorance and availability of standardized and validated methodologies for evaluating evidence.
- Disparities between the decisions taken by the INVIMA and analyzed agencies, may reflect problems of standardization in assessment methods, difficulties in communication and interaction with counterpart agencies and limitations in the observed number and profile of expert evaluators. (Vacca, et al., 2012)

2) <u>Proposals for improvement: (Outcomes from the questionnaire and bibliographic search)</u>

- It is still not yet clear whether the differences in coverage decisions between countries are understandable or acceptable, given the variety of factors that determine, beyond the assessment of the effectiveness of technology, eg budget availability , cultural preferences or priorities of equity; the need or not of independency of decisions is definitely an issue that has to be deeply analyzed however establishing mechanisms for consultation and interaction with counterpart agencies, the development of international networks and bank experts should support decision making. Following are concrete actions that would support on the harmonization with the rest of the world:
  - **a)** Mechanisms of transparency and increased communication between agencies to improve processes and decisions of marketing.
  - **b)** Also the potential synergies of expert teams, free of conflicts of interest and the development of policies to reduce decision bias.
  - **c)** Formal mechanisms for information exchange and strengthen national teams with direct consultation experts from other agencies through conventions.
  - **d)** The support of exchange of information, sharing of experiences leveraging and capacity building in evaluation of interventions and technologies through collaboration mechanisms at global, regional and country levels, in addition to ensure that these partnerships are active, effective and sustainable. (WHA, 2014)
  - **e)** Streamlining the regulatory process by sharing regulatory assessment reports is a win-win proposition for agencies in the world*;* such collaboration will save resources, lead to better review quality and earlier approval of and access to medicines. (Peterson, 2011)

5. SUMMARY AND DISCUSSION

Taking into account the complexity of the topic of entry of new Oncological Medicinal Products in Colombia, where not only the scientific aspects play a role but also the political and the economic ones, the discussion will be focused on how from a scientific point of view, specifically from the Regulatory Affairs point of view, a good approach should be established in order to ensure the access of innovative oncological medicinal products to the patient.

This master thesis offers an up-to-date compilation of the aspects to be considered regarding the entry of oncological medicinal products in Colombia. The problem faced today because of the conflict of interest from the different actors involved: government, patients and industry.

It can be seen that because of the concerns of the government regarding the low efficiency, lowered access, high health costs and a poor quality of the health system, the government was willing to implement new measures to find a solution to those deficiencies. The principle of such measures should always consider the health as a fundamental right. From these measures, the ones directly influencing the entry of oncological medicinal products are the reform to the health system where the important concept of health as a fundamental right with exclusions is included. This also includes the new biological regulation whose aim it to promote the competition and in this way help to the decrease of prices.

Finally an strengthening of the price regulation as a consequence that the current system of free price allowing the market to be regulated by itself, conducted Colombia to be one of the countries with the highest prices of medicinal products in Latin-American countries.

From those initiatives many opinions from different sectors arise, either as agreement or as a disagreement. As a consequence of the health reform, many contributors find that the definition of the health as a fundamental right limited by the exceptions of what will not be offered; the health right is not being respected. On the other hand regarding the new biological regulation, a strong opposition of the industry appears with the argument that this law promotes a risk for the public health. This opinion takes into account that biological products are more complex than chemical products and therefore require better measures for the ensurement of the efficacy and security. Additionally, of course, the easy entry of generics after the protection period dismisses the profitability of the industry and therefore also the interest in development. But it is the patient who is really in the middle of all the debate. Cancer patients having the hope of a cure and expecting to get the best medical care possible.

Furthermore, the initiatives that were or are taking place at the moment in relation to the health system, the creation of new laws for biological products, and the free trade agreements with USA create a very complex scenario with political and scientific

components which are in some degree difficult to be separated and have also been discussed.

Besides the political components which are also briefly explained, this master thesis is aimed to focus on the scientific aspect, through the analysis of the quality of the Regulatory Affairs Environment as a tool for ensuring access to the market of innovative oncological medicines.

Analyzing the data of approvals of oncological medicinal products in the last years, a decreasing tendency of approvals could be identified. Approvals by the health authority in Colombia is decreasing and this behavior and tendency is also analyzed in this thesis, together with the fact that in some cases medicinal products that have been already approved either in USA or in EU are refused in Colombia. The reasons for that, and the adequacy of those decisions were also evaluated.

Of course in all discussions there is an ethical component involved. Subjective aspects like what can be catalogued as an improvement of a medicinal product in regard with the standard therapy? Are two additional months of survival enough justification for the acceptance of an additional and maybe more expensive alternative? How to manage the access to medicinal products, either a small part of the population receiving support for very expensive therapies or a high amount of the population receiving the benefits of the system but letting less protected those areas where the cost conduct to the crisis of the health system must also be considered

To find balance is not an easy task but as expressed in the introduction of this master thesis “No country in the world can give to their citizens the best medicinal alternative existent in the world at the moment but the best possible within that, that according to the economic and human resources is available” (Ronderos, 2009)

Not only should the population be obtaining resources, but these should be quality health services.

Timely, high-quality, predictable and transparent processes for the measurement of performance such as the Benchmarking and Quality Scorecard programs can help underpin good regulatory decisions on approval of medicinal products, create a basis for improvement and aid in more predictable decision making, this should be supported with the adequate personal that fulfills the profile and counts with the adequate expertise required for the complexity of the evaluations.

Strategies to accomplish this objective successfully in an increasingly complex global environment include regional harmonization, scientific advice prior to submission, measuring performance, and use of GRP and a benefit-riskframework. Strategies for efficiencies meanwhile, include sharing regulatory assessment reports, parallel reviews, multinational regulatory consortia, use of other regulator’s decisions and regional safety surveillance (Peterson, 2011)

Key enablers of a quality review process were identified; the most important was the ability for companies to maintain a dialogue with agencies through the review process.

Other key enablers were that the HA should be able to provide details describing the submission process and requirements, that these requirements should be consistent with international standards, that agencies should adhere to published timelines, offer a summary basis for approval or equivalent document illustrating their review finings (Liberti, et al., 2013)

Health is a fundamental right. When limits are established it is of course a valid principle. But on the other hand, the aim is to provide the best alternative possible within the economic boundaries and humane as possible. Is not simply about providing more access to medicinal products with a lower quality. For that reason additional to the scientific evaluations, also other aspects play a role and will from a political and economic point of view, provide the final picture.

The actions to be taken (scientific, political, economic) are summarized as follows:

1) Regulatory Affairs Environment Improvement that ensure entry of safe, efficient and quality medicinal products without generating unnecessary barriers.

2) Health economics strengthening in order to improve the way on how resources should be invested.

