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REGULATORY AND REIMBURSEMENT FRAMEWORKS OF MEDICINES: A STUDY OF THE DIFFERENCES ACROSS JURISDICTIONS

LOS MARCOS REGULATORIOS Y DE FINANCIACIÓN DE MEDICAMENTOS: UN ESTUDIO DE LAS DIFERENCIAS ENTRE JURISDICCIONES

MAYRA LATORRE MARTÍNEZ

Degree in Pharmacy (Licenciado en Farmacia)

Universidad Nacional de Educación a Distancia (UNED)
Departamento de Economía Aplicada y Gestión Pública
Facultad de Ciencias Económicas y Empresariales

Director: Dr. Antonio Sarria Santamera
Co-Director: Dra. Carolina Navarro Ruíz

DEPARTAMENTO DE ECONOMÍA APLICADA Y GESTIÓN PÚBLICA

FACULTAD DE CIENCIAS ECONÓMICAS Y EMPRESARIALES

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MAYRA LATORRE MARTINEZ

DEGREE IN PHARMACY (LICENCIADO EN FARMACIA)

Director: Dr. Antonio Sarria Santamera

Co-Director: Dra. Carolina Navarro Ruiz

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I dedicate this Thesis to my family.

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LIST OF ABBREVIATIONS

ACER: Average Cost-Effectiveness Ratio

ATPM: Advanced Therapy Medicinal Product

CBA: Cost-benefit analysis

CDEC: Canadian Drug Expert Committee

CEA: Cost-effectiveness analysis

CF: Cystic Fibrosis

CFTR: Cystic Fibrosis Transmembrane conductance Regulator

CFQ-R: Cystic Fibrosis Questionnaire-Revised

CHMP: Committee for Human Medicinal Products

CMA: Cost-minimisation analysis

CMA: Conditional Marketing Authorisation

CMC: Chemical Manufacturing Control

COMP: Committee Orphan Medicinal Products

CPAG: Clinical Priorities Advisory Group

CTD: Common Technical Document

CTLA-4: Cytotoxic T-lymphocyte antigen-4

CUA: Cost-utility analysis

DACEHTA: Danish Centre for Health Technology Assessment

EAHC: Executive Agency for Health and Consumers

EAMS: Early Access Medicines Scheme (UK)

EC: European Commission

EEA: European Economic Area

EFPIA: European Federation of Pharmaceutical Industries and Associations

EFTA: European Free Trade Association

EMA: European Medicines Agency

EPAR: European Public Assessment Report

ERN: European Reference Network

EU: European Union

EUCERD: European Union Committee of Experts on Rare Diseases

EUDRALEX: European Union Drug Regulatory Authorities

EUneHTA: European Network for Health Technology Assessment

FDA: Food and Drug Administration

FVE_1: Maximum amount of air that a person can breathe out in one second

GCP: Good Clinical Practices

GP: General Practitioner

HAS: Haute Authorite Sante

HRQOL: Health Related Quality of Life

HTA: Health Technology Assessment

HTAN: Health Technology Assessment Network

ICDRA: International Conference of Drug Regulatory Authorities

ICER: Incremental cost-effectiveness ratio

ICH: International Conference of Harmonization

IFNa: Interferon alpha

IFPMA: International Federation of Pharmaceutical Manufacturers and Associations

IL-2: Interleukine-2

IMIS: Information Management Infrastructure and Services

IMM: Irreversible Morbidity or Mortality

INAHTA: International Network of Agencies for Health Technology Assessment

IPT: Informe Posicionamiento Terapéutico

IQWIG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

irAES: Immune Related Adverse Events

ISPOR: International Society for Pharmacoeconomics and Outcomes Research

IT: Information Technology

JA: Joint Action

LBI: Ludwig Boltzmann Insitute

MA: Marketing Authorisation

MAPs: Medicines Adaptative Pathways

MAPPs: Medicines Adaptative Pathways to Patients

MHRA: Medicines and Healthcare Products Regulatory Agency

MS: Member State

MTD: Maximum Tolerable Dose

NCPE: National Centre for Pharmacoeconomics

NHS: National Health System (UK)

NICE: The National Institute for Health and Care Excellence

NIHR: NHS Institute for Health Research

NRS: Non-randomised studies

ORR: Overall Response Rate

OS: Overall Survival

PBAC: Pharmaceutical Benefits Advisory Committee

PAES: Post-Approval Efficacy Study

PAS: Patient Access Scheme

PASAG: Patient Access Scheme Assessment Group

PASS: Post-Approval Safety Study

PFS: Progression Free Survival

PIM: Promising Innovative Medicine

PRO: Patient Reported Outcome

PSURS: Periodic Safety Update Reports

QALY: Quality Adjusted Life Year

QoL: Quality of Life

RCT: Randomised Clinical Trial

REA: Relative Effectiveness Assesment

R&D: Research and Development

SCG: Specialised Commissioning Group

SEED: Shaping European Early Dialogues for health technologies

SMC: Scottish Medicines Consortium

SME: Small and medium size Enterprise

SmPC: Summary of Product Characteristics

SOC: Standard of Care

STAMP: Commission Expert Group on Safe and Timely Access to Medicines for Patients

TFEU: Treaty on the Functioning of the European Union

UK: United Kingdom

US: United States

WHO: World Health Organisation

WP: Work Package

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ABSTRACT

In the European Union (EU) the protection of public health is a recognized right and a priority for governments. Therefore, the regulatory standards required for the development, manufacture, control and post-marketing surveillance of medicinal products are very high.