3) Strengthening of price policies, as inoperative prices policy and weaknesses in the monitoring of the prices have had terrible financial consequences

3) Reduce waste of resources and promote rational use of health services.

4) Corruption has to be completely avoided (generated due to EPSs and health system structure in general)

5) Efficient health system

6) Biological law to increase competition.

6. CONCLUSION AND OUTLOOK

The entry of innovative oncological medicinal product in Colombia is a complex topic with scientific, politic and economic components, which all influence each other and where the interests of government, industry, patients and physicians have to be taken into account. Trying to be in the middle of all interested parties and understanding their individual interests is not easy, especially when the main goal is to provide access of efficient, safe and quality medicinal products to the patient, giving value to the effort in innovation that companies provide and considering the resources that every country has available for supplying the needs of their habitants.

The issue therefore is, if those components are irreconcilable or if there is a middle point that balances the interests involved in a social benefit, represented in better health outcomes and a more efficient public spending.

The final panorama of how health care and access to medical care takes place differs from country to country depending on the resources available. Even though the Regulatory Affairs can be a useful tool that regardless of the political and economic decisions help with the best approach to establish a good process for the access of medicinal products to the patients. Not sacrificing safety, efficacy and quality but also avoiding the implementation of unnecessary barriers for the access to medicinal products.

This master thesis has demonstrated how from 2010 to 2014 there has been a decrease in approved medicinal products for the treatment of cancer in Colombia and has analyzed how was the INVIMA behavior when comparing with the decisions taken by the FDA and by the EMA. Based on this analysis, it has been evaluated how the Regulatory Affairs Environment currently looks like, identifying the deficits and how it could be improved.

Additionally, economic and political consideration and measures have been also briefly described, including controlling prices, establishment of a national pharmaceutical policy and a health reform, a biological new law, health economics considerations, rational used of health services, PI rights negotiated in free trade agreements and last but not less corruption abolition.

REFERENCES

ActasInvima. INVIMA. [Online] [Cited: 12 16, 2014.] https://www.invima.gov.co/index.php?option=com_content&view=article&id=1076%3Asala-especializada-de-medicamentos-y-productos-biologicos&catid=239%3Asala-especializada-de-medicamentos-y-productos-bio&Itemid=581.

AFIDRO. 2014. AFIDRO. *Carta Abierta al presidente de colombia doctor Juan Manuel Santos Calderón.* [Online] 2014. [Cited: 12 18, 2014.] http://www.afidro.org/wp-content/uploads/Carta-de-AFIDRO-al-Presidente-de-Colombia.pdf.

Alvarez, Mario Hernandez. 2014. razonpublica. *La ley estatutaria en salud no es como la pintan.* [Online] 06 02, 2014. [Cited: 09 13, 2014.] http://www.razonpublica.com/index.php/politica-y-gobierno-temas-27/7662-la-ley-estatutaria-en-salud-no-es-como-la-pintan.html.

Amaya Rodriguez, Pablo. 2015. *Pharmaceutical pricing and reimbursement in Latin America.* Bonn : s.n., 2015.

Autor-Eltiempo. 2014. El Tiempo. *Abecé de los fármacos más modernos del planeta.* [Online] 09 20, 2014. [Cited: 12 17, 2014.] http://www.eltiempo.com/estilo-de-vida/salud/abece-de-los-medicamentos-biotecnologicos/14565138.

Berntgen, Dr. Michael. 2003. *Exploring Paediatric Indications for Off-patent Drug Substances - Strategic Input of Regulatory Affairs .* Bonn : s.n., 2003.

Betancourt, Diego Palacio. 2008. alcaldia Bogotá. *RESOLUCIÓN 003754 DE 2008.* [Online] 10 02, 2008. [Cited: 03 31, 2015.] http://www.alcaldiabogota.gov.co/sisjur/normas/Norma1.jsp?i=33501.

Biden, Joseph R. 2014. keionline. *USA Vicepresident letter to Juan Manuel Santos.* [Online] 08. 09 2014. [Zitat vom: 17. 12 2014.] http://keionline.org/sites/default/files/Biden_Colombia_8sep2014.pdf.

BIO. 2013. BIO. *Biotechnology Industry Organization.* [Online] 10 04, 2013. [Cited: 12 17, 2014.] https://www.bio.org/sites/default/files/BIO%20WTO%20Comments_Colombia%20Proposed%20Biologics%20&%20Biosimilars%20Regulations.pdf.

Bio. 2013. Keionline. *Re: Public Consultation: Third Round of Discussion.* [Online] 02 13, 2013. [Cited: 12 18, 2014.] http://keionline.org/sites/default/files/BIO_29feb2013_Colombia_Biosimilars.pdf.

BoletinDePrensa. 2014. Minsalud. *¿Hasta dónde la Ley Estatutaria es compatible con lo que tenemos en el sistema de salud?* [Online] 10 03, 2014. [Cited: 12 18, 2014.] http://www.minsalud.gov.co/Paginas/MinSalud-expone-impacto-real-de-la-Ley-Estatutaria.aspx.

Brilliant, Myron. 2014. Minsalud. [Online] 07 25, 2014. [Cited: 12 18, 2014.] http://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/MET/U.S.%20Chamber%20of%20Commerce.pdf.

Casella, Giuseppe. 2013. keionline. *Comments from the European Union concerning Notification G/TBT/N/COL/196.* [Online] 10 08, 2013. [Cited: 12 18, 2014.] http://keionline.org/sites/default/files/COL196_EN_3.pdf.

CHMPAnticancer-Guideline. 2012. European Medicines Agency. *Guideline on the evaluation of anticancer medicinal products in man.* [Online] 12 13, 2012. [Cited: 12 18, 2014.] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137128.pdf.

Chouaïd C, Crequit P, Borget I, Vergnenegre A. 2014. PubMed. *Economic evaluation of first-line and maintenance treatments for advanced non-small cell lung cancer: a systematic review.* [Online] 12 15, 2014. [Cited: 02 23, 2015.] http://www.ncbi.nlm.nih.gov/pubmed/25548525.

CIMUN. 2013. Centro de información de medicamentos. *La industria multinacional mobiliza asociaciones de pacientes contra la transparencia en ensayos clínicos.* [Online] 07 21, 2013. [Cited: 03 27, 2015.] http://cimuncol.blogspot.de/2013/07/la-industria-multinacional-mobiliza.html.

CNPMDM. 2013. *Communication No. 3 establishing the methodology for direct pricing control of medicines.* Colombia : s.n., 2013.

Cone, Margaret and Walker, Stuart. 2014. Centre For Innovation in Regulatory Science. *Regulatory Performance.* [Online] 04 2014. [Cited: 02 01, 2015.] http://cirsci.org/node/73.

Cone, Margaret. Walker, Stuart. 2004. Centre For Innovation in Ragulatory Science. *Regulatory Performance: Critical Success Factors in Today's.* [Online] 04 2004. [Cited: 05 15, 2015.] http://cirsci.org/node/73.

ConstitucionPolitica. 1991. Constitucion Politica de Colombia. *CONSTITUCION POLITICA DE COLOMBIA 1991.* [Online] 1991. [Cited: 07 30, 2014.] http://wsp.presidencia.gov.co/Normativa/Documents/Constitucion-Politica-Colombia.pdf.

Contreras, Johana. 2014. CM&. *Presiones de congresistas de EUA por los biotecnológicos.* [Online] 29. 07 2014. [Zitat vom: 30. 07 2014.] http://www.cmi.com.co/?n=235629.

Correa, Jorge. 2013. El tiempo. *A favor y en contra, en puja sobre drogas biotecnológicas.* [Online] 08 20, 2013. [Cited: 07 30, 2014.] http://www.eltiempo.com/archivo/documento/CMS-13005152.

Correa, Pablo. 2014. el Espectador. *EE.UU. y las presiones por biotecnológicos .* [Online] 07 25, 2014. [Cited: 07 30, 2014.] http://www.elespectador.com/noticias/nacional/eeuu-y-presiones-biotecnologicos-articulo-506680.

—. 2014. El espectador. *Decreto que asusta a las farmacéuticas .* [Online] 07 12, 2014. [Cited: 12 18, 2014.] http://www.elespectador.com/noticias/salud/decreto-asusta-farmaceuticas-articulo-504031.

Cortes, Miguel Ernesto. Sanchez, Edna. Lopez, Julian. 11. Recalca. *EL TLC Y EL ACCESO A LOS MEDICAMENTOS.* [Online] 09 2012, 11. [Cited: 08 06, 2014.] http://www.recalca.org.co/el-tlc-y-el-acceso-a-los-medicamentos/.

de Moor JS1, Alfano CM, Breen N, Kent EE, Rowland J. 2015. PubMed. *Applying evidence from economic evaluations to translate cancer survivorship research into care.* [Online] 02 18, 2015. [Cited:

02 23, 2015.]
http://www.ncbi.nlm.nih.gov/pubmed/?term=Applying+evidence+from+economic+evaluations+to+translate+cancer+survivorship+research+into+care.

Decreto1782. 2014. INVIMA. [Online] 09 18, 2014. [Cited: 12 16, 2014.]
https://www.invima.gov.co/images/pdf/normatividad/medicamentos/decretos/DECRETO%201782%20DEL%2018%20DE%20SEPTIEMBRE%20DE%202014.pdf.

Decreto2085. 2002. INVIMA. [Online] 2002. [Cited: 12 16, 2014.]
https://www.invima.gov.co/images/pdf/medicamentos/decretos/decreto_2085_2002.pdf.

Decreto677. 1995. INVIMA. [Online] 04 26, 1995. [Cited: 12 16, 2014.]
https://www.invima.gov.co/images/pdf/medicamentos/decretos/decreto_677_1995.pdf.

DeLaTorre, Alejandro. 2014. El tiempo. *La reforma de salud, un reto importante.* [Online] 12 18, 2014. [Cited: 12 18, 2014.] http://m.eltiempo.com/estilo-de-vida/salud/la-reforma-de-salud-un-reto-importante-alejandro-de-la-torre/14500935.

DerechoSalud. 2014. Youtube. *Medicamentos biotecnologicos seguros.* [Online] 08 15, 2014. [Cited: 12 18, 2014.] https://www.youtube.com/watch?v=NcyXHF93EBk&feature=share.

Directive2001/83. 2001. European Commision. *2001/83/EC.* [Online] 11 06, 2001. [Cited: 12 17, 2014.] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf.

Drahos, Peter and Braithwaite, John. 2004. The Corner House. [Online] 09 30, 2004. [Cited: 12 16, 2014.] http://www.thecornerhouse.org.uk/resource/who-owns-knowledge-economy.

EDQMResponse. 2014. AFIDRO. *Response to Republic of Colombia regarding decree.* [Online] 08 14, 2014. [Cited: 12 17, 2014.] http://www.afidro.org/wp-content/uploads/2014-08-EDQM-reply-Columbia-Decree3.pdf.

EMA-BioGuideline. 2014. European Medinices Agengy. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance.* [Online] 05 22, 2014. [Cited: 12 18, 2014.]
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf.

EMACeritinib. 2014. European Medicines Agency. *Applications for new human medicines under evaluation.* [Online] 12 5, 2014. [Cited: 12 18, 2014.]
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500178889.pdf.

EPARCyramza. 2015. European Medicines Agency. [Online] 01 22, 2015. [Cited: 02 11, 2015.]
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002829/human_med_001825.jsp&mid=WC0b01ac058001d124.

EPARGiotrif. 2013. European Medicines Agengy. [Online] 10 16, 2013. [Cited: 12 16, 2014.]
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002280/human_med_001698.jsp&mid=WC0b01ac058001d124.

EPARIstodax. 2012. European Medicines Agency. [Online] 11 16, 2012. [Cited: 12 16, 2014.] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002122/human_med_001590.jsp&mid=WC0b01ac058001d124.

EPARJenzyl. 2013. European Medicines Agency. [Online] 02 18, 2013. [Cited: 12 16, 2014.] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002259/wapp/Initial_authorisation/human_wapp_000149.jsp&mid=WC0b01ac058001d128&source=homeMedSearch&category=human.

EPARStivarga. 2014. European Medicines Agency. [Online] 18. 09 2014. [Zitat vom: 16. 12 2014.] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002573/human_med_001684.jsp&mid=WC0b01ac058001d124.

EPARVargatef. 2015. European Medicines Agency. [Online] 01 08, 2015. [Cited: 01 30, 2015.] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002569/human_med_001822.jsp&mid=WC0b01ac058001d124.

EPARXalcori. 2014. European Medicines Agency. [Online] 10 03, 2014. [Cited: 12 16, 2014.] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002489/human_med_001592.jsp&mid=WC0b01ac058001d124.

EPARXtandi. 2013. European Medicines Agengy. [Online] 07 02, 2013. [Cited: 12 16, 2014.] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002639/human_med_001663.jsp&mid=WC0b01ac058001d124.

Ernesto Cortés, Miguel, Sánchez, Edna and López, Julián. 2012. RECALCA. [Online] 11 09, 2012. [Cited: 12 16, 2014.] http://www.recalca.org.co/el-tlc-y-el-acceso-a-los-medicamentos/.