The regulatory evaluation of a medicinal product comprises the assessment of the quality, the safety and the efficacy of the drug based on its own merits.

This regulatory evaluation system operates in a coordinated and harmonized manner across the EU. A common core of legislation issued by the European Commission (EC) is followed by all European Union authorities, establishing agreed scientific and methodological standards.

The birth of the EU regulatory system dates back to 1965, with the adoption of Directive 65/65/CEE triggered by the Thalidomide catastrophe. Over the subsequent 50 years to date, the Competent Health Authorities of the EU Member States (MS) have increased the degree of communication, exchange of information and cooperation, having reached nowadays an impressive status where the whole EU works in unified manner, making use of harmonized scientific criteria, procedures and mutual recognition of evaluations. The system is supported and coordinated by a central body, the European Medicines Agency (EMA).

The development of this EU regulatory system was impelled and driven both by the need to attain common scientific standards for the evaluation of medicines and also by the necessity to pool and optimize resources within Health Authorities institutions avoiding duplication of work.

Obtaining a positive regulatory evaluation is the first step on the way of a medicine to the market.

In addition to this regulatory evaluation, in the EU, a medicinal product also needs to undergo successful financing and reimbursement negotiations with European national governments.

European health care systems are nowadays under a high pressure towards the implementation of mechanisms that allow the control of the health care expenditure.

Static or shrinking health budgets together with a constant increase in the demand of the expenditure by the European population threatens the long-term financial sustainability of the national European health care systems.

Under such a situation, it is of utmost importance for health care providers and payers to choose those health technologies that provide added value to the system ensuring the sustainability of the welfare state of the population and at the same time help meet the national budgets.

The evaluation of the value of health technologies, known as HTA (Health Technology Assessment) is the main tool used for the financing and reimbursement decision making process of the different pharmacological alternatives available.

As a result of these two systems and in order to reach the national European markets, a medicinal product needs to fulfil the requirements of the regulatory framework and also the requirements of the HTA framework.

Health Authorities assess the **quality, safety** and **efficacy** of a medicinal product **based on its own merits** whereas **Health Technology Assessment bodies** evaluate the safety and efficacy of a drug **comparatively to other available treatments on the market (i.e. relative cost-effectiveness).**

When a new medicine reaches the market, it is accompanied by an extensive data package that provides information about the **safety and efficacy** of the medicine in a **clinical trial setting.**

However, assessing the expected future value of the medicines when used in **"real world" clinical practice (i.e. effectiveness),** requires additional information beyond traditional (pre-authorisation) clinical trials.

As a consequence, industry faces the challenge that the data set required to undertake the two evaluations are not necessarily the same due to the fact that Regulators and HTA bodies have differences in scope and aim.

Both groups of entities have traditionally worked independently too what explains the current disharmony that exists with these two types of assessments.

Being aware of this situation that hinders the competitive development of the pharmaceutical industry in Europe, and can have in the long-term a negative impact in the research and development of new innovative medicines, the EU institutions have launched a series of legal initiatives to provide a political mandate that allows cooperation and improvements in this area.

The legal basis to achieve the ambitious goal of harmonizing the work of HTA bodies across the EU and at the same time create a solid interface with the regulatory world can be found in different pieces of legislation which are to be seen as complementary and interlinked:

The Treaty of Lisbon:

The Lisbon Treaty came into force on the 1st of December 2009.

The Treaty of Lisbon strengthens the social dimension of the European Union, as it recognises the social values of the Union in the founding Treaties and includes new objectives for social matters.

In this respect, the Treaty of Lisbon recognises the legal value of the Charter of Fundamental Rights of the EU, so that the principles here reflected become binding.

Article 35 of the Charter regarding health care reads as follows:

"Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities".

Even though the development and implementation of social policies remains principally the responsibility of Member States, the Treaty introduces some relevant innovations in the area of health care under Article 156 of the Treaty on the Functioning of the EU (TFEU):

"With a view to achieving the objectives of Article 151 and without prejudice to the other provisions of the Treaties, the Commission shall encourage cooperation between the Member States and facilitate the coordination of their action in all social policy fields under this chapter, particularly in matters relating to: – employment; – labour law and working conditions; – basic and advanced vocational training; – social security; – prevention of occupational accidents and diseases; – occupational hygiene; – the right of association and collective bargaining between employers and workers. To this end, the Commission shall act in close contact with Member States by making studies, delivering opinions and arranging consultations both on problems arising at national level and on those of concern to international organizations, in particular initiatives aiming at the establishment of guidelines and indicators, the organisation of exchange of best practice, and the preparation of the necessary elements for periodic monitoring and evaluation. The European Parliament shall be kept fully informed. Before delivering the opinions provided for in this article, the Commission shall consult the Economic and Social Committee".

With this Article, the open method of coordination is institutionalised with the recognition that the Commission may undertake initiatives in order to encourage cooperation between Member States in the social domain and to facilitate the coordination of their actions. For example, these initiatives may take the form of studies or opinions with a view to establishing guidelines and indicators, and to organising the exchange of best practice with the organisation of a periodic evaluation.

The EU Directive 2011/24/EU:

Directive 2011/24 on the application of patients' rights in cross-border healthcare was adopted on 19 January 2011 and was published in the EU's Official Journal on 9 March 2011. It entered into application on 25 of October 2013.

As per Article 15 of this Directive, a voluntary network connecting the national authorities or bodies responsible for HTA designated by Member States is to be established and supported by the Union.

The Union's support for cooperation on Health Technology Assessment in accordance with Article 15 of Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border health care aims to optimise and coordinate HTA methodologies which should ultimately also reduce delays in pricing and reimbursement procedures of medicinal products for which Member States use HTA as part of their decision-making process.

Directive on Transparency:

The main objective of Directive 89/105/EEC is to facilitate the functioning of the internal market for medicinal products.

The legal basis is therefore Article 114 of the Treaty on the Functioning of the European Union.

Directive 89/105/EEC codifies the minimum requirements set forth by the Court of Justice. It was adopted to enable market operators to verify that national measures regulating the pricing and reimbursement of medicines do not contravene the principle of free movement of goods.

National pricing and reimbursement measures have a clear transnational impact linked, in particular, to the potential disruption they might cause to the internal market for medicinal products.

The proper functioning of the internal market therefore requires timely and transparent decisions to be made by Member States. However, the notion of procedural transparency is

understood differently across the EU so that action by individual Member States would not provide sufficient guarantees of transparency for economic operators. Therefore the action at EU level is of relevance in this area.

Pursuant to Article 168(7) of the Treaty on the Functioning of the European Union, Member States are responsible for the organisation of their health care systems and for the delivery of health services and medical care, including the allocation of resources assigned to them.

In this framework, each Member State can take measures to manage the consumption of medicines, regulate their prices or establish the conditions of their public funding.

Therefore, the Directive lies at the interface between EU responsibilities for the internal market and national competences in the area of public health in accordance with Article 168(7) of the Treaty on the Functioning of the European Union (TFEU).

A proposal of an amended Transparency Directive has been launched. This is to be seen in the context of the Commission's efforts to reinforce the internal market and to generate favourable conditions for a competitive pharmaceutical industry to provide safe, innovative and accessible medicines to European citizens.

This proposal to amend the Directive on Transparency is related to other recent on-going initiatives, as it is the voluntary cooperation between Member States on Health Technology Assessments, which is currently taking place in the framework of the European Union Network for Health Technology Assessment (EUnetHTA) Joint Actions and to be formalised through the implementation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare.

In addition, the principles of the Transparency Directive determines that elements already assessed in the framework of the marketing authorisation process (quality, safety and efficacy, including bioequivalence) may not be reassessed in the framework of pricing and reimbursement procedures.

Empowered by this political mandate mentioned above, HTA bodies and Regulators have started a series of different initiatives in the interface Regulators-HTA.

SEED (Shaping European Early Dialogues for health technologies) is a project financed by the European Commission whose objective is to reduce the risk of production of data that would be inadequate to support a company's future reimbursement request.

Early dialogues allow companies developing health products to meet with European HTA bodies in order to present their development plan for the product in question and to ask specific questions relative to their plan.

Regulators are also leading numerous areas of collaboration to facilitate coordination and exchange of information with HTA bodies being led by the EMA. Actually**,** the European Medicines Agency has been working closely with HTA bodies since 2008.

The key goal of all these programmes and interactions is to understand clearly the regulatory and HTA requirements and set objectives for the future.

The objective is to define the scientific aspects behind the requirements imposed by both frameworks and ultimately try to establish regulatory processes that will allow dialogue between HTA bodies, Regulators and industry in a standardized manner and at the right time during the development of a new drug.

There is however a long way to harmonization ahead.

The study presented in this thesis departs from the hypothesis that despite recent attempts to harmonize the HTA appraisals among the European Union HTA bodies and also find an interface in relation to the regulatory framework requirements, still many discrepancies exist based not only on local economic demands but also due to differences in scientific methodological approaches.

This situation if not solved, will make it difficult to implement the provisions of the European Directives in relation to the equity in the access to health care.

The application of a common HTA methodology in Europe could highly improve the harmonization and transparency in HTA decisions

The study analyses the specific characteristics of both the regulatory and the HTA frameworks with the objective to identify those areas of discrepancies that could be harmonized.

For this study research, two medicinal products (Kalydeco and Yervoy) were chosen. Given the indications for which they are intended (i.e. life threatening diseases), with absence of similar pharmacological alternatives of treatment, they offered an optimal setting for the analysis of regulatory and HTA decision elements. Moreover, the fact that one is intended for a chronic life-threatening disease (Kalydeco) and the other for a terminal disease (Yervoy) also offered the opportunity to investigate the effect on decisions of long-term budget considerations.

The main goal of this research is to show areas of opportunity that could help delineate strategies for the future.

The European regulatory and HTA systems should have harmonized methodologies and guidance in relation to the requirements to be met to achieve a successful evaluation.

The pharmaceutical industry needs to have at its disposal harmonized and transparent guidance in order to be able to plan their research programs. They need to have the capacity to meet the requirements of both frameworks in a way that promotes the optimization of the design of their research programmes and therefore the use of resources.

OBJECTIVES OF THE STUDY

The objectives of the current research are the following:

- **Analysis of the current European regulatory framework in relation to the requirements for the authorization of medicines.**
- **Analysis of the HTA methodology used by the European HTA bodies for reimbursement and financing recommendations.**
- **Analysis of the current political scenario in the European Union and the initiatives to harmonize the regulatory and HTA frameworks.**
- **Investigate the differences in requirements and methodological approaches followed for the authorisation of medicines and the HTA appraisals. Identification of key areas of discrepancies.**
- **Investigate which areas could have the potential for further harmonization respecting the current European regulations in force for the evaluation of medicines and also preserving the need to maintain local HTA requirements.**

METHODOLOGY

The methodology of the study is as follows:

- **Review and analysis of the European Union pharmaceutical legislation in relation to the requirements for the authorisation of medicinal products. Expectations in relation to the quality, safety and efficacy data to be generated.**

  The research is presented in Chapter 1.