Espectador. 2013. El espectador. *Con salvedades, organización de pacientes del país aplaude reforma a la salud.* [Online] 26. 02 2013. [Zitat vom: 16. 12 2014.] http://www.elespectador.com/noticias/salud/salvedades-organizacion-de-pacientes-del-pais-aplaude-r-articulo-407070.

F. Antonanzas, C. A. Juarez-Castello, R. Rodrıguez-Ibeas. 2014. Pubmed. *Some economics on personalized and predictive medicine.* [Online] 11 08, 2014. [Cited: 02 23, 2015.] http://www.ncbi.nlm.nih.gov/pubmed/25381039.

FDA. 2015. U.S. Food and Drug Administration. *La FDA aprueba el Farydak para el tratamiento del mieloma múltiple.* [Online] 02 23, 2015. [Cited: 04 15, 2015.] http://www.fda.gov/NewsEvents/Newsroom/ComunicadosdePrensa/ucm435575.htm.

FDA, US.Dep of Healht and Human Services. 2007. FDA Guidances. *Guidance for Industry Clinical Trial Endpoints for the approval of Cancer Drugs and Biologics.* [Online] 05 2007.

FDAAfatinib. 2013. FDA. *Afatinib.* [Online] 12 07, 2013. [Cited: 12 16, 2014.] http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm360574.htm.

FDACeritinib. 2014. FDA. [Online] 04 29, 2014. [Cited: 12 18, 2014.] http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm395386.htm.

FDACrizotinib. 2013. FDA. *Crizotinib.* [Online] 11 21, 2013. [Cited: 12 16, 2014.] http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm376058.htm.

FDAEnzalutamide. 2012. FDA. [Online] 09 04, 2012. [Cited: 12 16, 2014.] http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm317997.htm.

FDAPanobinostat. 2015. U.S. Food and Drug Administration. [Online] 02 23, 2015. [Cited: 04 13, 2015.] http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm435339.htm.

FDARamucirumab. 2014. FDA. [Online] 12 12, 2014. [Cited: 02 11, 2015.] http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm426735.htm.

FDARegorafenib. 2012. FDA. *Regorafenib.* [Online] 09 27, 2012. [Cited: 12 16, 2014.] http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm321378.htm.

FDARomidepsin. 2010. FDA. [Online] 02 18, 2010. [Cited: 12 18, 2014.] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm189466.htm.

Gaviria Uribe, Alejandro. 2014. MinSalud. *Resolución 5926 de 2014.* [Online] 12 23, 2014. [Cited: 03 31, 2015.] http://www.minsalud.gov.co/Normatividad_Nuevo/Resoluci%C3%B3n%205926%20de%202014.pdf.

Gaviria, Alejandro. 2014. *Answer from colombian healht minister to AFIDRO.* [Online] 09 16, 2014. [Cited: 12 17, 2014.] http://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/MET/respuesta-carta-abierta-afidro-sep-2014.pdf.

Gomez, Francisco and Bravo, Alberto. 2014. LR. *Medicamentos biotecnológicos, entre la salud y la libre competencia.* [Online] 08 23, 2014. [Cited: 12 18, 2014.] http://www.larepublica.co/medicamentos-biotecnol%C3%B3gicos-entre-la-salud-y-la-libre-competencia_160066.

Gomez-Maser, Sergio. 2014. El Tiempo. *Estados Unidos, preocupado por biotecnológicos, camiones y etanol.* [Online] 09 13, 2014. [Cited: 12 19, 2014.] http://www.eltiempo.com/politica/gobierno/carta-del-vicepresidente-de-ee-uu-joe-biden-al-presidente-santos/14530043.

Gossain, Juan. 2014. El tiempo. *Empiezan a bajar precios de unos medicamentos, otros siguen subiendo.* [Online] 07 31, 2014. [Cited: 07 31, 2014.] http://www.eltiempo.com/estilo-de-vida/salud/cronica-de-juan-gossain-sobre-precios-de-medicamentos/14325338.

Guaia, Maria Ines. Regulatory Affairs in America. [Online] [Cited: 12 16, 2014.] http://latampharmara.com/colombia/.

Hassett MJ, Neville BA, Weeks JC. 2014. PubMed. *The relationship between quality, spending and outcomes among women with breast cancer.* [Online] 09 13, 2014. [Cited: 02 23, 2015.] http://www.ncbi.nlm.nih.gov/pubmed/25217776.

Hernando, Cesar. 2012. Semana. *COLAPSÓ EL SISTEMA DE SALUD EN COLOMBIA.* [Online] 09 17, 2012. [Cited: 07 23, 2014.] http://www.semana.com/opinion/expertos/articulo/colapso-el-sistema-de-salud-en-colombia/325008.

Huertas Vega, Nancy Rocio. 2014. youtube. *Política Farmacéutica Nacional de Colombia y Reforma al Sistema de Salud .* [Online] 12. 09 2014. [Zitat vom: 13. 09 2014.] https://www.youtube.com/watch?v=KRoffyAMa6M&app=desktop.

IETS. IETS. *Quienes Somos.* [Online] [Cited: 04 13, 2015.] http://www.iets.org.co/quienes-somos/Paginas/Qu%c3%a9-es-el-IETS.aspx.

IFPMA. 2012. IFPMA. [Online] 2012. [Cited: 12 16, 2014.] http://www.ifpma.org/innovation/rd/about-research-development.html.

IFPMA-IP. 2014. International Federation of Pharmaceutical Manufacturers & Associations. [Online] 2014. [Cited: 12 16, 2014.] http://www.ifpma.org/innovation/ip-rights/about-ip-rights.html#.

Justicia. 2014. El tiempo. *¿Qué cambios les trae a los pacientes la ley estatutaria de salud?* [Online] 29. 05 2014. [Zitat vom: 13. 09 2014.] http://www.eltiempo.com/politica/justicia/los-cambios-en-el-sistema-de-salud-gracias-a-la-ley-estatutaria/14053877.

Ley100. 23.12.1993. Ley 100 de 1993 Libro segundo. *Por la cual se crea el sistema de seguridad social integral y se dictan otras disposiciones.* 23.12.1993.

Liberti, Lawrence, Patel, Prisha and McAuslane, Neil. 2013. Centre for Innovation in Regulatory Science. *What are the attributes that companies believe would help agencies to make quality regulatory review decisions?* [Online] 06 2013. [Cited: 01 03, 2015.] http://cirsci.org/content/posters.

Londoño Soto, Beatriz. 2012. alcaldia Bogotá. *Resolución 782 de 2012 .* [Online] 04 11, 2012. [Cited: 03 31, 2015.] http://www.alcaldiabogota.gov.co/sisjur/normas/Norma1.jsp?i=47117.