- **Review and analysis of the requirements and methodology employed in the HTA evaluations by EU HTA bodies. Expectations of HTA bodies in terms of data and evidence to be generated to prove added value.**

  The research is presented in Chapter 2.

- **Review and analysis of the current European legal framework in relation to the equity of access to healthcare.**

  The research is presented in Chapter 3.

- **Review and analysis of the European initiatives for collaboration and harmonization in the areas of regulatory and HTA appraisal of medicines.**

  The research is presented in Chapter 4.

- **Elaboration of a model design for the research and identification of the potential divergent criteria in methodologies and appraisals between Regulators and HTA bodies in the European Union.**

  The research is presented in Chapter 5.

- **Research study of the differences in regulatory and HTA evaluations of two centrally authorised drugs: Kalydeco and Yervoy.**

  The research is presented in Chapter 5.

For the study of the differences in the scope and focus between the regulatory and HTA evaluations, a model was designed.

The model was designed with the objective to enable the study of the elements that Regulators and HTA bodies take into account when performing their respective evaluations,

directed to grant a marketing authorisation in the case of Regulators or to provide recommendations / decisions for financing and reimbursement in the case of HTA bodies. And also identify the origin of the divergent opinions among HTA bodies when confronted with the same clinical evidence.

This model is to be applied to the study of each individual medicinal product selected (i.e. Kalydeco and Yervoy).

The sources of information that were used in this study are:

- **Regulatory documents:** European Public Assessment Reports (EPARs) published by the European Medicines Agency (EMA) for the selected medicinal product.
- **Health Technology Assessment documents:** Reports publicly available in English, Spanish and German from EU HTA bodies for the selected medicinal product.

The elements selected for the study are as follows:

- The HTA Core Model table developed by EUnetHTA was taken as the basis of the agreed methodology among EU HTA bodies.
- The main elements of a clinical study design.
- Key elements considered as pre-approval clinical evidence.

For each of the selected medicinal products, a comparative analysis of the elements contained in the European Public Assessment Report (EPAR) and the elements contained in the HTA reports was undertaken following a 3 steps scheme:

- Analysis following the HTA Core Model developed by EUnetHTA to determine the domains common to the regulatory and HTA fields.
- Analysis of the study design elements which are key to accept the clinical evidence presented and which are also recognized areas frequently source of discrepancies between regulators and HTA bodies (i.e. comparators, study population and endpoints).

- Analysis of the clinical evidence elements available pre-approval. The items considered were the benefit/risk balance, post-approval studies, degree of uncertainty and clinical added value. Study of the similarities and differences in the opinions among HTA bodies in view of the same clinical evidence which is taken from the EPAR published by the EMA.

A set of Key Questions was also developed to facilitate the analysis and discussion of the results.

The research performed on Kalydeco and Yervoy confirms the initial hypothesis that despite the last years programmes directed to harmonize the HTA evaluations among the European Union HTA bodies and also in relation to the regulatory framework requirements, still many discrepancies exist based not only on local economic demands but also due to scientific methodological approaches.

The analysis of the selected HTA reports shows that the methodological elements proposed by the EUnetHTA initiative have been followed to a certain extent. However, it is to be noted that not all the elements of the Core Model can be appreciated systematically in all the HTA reports.

The analysis of Kalydeco shows not only the divergence in appraisals that can exist between Regulators (EMA) and EU HTA bodies but also evidences the discrepant views and recommendations that the different EU HTA bodies can reach in the presence of the same clinical evidence.

In the case of Kalydeco, the research concludes that the economic cost of treatment was clearly the main driver in the evaluation.

The analysis of Yervoy also renders interesting conclusions among them the fact that the safety and efficacy elements appraised by EMA at central EU level are challenged on occasions by national HTA bodies.

In summary, this research has enlightened some of the current challenges and barriers that this ambitious harmonization process faces at present.

The application of a common HTA methodology in Europe could highly improve the harmonization and transparency in HTA decisions. And provide EU HTA bodies' recommendations and governments' final decisions on financing with improved transparency and legitimacy towards the patients and general public.

Moreover, the improvement of the interface regulatory-HTA is crucial for industry to design its expensive clinical trials.

Areas of Opportunity and Strategies for the Future:

- Acceptance by EU HTA bodies of the scientific opinions and decisions made by Regulators in their area of competency. It is not justifiable that the decisions made by a legally recognized competent institution at EU level regarding the benefit/risk balance are not automatically endorsed by EU national HTA bodies.

- Establishment of common, clear and transparent methodological guidance and processes among EU HTA bodies and where needed, with Regulators involvement (especially regarding the degree of uncertainty and the mitigating measures to be accepted).

- Clear definition of the scope of HTA appraisals together with explicit indication of the clinical evidence (i.e. studies) taken into account for the evaluation.

- Creation of an EU HTA institution responsible for the appraisal of non-context specific elements, in order to ensure the same decision in view of the same evidence or otherwise the establishment of a procedure for the mutual recognition of appraisals among EU HTA bodies.

- Higher and more transparent involvement of patients' organisations in the consultation of relevant endpoints and the decision making process.

Nevertheless, increased transparency as to what each government is able/willing to pay for each treatment is also crucial as price proves to play a key role in final decisions. The pharmaceutical industry also needs to be made aware of what are the price caps and thresholds governments are capable to finance so that they also recognize the role they have in making innovative treatments available to patients at a fair price.