McAuslane N., Cone M.,Collins J.,Walker S. 2009. Centre for Innovation in Regulatory Science. *Emerging markets and emerging agencies: A comparative study of how key regulatory agencies in Asia, Latin America, the Middle East, and Africa are developing regulatory processes and review models for new medicinal products.* [Online] 05 01, 2009. [Cited: 02 13, 2015.] http://cirsci.org/articles.

McAuslane, Neil. Anderson, Carly. Walker, Stuart. 2004. The changing regulatory environment:. *R&D Briefing.* 2004.

Mihajlović J, Dolk C, Tolley K, Simoens S, Postma MJ. 2014. PubMed. *Reimbursement of Targeted Cancer Therapies Within 3 Different European Health Care Systems.* [Online] 12 2014. [Cited: 02 23, 2015.] http://www.ncbi.nlm.nih.gov/pubmed/25638534.

Min, Salud. 2014. MinSalud. *Preguntas y respuestas sobre la ley estatutaria.* [Online] 06 2014. [Cited: 09 13, 2014.] http://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/ley-estatutaria-abc-jun-2014.pdf.

MinCIT. 2014. MinCIT. *En 20 meses de vigencia del TLC, más de 1.600 empresas exportaron por primera vez a EE.UU.* [Online] 01. 04 2014. [Zitat vom: 06. 08 2014.] http://www.mincit.gov.co/publicaciones.php?id=9396.

—. MinCIT. *Acuerdo de Promoción Comercial entre la República de Colombia y Estados Unidos de América.* [Online] [Cited: 08 06, 2014.] http://www.tlc.gov.co/publicaciones.php?id=14853.

MINCOMERCIO. MINCOMERCIO. [Online] [Cited: 12 16, 2014.] http://www.tlc.gov.co/publicaciones.php?id=723.

Minsalud. 2012. Minsalud. *ABC de la Unificación del POS.* [Online] 07 16, 2012. [Cited: 03 31, 2015.] http://www.minsalud.gov.co/Paginas/ABC%20de%20la%20Unificaci%C3%B3n%20del%20POS.aspx.

MinSalud-Estatutaria. 2013. MinSalud. *Ley Estatutaria: La arquitectura y base de la Ley Ordinaria.* [Online] 06 2013. [Cited: 12 16, 2014.] http://www.minsalud.gov.co/Documentos%20y%20Publicaciones/Enlace%20MinSalud%20-%20Ley%20Estatutaria.pdf.

Minsalud-ordinaria. 2013. Minsalud. *Lista ponencia para Ley Ordinaria de Salud.* [Online] 05 29, 2013. [Cited: 12 17, 2014.] http://www.minsalud.gov.co/Paginas/Ley-Ordinaria-de-Salud.aspx.

MoellerIPAdvisors. 2008. IPO. [Online] 09 2008. [Zitat vom: 16. 12 2014.] http://www.ipo.org/wp-content/uploads/2013/03/TestDataProtection_Municoy.pdf.

MyelomaBeacon. 2014. The myeloma Beacon. [Online] 11 25, 2014. [Cited: 04 23, 2015.] http://www.myelomabeacon.com/news/2014/11/25/fda-postpones-panobinostat-farydak-decision/.

Novartis. 2015. Novartis. *Pharmaceuticals.* [Online] 01 2015. [Cited: 04 13, 2015.] http://www.novartis.com/downloads/newsroom/corporate-fact-sheet/2a_Pharmaceuticals_EN.pdf.

Palacio Betancourt, Diego. 2008. alcaldia Bogotá. *RESOLUCIÓN 003099 DE 2008.* [Online] 08 19, 2008. [Cited: 03 31, 2015.] http://www.alcaldiabogota.gov.co/sisjur/normas/Norma1.jsp?i=32044.

Peterson, Robert. 2011. Center For Information in Regulatory Science. *Regional Alignment in.* [Online] 26-27. 01 2011. [Zitat vom: 15. 03 2015.] http://cirsci.org/workshop-synopses.

PFN. 2012. Minsalud. *POLITICA FARMACÉUTIICA NACIONAL.* [Online] 08 30, 2012. [Cited: 07 23, 2014.] http://www.minsalud.gov.co/Documentos%20y%20Publicaciones/Politica%20Farmac%C3%A9utica%20Nacional.pdf.

Pharma. 2014. Minsalud. *Colombia's Fifth Draft Decree on the Registration Process for Biological Medications— PhRMA Comments.* [Online] 07 25, 2014. [Cited: 12 18, 2014.] http://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/MET/PhRMA.pdf.

—. 2014. Pharma. *Intellectual Property Protections Are Vital to Continuing Innovation in the Biopharmaceutical Industry - See more at: http://www.phrma.org/innovation/intellectual-property#sthash.iYA823h7.XhTXEV1Y.dpuf.* [Online] 2014. [Cited: 12 16, 2014.] http://www.phrma.org/innovation/intellectual-property#.

PORTAFOLIO. 2014. PORTAFOLIO. *Los diez medicamentos más vendidos en Colombia.* [Online] 06 03, 2014. [Cited: 12 21, 2014.] http://www.portafolio.co/economia/los-diez-medicamentos-mas-vendidos-colombia.

RDDPanobinostat. 2010. Orphan designation. *European Medicines Agency.* [Online] 03 03, 2010. [Cited: 04 13, 2015.] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2010/03/human_orphan_000745.jsp&mid=WC0b01ac058001d12b.

RedaccionSalud. 2014. El Tiempo. *Hasta en un 60 % bajarían los precios de los medicamentos biológicos .* [Online] 09 19, 2014. [Cited: 12 18, 2014.] http://www.eltiempo.com/estilo-de-vida/salud/medicamientos-biologicos-bajarian-en-un-60-por-ciento/14556816.

RedaccionSalud1. 2014. El Tiempo. *Santos da vía libre a regulación de fármacos biotecnológicos.* [Online] 09 18, 2014. [Cited: 12 18, 2014.] http://www.eltiempo.com/estilo-de-vida/salud/presidente-santos-firmo-decreto-que-regula-medicamentos-biotecnologicos/14554096.

RedacionSalud. 2013. El tiempo. *Cada cinco minutos hay una nueva tutela de salud en el país.* [Online] 04. 09 2013. [Zitat vom: 16. 12 2014.] http://www.eltiempo.com/archivo/documento/CMS-13045163.

ResearchandMarkets. 2009. Research and Markets. *The Patent Cliff: Strategies and Tactics for Survival.* [Online] 09 2009. [Zitat vom: 16. 12 2014.] http://www.researchandmarkets.com/reports/1213684/the_patent_cliff_strategies_and_tactics_for .