PREFACE

This Thesis has been elaborated by Mayra Latorre Martinez under the direction of Dr. Antonio Sarria Santamera and Dra. Carolina Navarro Ruiz.

This Thesis presents a research study on the regulatory and reimbursement frameworks of medicinal products in the European Union.

INTRODUCTION

Why this Dissertation?

European health care systems are nowadays under a high pressure towards the implementation of mechanisms that allow the control of the health care expenditure.

Static or shrinking health budgets together with a constant increase in the demand of the expenditure by the European population threatens the long-term financial sustainability of the national European health care systems.

Under such a situation, it is of utmost importance for health care providers and payers to choose those health technologies that provide added value to the system and at the same time help meet the national budgets plans.

The regulatory evaluation framework for the authorisation of medicines has developed and reached a high level of harmonization within the European Union.

A common core of legislation issued by the European Commission is followed by all European Union authorities, establishing common scientific and methodological standards. Moreover, a system for a central coordination at European Union level is in place by means of supranational institutions like the European Medicines Agency (EMA).

The evaluation of the value of health technologies, known as HTA (Health Technology Assessment) is the main tool used for the financing and reimbursement decision-making process of the different pharmacological alternatives available.

In order to reach the national European markets, a medicinal product needs to fulfil the requirements of both systems, the regulatory framework and also the requirements of the HTA framework.

In view of the recent European legislative developments in the field of equity in the access to health, it is an expectation that any European Union citizen can enjoy an equivalent degree of health protection.

The study presented in this thesis departs from the hypothesis that despite recent attempts to harmonize the HTA evaluation among the European Union HTA bodies and also find an interface in relation to the regulatory framework requirements, still many discrepancies exist based not only on local economic demands but also due to differences in scientific methodological approaches.

The study analyses the specific characteristics of both the regulatory and the HTA frameworks, with the objective to identify those areas of discrepancies that could be harmonized.

For this study research, two medicinal products (Kalydeco and Yervoy) were chosen. Given the indications for which they are intended (i.e. life threatening diseases), with absence of similar pharmacological alternatives of treatment, they offered an optimal setting for the analysis of regulatory and HTA decision elements. Moreover, the fact that one is intended for a chronic life-threatening disease (Kalydeco) and the other for a terminal disease (Yervoy) also offered the opportunity to investigate the potential effect on decisions of needed long-term budget considerations.

The main goal of this research is to show areas of opportunity that could help delineate strategies for the future.

The European regulatory and HTA systems should have harmonized methodologies and guidance in relation to the requirements which are to be met in order to achieve a successful evaluation.

It is important that the pharmaceutical industry has at its disposal harmonized and transparent guidance as industry needs to be able to plan research programs in an efficient manner. Industry needs to have the capacity to meet the requirements of both frameworks in a way that promotes the optimization of the design of their research programmes and therefore the use of resources.

Current Situation of the Knowledge in this Field

The Situation: Two Systems

Legal and Political Scenario: Political Environment

Principles of Pharmacoeconomics

The Clinical Trial

The Situation: Two Systems

The Regulatory Framework

The approval of medicinal products[1] is a highly regulated field. The initiation of the modern medicines legislation in Western countries dates back to the beginning of the 19th century. However, it was the occurrence of several severe disasters like the sulphanilamide elixir and the diethylene glycol poisoning in the United States (1937) and the sadly famous Thalidomide teratogenic catastrophe in Europe in the 60s that urged governments to put much stricter regulatory and legal measures in place to prevent such terrible events happening again [1].

The birth of the unified European legislation of medicines took place in 1965 with the adoption of Directive 65/65/CEE [2].

The sponsor of any new medicinal product should demonstrate the **quality**, the **safety and** the **efficacy** of a drug prior to being granted the permission by the authorities to put the product on the market at the disposal of patients.

The level of requirements and data needed to prove these three items, the so-called three basic guarantees of a medicinal product, have raised and become more stringent over the years in consonance with the technical and scientific progress in pharmaceutics.

[1] The terms medicinal product, medicine and drugs are used as synonyms.

The Reimbursement and Financing Framework: Health Technology Assessment (HTA)

As the social and economic environment in Western countries evolves and the population age, the costs to be borne by health care systems (publicly or privately funded) also increase.

In this situation, the maintenance of the welfare state reached by developed countries is becoming more and more challenging and the evaluation of the **(relative) cost-effectiveness** of the medical treatments and drugs has become the new must.

The science of Health Technology Assessment (HTA) is therefore taking more and more relevance every day, for authorities, for payers and for industry.

Proven quality, safety and efficacy, the three basic guarantees, are no longer enough to allow patients' access to a new medicine. Now, a medicinal product also has to demonstrate its relative cost-effectiveness, when compared to other available treatments, the so-called fourth guarantee prior to being able to reach the European markets. As a result, sponsors of new medicines are required by EU governments to comply with these four guarantees prior to getting green light for financing and reimbursement and therefore access to the market.

However, the assessment of a medicine from a quality, safety and efficacy perspective which is carried out by regulatory Health Authorities does not fit the same purpose as the evaluation which is performed by Health Technology bodies, making it difficult and on occasions very inefficient the planning of clinical studies.

The way to Harmonization Regulatory vs. HTA: What are the Decision-Making Elements?

Health Authorities assess the **quality, safety** and **efficacy** of a medicinal product **based on its own merits** whereas Health Technology bodies evaluate the safety and efficacy of a drug **comparatively to other available treatments on the market (i.e. relative cost-effectiveness).**

When a new medicine reaches the market, it is accompanied by an extensive data package that provides information about the **safety and efficacy** of the medicine, usually gained in a clinical trial setting.