ResponsetoFDA. 2014. Minsalud. *Response to the comment submilted by FDA to Colombia's draft regulation 01.* [Online] 08 2014. [Cited: 12 17, 2014.] http://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/MET/response%20to%20the%20comment%20FDA.pdf.

Restrepo, Luis, et al. 2014. *Medicamentos Biologicos Sin Barreras.* [Online] 06 2014. [Cited: 12 16, 2014.] http://www.mision-salud.org/medicamentos-biologicos-sin-barreras-julio-de-2014/.

Reuters, Thomson. 2015. Cortellis. *Cortellis Regulatory Intelligence.* [Online] 2015. [Cited: 04 16, 2015.] https://cortellis.thomsonreuterslifesciences.com/ngg/login.do.

Rickwood S, B.S. 2013. Searching for terra firma in the biosimilars and non-original biologics market. [Online] 2013. [Zitat vom: 16. 12 2014.] http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Healthcare/Life%20Sciences%20Solutions/Generics/IMSH_Biosimilars_WP.pdf.

Rocha Jimenez, José. 2008. Scribd.com. *Colombia: Corte Constitucional comunicado Sentencia T-760 de 2008.* [Online] 07 31, 2008. [Cited: 07 23, 2014.] http://de.scribd.com/doc/5089190/Colombia-Corte-Constitucional-comunicado-Sentencia-T-760-de-2008.

Rodriguez Garavito, Cesar. 2014. El espectadaor . [Online] 28. 07 2014. [Zitat vom: 30. 07 2014.] http://www.elespectador.com/opinion/cabeza-del-ministro-de-salud-columna-507252.

Rodriguez Garavito, Cesar. 2014. El espectador. *Preguntas para las farmacéuticas.* [Online] 08 04, 2014. [Cited: 08 05, 2014.] http://www.elespectador.com/opinion/preguntas-farmaceuticas-columna-508639.

Ronderos, Maria Teresa. 2009. Semana. *Lo mejor y lo más débil del sistema de salud colombiano.* [Online] 07 06, 2009. [Cited: 07 23, 2014.] http://www.semana.com/nacion/salud-seguridad-social/articulo/lo-mejor-mas-debil-del-sistema-salud-colombiano/104899-3.

Salek, Sam. Mallia-Milanes, Andrea. McAuslane, Neil. Walker, Stuart. 2012. Development and Application of Scorecards to Assess the Quality of a Regulatory Submission and its Review. *Drug Information Journal.* 2012.

SCUBED. 2012. SCUBED. *Scientific Advice.* [Online] 2012. [Cited: 04 13, 2015.] http://www.s-cubed.dk/services/regulatory/scientific.php.

Semana. 2015. Semana. *¿Por qué aquí se pagan los medicamentos más caros de A. Latina?* [Online] 03 10, 2015. [Cited: 03 31, 2015.] http://www.semana.com/nacion/articulo/colombia-paga-los-medicamentos-mas-caros-de-a-latina/420482-3.

Silva Numa, Sergio. 2014. El espectador. *El hombre que incomoda a las farmacéuticas .* [Online] 09 13, 2014. [Cited: 09 16, 2014.] http://www.elespectador.com/noticias/salud/el-hombre-incomoda-farmaceuticas-articulo-516485.

—. 2015. El espectador. *El medicamento de los $400 mil millones.* [Online] 03 11, 2015. [Cited: 31 03, 2015.] http://www.elespectador.com/noticias/salud/el-medicamento-de-los-400-mil-millones-articulo-548865.

Sommer, Stephanie. 2014. *Regulatory acceptability of clinical surrogate endpoints for accelerated (US) or conditional (EU) approval of haematological anti-cancer drugs in the light of the new CHMP anti-cancer guideline (CHMP/205/95 Rev. 4 and appendices) and the new FDA draft gui.* Bonn : s.n., 2014.

Torres, Guillermo. 2014. Semana. *Enfermos con cáncer temen por su futuro.* [Online] 02 05, 2014. [Cited: 07 23, 2014.] http://www.semana.com/nacion/articulo/reforma-de-la-salud-afectaria-pacientes-con-cancer/376158-3.

U.S.Government. 2014. Minsalud. *Comment letter from U.S. to 5th draft of biological decree.* [Online] 2014. [Cited: 12 17, 2014.] http://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/MET/United%20states%20department%20of%20health%20and%20human%20services.pdf.

Uribe Gaviria, Alejandro. 2013. Minsalud. *Ley Ordinaria .* [Online] 2013. [Cited: 12 17, 2014.] http://www.minsalud.gov.co/Documents/Ley%20Reforma%20a%20la%20Salud/Proyecto%20de%20Ley%20Ordinaria.pdf.

Uribe Vélez, Alvaro. 2006. *Tratado de libre comercio Colombia - Estados Unidos.* [Online] 02 27, 2006. [Cited: 08 06, 2014.] http://www.sice.oas.org/TPD/AND_USA/Studies/COLResumen_s.pdf.

Uribe Velez, Alvaro. 2004. Ministerio de la protección social. *DECRETO 481.* [Online] 02 18, 2004. [Cited: 03 27, 2015.] http://www.epssura.com/files/decreto481_2004.pdf.

Vacca, Claudia, et al. 2012. *Vínculo entre procesos de evaluación de eficacia y seguridad en agencias sanitarias y decisiones de cobertura: Referenciación .* Colombia : s.n., 2012.

Velasco Agudelo, Fernando. 2013. LaTarde.com columnistas. *El Sistema Nacional de Salud colapsó.* [Online] 11 11, 2013. [Cited: 07 23, 2014.] http://www.latarde.com/opinion/columnistas/124810-el-sistema-nacional-de-salud-colapso.

vfa. 2012. Die forschenden Pharma-Unternehmen. [Online] 2012. [Cited: 12 16, 2014.] http://www.vfa.de/en/statistics/statistics-2012-forschung1.

—. 2012. vfa position on endpoints for oncological therapies. [Online] 09 2012. [Cited: 12 2014, 12.] http://www.google.de/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=1&ved=0CCUQFjAA&url=http%3A%2F%2Fwww.vfa.de%2Fpos-endpoints-for-oncological-therapies.pdf&ei=TtIKVeWPHYGvUf3Pg9AB&usg=AFQjCNGfnYGHAv0KyCCvnufC1EP8KUGEGQ&sig2=IJn8xqg38hK8b9ZwH17plA&bvm=bv.8.

vfa-Research. 2014. Die forschenden Pharma-Unternehmen. [Online] 2014. [Zitat vom: 16. 12 2014.] http://www.vfa.de/en/statistics/statistics-2012-forschung1.

Walker, Stuart, Cone, Margaret and Collins, Jennifer. 2005. Center For Innovation in Regulatory Science. *Assessing the regulatory environment and its impact on patients' access to new medicines Middle East and Africa.* [Online] 09 2005. [Cited: 01 28, 2015.] http://cirsci.org/node/73.

—. 2005. Centre for Innovation in Regulatory Science. *Assessing the regulatory environment and its impact on.* [Online] 09 2005. [Cited: 01 30, 2015.] http://cirsci.org/node/73.

WHA. 2014. WHO. *Evaluación de las intervenciones y las tecnologías sanitarias en apoyo de la cobertura sanitaria universal.* [Online] 05 24, 2014. [Cited: 03 27, 2015.] http://apps.who.int/medicinedocs/documents/s21463es/s21463es.pdf.

Wiecek, Andrzej and Mikhail, Ashraf. 2006. ndt. *European regulatory guidelines for biosimilars.* [Online] 2006. [Cited: 12 18, 2014.] http://ndt.oxfordjournals.org/content/21/suppl_5/v17.short.

Wikipedia. 2014. Sistema de salud en Colombia. [Online] 07 22, 2014. [Cited: 07 23, 2014.] http://es.wikipedia.org/wiki/Sistema_de_salud_en_Colombia.

Zapata, J.G, et al. 2012. *Pertinencia de incentivar la competencia en el mercado de medicamentos biotecnológicos en Colombia y su impacto sobre las finanzas del sector de la salud. Fedesarrollo.* 2012.

Annex 1. Complete list of quality dossier requirements for medicinal products following CTD structure.

Requirement	Colombia
1.3.1 Labelling Information and Package Leaflet	No
1.4.1 Quality	No
1.4.2 Non-Clinical	No
1.4.3 Clinical	No
Environmental Assessment	No
1.8.1 Pharmacovigilance System	No
1.8.2 Risk-management System	No
2.1 CTD TABLE OF CONTENTS (MODULE 2-5)	No
2.2 INTRODUCTION	No
2.3 QUALITY OVERALL SUMMARY	No
2.4 NONCLINICAL OVERVIEW	Yes
2.5 CLINICAL OVERVIEW	Yes
2.6.1 Introduction	Yes
2.6.2 Pharmacology Written Summary	Yes
2.6.3 Pharmacology Tabulated Summary	Yes
2.6.4 Pharmacokinetics Written Summary	Yes
2.6.5 Pharmacokinetics Tabulated Summary	Yes
2.6.6 Toxicology Written Summary	Yes
2.6.7 Toxicology Tabulated Summary	Yes
2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods	No
2.7.2 Summary of Clinical Pharmacology Studies	Yes
2.7.3 Summary of Clinical Efficacy	No
2.7.4 Summary of Clinical Safety	No
2.7.5 Literature References	No
2.7.6 Synopses of Individual Studies	No
3.1 TABLE OF CONTENTS OF MODULE 3	No
Facilities and Equipment (BIO)	No
Adventitious Agents Safety Evaluation – TSE/BSE	No
Adventitious Agents Safety Evaluation - Viral Agents (BIO)	No
Novel Excipients Information	No
Description and Composition of the Drug Product	Yes
Pharmaceutical Development	No
Clinical Trial Formulations and Batches	No
Manufacturer	Yes
Batch Formula	Yes
Description of Manufacturing Process and Process Controls	Yes
Packaging Procedure	Yes
Master Batch Record	Yes
Justification of Controls of Critical Steps	No

Specification (intermediate product)	Yes
Analytical Procedure (intermediate product)	No
Validation of Analytical Procedure (intermediate product)	No
Justification of Specification (intermediate product)	No
Process Evaluation	No
Process Validation	No
Sterilization Process Validation	No
Reference to Compendia	No
Specification	Yes
Analytical Procedure	No
Validation of Analytical Procedure	No
Justification of Specification	No
Certificate of Analysis	Yes
Excipients of Human or Animal Origin	Yes
Novel Excipient	No
Specification	Yes
Analytical Procedure	Yes
Validation of Analytical Procedure	Yes
Batch Analyses	Yes
Certificate of Analysis	Yes
Impurities	No
Justification of Specification	No
Justification of Dissolution Specification	No
Reference Standard(s)	Yes
Description of the Container Closure System	Yes
Specification	Yes
Analytical Procedure	No
Validation of Analytical Procedure	No
Justification of Specification	No
Certificate of Analysis	Yes
Stability Summary and Conclusions	Yes
Post-Approval Stability Protocol and Stability Commitment	Yes
Stress Stability Data	Yes
Accelerated and Long-Term Stability Data	Yes
In-Use Stability Data	Yes
Bulk Stability Data	No
Process Validation Scheme of the Drug Product	No
Application/Approval Form	No
Executed Batch Records	Yes
Tabulations for materials of animal and/or human origin	Yes
Manufacturing Process Parameters and Proven Acceptable Ranges	Yes
Method Validation Package	No
Declaration of Conformity or CE Certificate	No
Letter of Authorization to a DMF	No

Certificate of Suitability to the Monograph of the European Pharmacopoeia	Yes
Comparability Protocol	No
Nomenclature	Yes
Structure	Yes
General Properties	Yes
Manufaturer	No
Description of Manufacturing Process and Process Controls	No
Justification for Starting Material Designation	No
Specification (starting material)	No
S233 Analytical Procedure (starting material)	No
Specification (raw material)	No
Justification of Controls of Critical Steps	No
Specification (intermediate)	No
Analytical Procedure (intermediate)	No
Process Evaluation	No
Sterilization Process Validation	No
Manufacturing Process Development	No
Elucidation of Structure	No
Physicochemical Characteristic	No
Solid State Forms	No
Impurities	No
Specification	Yes
Analytical Procedure	Yes
Validation of Analytical Procedure	Yes
Batch Analyses	No
Certificate of Analysis	No
Justification of Specification	No
Reference Standard(s)	No
Description of the Container Closure System	No
Container Closure Suitability	No
Specification	No
Analytical procedure	No
Validation of Analytical Procedure	No
Stability Summary and Conclusions	No
Post-Approval Stability Protocol and Stability Commitment	No
Stress Stability Data	No
Accelerated and Long-Term Stability Data	No
4.1 TABLE OF CONTENTS OF MODULE 4	No
4.2.1.1 Primary Pharmacodynamics	Yes
4.2.1.2 Secondary Pharmacodynamics	Yes
4.2.1.3 Safety Pharmacology	Yes
4.2.1.4 Pharmacodynamic Drug Interactions	Yes
4.2.2.1 Analytical Methods and Validation Reports	Yes
4.2.2.2 Absorption	Yes