However, assessing the expected future value of the medicines when used in **"real world" clinical practice (i.e. the so-called effectiveness),** requires additional information which is to be obtained beyond the traditional (pre-authorisation) clinical trials.

As a consequence, industry faces the challenge that the data set required to undertake the two evaluations are not necessarily the same. Regulators and HTA bodies do not only have differences in scope and aim, also the fact that both groups of entities have traditionally worked independently explains the current disharmony that exists with these two types of assessments.

As an additional challenge, both Regulators and HTA bodies and on occasions also other healthcare decision- makers have to make decisions under **conditions of uncertainty.**

Uncertainty is caused due to the fact that clinical trials are performed on a sample of the target population and during a limited timeframe. Currently, data packages which aim to minimise uncertainty on safety and efficacy may still leave significant uncertainty in assessments of real world effectiveness of new medicines.

This results in further research commitments and requirements post-authorisation (e.g. Post Authorisation Safety Studies (PASS), Post Authorisation Efficacy Studies (PAES), reimbursement with evidence generation, etc.).

European Regulators and Health Technology bodies have become well aware of the fact that this situation is not sustainable in the long-term for a competitive industry environment and of

the important need and pressure to align to the maximum extent possible the requirements of information asked by Health Authorities and by HTA bodies.

Innovative industry is losing blockbusters as the patents expire while not so many new molecules to replace the old ones are discovered. At the same time, the regulatory requirements raise higher and higher making it an absolute necessity to optimize resources.

In such a context, it is of utmost importance to design correctly from the start the expensive clinical programs with the aim of fulfilling the obligations for the two areas of assessment efficiently and in parallel.

On average, the generation of regulatory data to support approval for a new experimental drug takes around 10 years. After that, the financing and reimbursement negotiations can take an average of two more years [3].

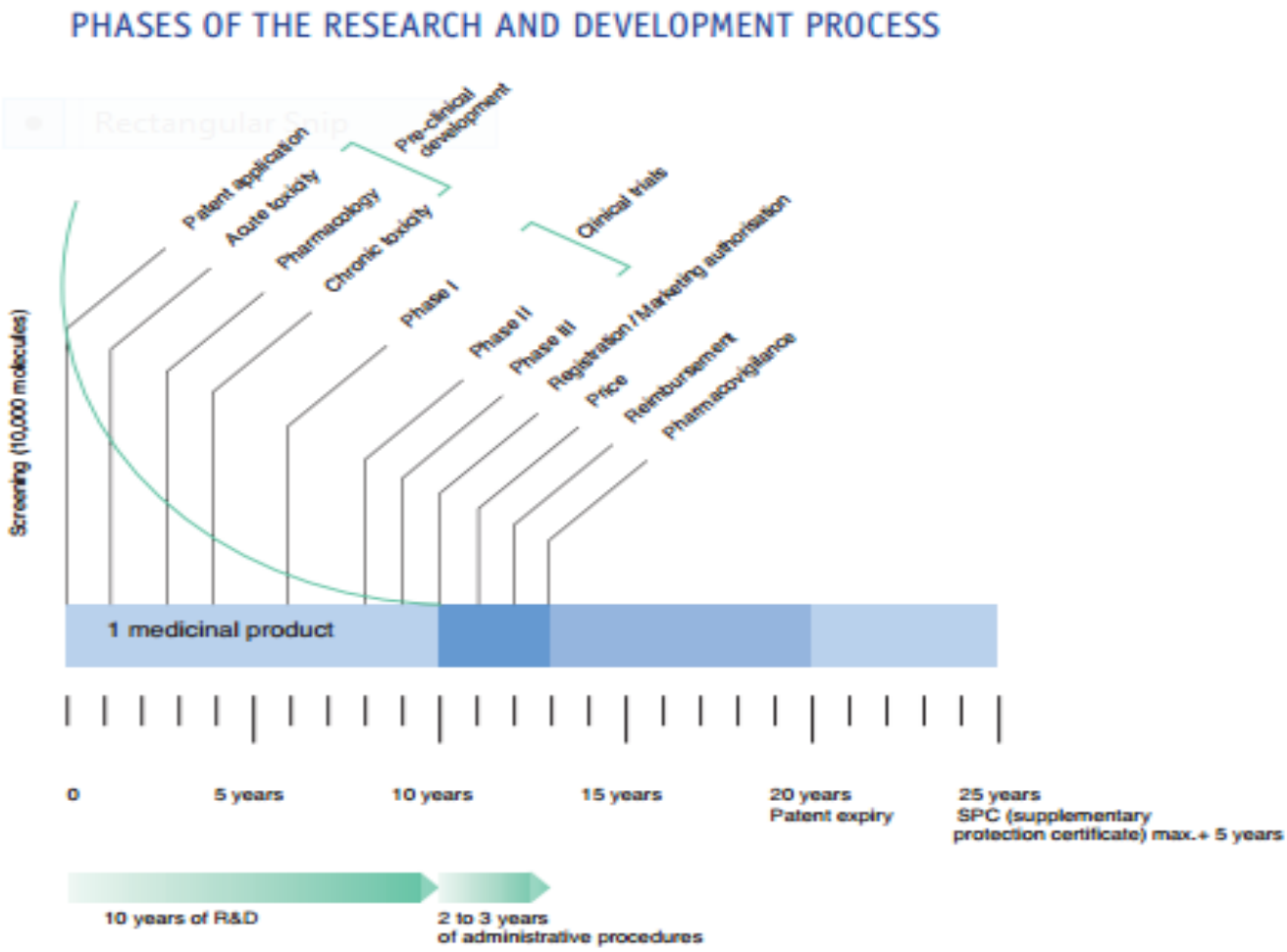

Figure 1. *Source: The Pharmaceutical Industry in Figures 2014 (European Federation of Pharmaceutical Industries and Associations EFPIA).*

European Health Authorities and HTA bodies, recognizing all these challenges and the existing room for harmonization have initiated the path towards knowledge sharing and collaboration in order to reach common approaches and establish harmonized rules as the purpose of governmental institutions is to foster innovation and not to hinder it by unnecessary bureaucracy.