4.2.2.3 Distribution	Yes
4.2.2.4 Metabolism	Yes
4.2.2.5 Excretion	Yes
4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)	Yes
4.2.2.7 Other Pharmacokinetic Studies	Yes
4.2.3.1 Single-Dose Toxicity	Yes
4.2.3.2 Repeat-Dose Toxicity	Yes
4.2.3.3.1 In Vitro	Yes
4.2.3.3.2 In Vivo	Yes
4.2.3.4.1 Long-term studies	Yes
4.2.3.4.2 Short-or medium-term studies	Yes
4.2.3.4.3 Other studies	Yes
4.2.3.5.1 Fertility and early embryonic development	Yes
4.2.3.5.2 Embryo-fetal development	Yes
4.2.3.5.3 Prenatal and postnatal development, including maternal function	Yes
4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed/and/or further evaluated	Yes
4.2.3.6 Local Tolerance	Yes
4.2.3.7.1 Antigenicity	Yes
4.2.3.7.2 Immunotoxicity	Yes
4.2.3.7.3 Mechanistic studies	Yes
4.2.3.7.4 Dependence	Yes
4.2.3.7.5 Metabolites	Yes
4.2.3.7.6 Impurities	Yes
4.2.3.7.7 Other	Yes
4.3 LITERATURE REFERENCES	Yes
5.1 TABLE OF CONTENTS OF MODULE 5	No
5.2 TABULAR LISTING OF ALL CLINICAL STUDIES	No
5.3.1.1 Bioavailability (BA) Study Reports	Yes
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports	Yes
5.3.1.3 In Vitro - In Vivo Correlation Study Reports	Yes
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies	Yes
5.3.2.1 Plasma Protein Binding Study Reports	Yes
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies	Yes
5.3.2.3 Reports of Studies Using Other Human Biomaterials	Yes
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	Yes
5.3.3.2 Patient PK and Initial Tolerability Study Reports	Yes
5.3.3.3 Intrinsic Factor PK Study Reports	Yes
5.3.3.4 Extrinsic Factor PK Study Reports	Yes
5.3.3.5 Population PK Study Reports	Yes
5.3.4.1 Healthy Subject PD and PK/PD Study Reports	Yes
5.3.4.2 Patient PD and PK/PD Study Reports	Yes
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	Yes
5.3.5.2 Study Reports of Uncontrolled Clinical Studies	Yes

5.3.5.3 Reports of Analyses of Data from More than One Study	Yes
5.3.5.4 Other Study Reports	Yes
5.3.6 Reports of Post-Marketing Experience	Yes
5.3.7 Case Report Forms and Individual Patient Listings	Yes
5.4 LITERATURE REFERENCES	Yes

Annex 2. Additional requirements for registration of medicinal products in Colombia.

Country	Requirement	Necessary	Other Information
Colombia	Modified Module 3 GMD Documents	Yes	
Colombia	Chromatograms DP	No	
Colombia	Chromatograms DS	No	
Colombia	CoA DP	No	
Colombia	CoA DS	Yes	Only needed for local manufacturers.
Colombia	CoA Excipient	No	
Colombia	CoA Packaging Component	No	
Colombia	CoA Reference Standard	No	
Colombia	Executed Batch Record	No	
Colombia	Other procedural Information	No	
Colombia	Patent Status/Registration Status	No	
Colombia	Other	No	
Colombia	Information	Yes	If country of origin (CoO) is a reference country, then the GMP is enough. If CoO is not a reference country but it's been inspected by a reference country, then an acreditation of that inspection would do. If no reference country acreditation is available, then an inspection has to be performed. Timeline for requesting the site inspection: 1 year before estimated submission of the product. Site Master File is only needed in case the CPP is not feasible to provide Reference country: United States, Canada and Japan, Germany, Switzerland, France, UK, Denmark, Netherlands, Sweden and Norway.
Colombia	PSUR/DSUR	No	
Colombia	CLIN SUB–GROUP ANALYSES	No	

Colombia	Other – any other clin docs	No	
Colombia	CPP - Certification of Pharmaceutical Product	Yes	CPP can be apostilled or Original with embassy legalization. In the certifying country, the product should be registered and marketed. First step of submission can be done without the CPP but CPP is needed for the second step
Colombia	GMP - Good Manufacturing Practice certificate for API, BDP, QCS, RelS	Yes	
Colombia	MA - Marketing Authorization certificate	No	
Colombia	ManA - Manufacturing Authorization certificate	No	
Colombia	TM - Trademark certificate	No	
Colombia	Patent – Patent Certificate	No	
Colombia	Packaging components	Yes	

Annex 3. Questionnaire

Pharmaceutical Industry and Heal authority (INVIMA) employees from Colombia have been asked to provide their opinion on following items from the Regulatory Affairs Environment in Colombia

a) Time of evaluation of applications for new Marketing Authorization
b) Scientific advice provided by the INVIMA before submission of applications for Marketing Authorization
c) Transparency
d) Knowledge and Training of the evaluators of application
a) Quality of dossier review
b) Quality of dossier submission
c) Harmonization in regard with the rest of the world.

The scale to evaluate those items was:

a) Very Good
b) Good
c) Regular
d) Bad
e) Very Bag
f) Don’t know

Additionally on all of the items evaluated, the participants were openly asked to give their opinion on what should be improved regarding each one of the evaluated items.

The questionnaire in Spanish language can be found on following link:

https://docs.google.com/forms/d/1CXP4tFkRh9SoGGxTFND9euDTNvjzR3ByxZcY64H4s-g/viewform?c=0&w=1

Acknowledgements

First of all I offer my sincerest gratitude to my supervisors Dr. Josef Hofer and Dr. Santiago Figueroa who supported me throughout my thesis with their knowledge and interest whilst allowing me the room to work in my own way .

Besides my supervisors, I would like to thank Silvia Gelvez, Egdda Patricia Vanegas, Rita Sousa, Leandro Cantante Cavaleiro, Maria Teresa Piccini, Suzin Choi, Pablo Amaya, Juan Rodriguez Vazquez and Kirsten Jacobs for their extensive and very useful comments on earlier versions of this thesis as well for their advice and insight throughout my work. Their ideas were very valuable for me.

Also many thanks to my friends and colleagues from Colombia who studied with me Pharmacy in the national university of Colombia who with their input and experience added value to this thesis, especially with the time by answering the questionnaire that permitted me some insight into the local situation in Colombia.

I would further like to thank the staff of the DGRA secretary, especially Barbara Röcher, Dr Bettina Gerlach and Dr Jasmin Fahnenstich for their great support during the MDRA.

Last but not least; I would like to thank my parents as they are my motivation in every step of my life. With their love, encouragement and sacrifices my parents made to ensure that I had an excellent education. For this and much more, I am forever thankful with them

Eidesstaatliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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Carolina Rodriguez Beltran

Mainz, 02.06.2015