An important milestone has been reached in Europe in this context with the establishment of the European Union Network of HTA (EUnetHTA) [4].

In 2004, the European Commission (EC) and the Council of the EU recognized the Health Technology Assessment as a high priority and urged for establishing a sustainable European network on HTA. Following this call, in 2005 a group of 35 organizations throughout Europe began the activities of the EUnetHTA Project.

Several initiatives are currently running under the EUnetHTA umbrella and so far, one of the most important milestones achieved by EUnetHTA in the way towards harmonization of methodologies and practices among EU HTA bodies is the creation of a core harmonized model for HTA evaluation. In this model (the HTA Core Model), the key elements to be assessed by HTA bodies in their appraisals are represented [5].

Furthermore, and as a response to the recommendations from the Pharmaceutical Forum in 2008, the European Medicines Agency and EUnetHTA started a collaboration to improve the contribution that European Public Assessment Reports (EPARs) prepared by EMA could make to the assessment of relative effectiveness of medicinal products [6].

In addition and to sum up to the initiatives undertaken for the understanding and cooperation between Regulators and HTA, the EMA also fostered the initiation of the pilot program for Parallel Scientific Advice with HTA bodies [7].

This pilot was launched in July 2010 and its aim is to allow sponsors to obtain guidance from Regulators and HTA bodies at the same time and early in the development of a medicine to help sponsors understand the evidence that both parties will need to determine a medicine's benefit/risk balance and value.

This program has now become a recognized initiative under the auspices of the European Commission.

Acting in its role of main European forum of discussion, bringing together Regulators and stakeholders from industry as well as from health care professionals and patients associations, EMA also hosted workshops in relation to the EMA-HTA Parallel Scientific Advice program with industry [8].

Further initiatives have been launched from the EMA side where HTA bodies and other stakeholders are invited to participate. A study of these programmes is explained in detail in Chapter 4.

The SEED (Shaping European Early Dialogues for health technologies) is another initiative financed by the EC to promote early discussions between industry, HTA bodies and Regulators [9].

All these activities are important not only to raise awareness of the different criteria and demands under which both systems operate but also, at the same time, to promote early dialogue and interactions among industry, Regulators and HTA bodies in an institutionalized manner.

They are also meant to increase the level of participation in future collaborative programs that may be launched with the EC support.

In summary, the key goal of all these interactions is to understand clearly the regulatory and HTA requirements and set objectives for the future.

Define the scientific aspects behind the requirements and ultimately try to establish regulatory processes that allow dialogue between HTA bodies, Regulators and industry in a standardized manner and at the right time during the development of a new drug.

In recent years, there has been considerable attention paid to the post-authorisation evaluation of treatments in real world clinical practice (i.e. study design and analytical methodology for assessing relative effectiveness and the use of registries and electronic healthcare data).

It may be possible to improve the value of information available at the time of the initial marketing authorisation by incorporating these techniques into pre-authorisation drug development in a way that HTA bodies and Regulators would become able to make better-

informed decisions, and developers of new medicines would be able to direct development efforts to areas where value is most likely to be delivered to patients.

However, the adoption of real world, relative effectiveness objectives in a pre-authorisation development strategy has many operational, methodological, regulatory, and ethical issues. Pharmaceutical research and development (R&D) organisations need more certainty as to what will be the impact of their development choices on the regulatory review process, the value of different programmes to HTA bodies and other decision makers. Industry needs to be able to plan in advance the best balance of pre-launch and post-launch effectiveness research and the coordination of various post-authorisation commitments and requirements.

In summary, both industry and governments now face a situation where the access of medicines to the market and therefore to patients needs to successfully fulfil the requirements of two different systems:

- **The regulatory system: where the evaluation focuses on the quality, safety and efficacy (the 3 basic guarantees) of a medicinal product based on its own merit.**
- **The Health Technology Assessment (HTA) system: where a drug is appraised based on its quality, safety, and efficacy and in addition its real world clinical effectiveness (i.e. the reassurance that there will be an extra gain (relative cost-effectiveness)). That is 4 guarantees.**

At present, there is little guidance on how to incorporate alternative study designs into a classical development programme to optimally meet the needs of all stakeholders over time. Regulators and HTA bodies are working on the issuance of more methodological guidance in the framework of several initiatives which are explained in Chapter 4.

Legal and Political Scenario: Political Environment

Lisbon Treaty: Social Chapter

With the entry into force of the Lisbon Treaty, certain responsibilities and competences on public health that were traditionally set at national level, have also been put at European level, with the aim of enabling and increasing cooperation and coordination in this area among the EU Member States, while respecting the principle of subsidiarity.

The Lisbon Treaty [10] came into force on the 1st of December 2009. The purpose was to modernise and reform a European Union of 27 Member States that had been operating with rules designed for an EU of 15 Member States.

This Treaty modernises the EU institutions and work practices, leading to greater efficiency in the decision-making process, and increases the democratic accountability by associating the European Parliament and the national parliaments.

The Treaty of Lisbon also strengthens the social dimension of the European Union, as it recognises the social values of the Union in the founding Treaties and includes new objectives for social matters.

The Treaty of Lisbon recognises the legal value of the Charter of Fundamental Rights of the EU [11], so that the Charter becomes binding and can be cited in legal proceedings.

This recognition constitutes an advance in social matters as the Charter ensures the social rights of persons resident in the EU.

Article 35 of the Charter addresses healthcare and reads as follows:

"Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities".

The implementation of social policy at European level forms part of the shared competences between the EU and the Member States. Even though the development and implementation of social policies remains principally the responsibility of Member States, the Treaty introduces some relevant innovations in the area of health care under Article 156 of the Treaty on the Functioning of the EU (TFEU) [12]:

"With a view to achieving the objectives of Article 151 and without prejudice to the other provisions of the Treaties, the Commission shall encourage cooperation between the Member States and facilitate the coordination of their action in all social policy fields under this chapter, particularly in matters relating to: – employment; – labour law and working conditions; – basic and advanced vocational training; – social security; – prevention of occupational accidents and diseases; – occupational hygiene; – the right of association and collective bargaining between employers and workers. To this end, the Commission shall act in close contact with Member States by making studies, delivering opinions and arranging consultations both on problems arising at national level and on those of concern to international organizations, in particular initiatives aiming at the establishment of guidelines and indicators, the organisation of exchange of best practice, and the preparation of the necessary elements for periodic monitoring and evaluation. The European Parliament shall be kept fully informed. Before delivering the opinions provided for in this article, the Commission shall consult the Economic and Social Committee".

By virtue of this Article, the open method of coordination is institutionalised with the recognition that the Commission may undertake initiatives in order to encourage cooperation between Member States in the social domain and to facilitate the coordination of their actions.

These initiatives may take the form of studies or opinions with a view to establishing guidelines and indicators, and to organising the exchange of best practice with the organisation of a periodic evaluation, so that for instance, cooperation between Member States on health services is encouraged in cross border areas.

Directive 2011/24/EU: Equity for European Patients

The EU Directive 2011/24/EU [13] on the application of patients' rights in cross-border healthcare was adopted on the 19th of January 2011 and was published in the EU's Official Journal on the 9th of March 2011. It entered into application on the 25th of October 2013.

This Directive sets a milestone in the recognition of equity in rights across European Union Members States. It does not only foster the right of EU patients to seek health care in countries different from their home country but it also introduces important provisions for the EU collaboration in the area of rare diseases and Health Technology Assessment.

As per Article 15 of this Directive, a voluntary network connecting the national authorities or bodies responsible for HTA designated by Member States is to be established and supported by the Union.

The Directive also contains very promising provisions regarding rare diseases. Some patients might see themselves in the need to seek health care out of their country of affiliation due to lack of expert diagnostic or treatment options. The Commission is devoted to support the Member States in cooperating with each other to develop better capacity for the diagnosis and treatment of rare diseases.

The main tool for this purpose will be European Reference Networks (ERN). Reference networks already exist in some disease areas, but the Directive gives them a legal basis and a specific focus on rare diseases.

The Directive calls on Member States to exploit better the possibilities offered by Orphanet [14] and the existing Social Security Regulation for the referral of patients abroad for the diagnosis and for treatments which are not available in the home country.

If a patient affected or suspected to be affected, by a rare disease needs to apply for prior authorisation, a clinical evaluation may be carried out, and if no experts can be found in the home country, the Member State can request scientific advice.

The idea is that the European Reference Networks bring together specialised centres and health care providers across Member States to pool resources and knowledge.

This is of special interest in the case of rare diseases where the expertise in very specific medical domains for both diagnosis and treatment might not be available in all Member States.

Directive on Transparency

The Transparency Directive (Council Directive 89/105/EEC) [15], aims to ensure the transparency of measures established by EU countries at national level to control the pricing and reimbursement of medicinal products.

It defines a series of procedural requirements designed to verify that national pricing and reimbursement decisions do not create obstacles to the pharmaceutical trade within the EU's Internal Market.

Therefore, this Directive lies at the interface between EU responsibilities for the assurance of the Internal Market and the free trade of goods and the national competences in the area of public health in accordance with Article 168(7) of the Treaty on the Functioning of the European Union [12].

The provisions of the Directive do not affect national policies on the setting of prices and the organisation of social security schemes, except as far as necessary to achieve transparency.

After having conducted a review, the Commission proposed a new Directive to replace the longstanding Transparency Directive.

The main objective is to streamline and reduce the duration of national decisions on the pricing and the reimbursement of medicines.

The new Directive represents an important simplification measure and will replace the longstanding Directive from 1989, as it does no longer reflect the increased complexity of pricing and reimbursement procedures in EU countries.

On the 18th of March 2013, the Commission adopted the amended proposal for a Directive of the European Parliament and of the Council on the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems [16].

National pricing and reimbursement measures have a clear transnational impact, associated in particular, to the potential disruption they might cause to the Internal Market for medicinal

products. Thus, the proper functioning of the Internal Market requires timely and transparent decisions to be made by Member States. However, as the notion of procedural transparency is understood differently across the EU, an action undertaken just by individual Member States would not provide sufficient guarantees of transparency for economic operators and therefore an intervention at EU level is justified and considered of relevance in this area.

The main objective of the Directive is to guarantee that any measure intended to regulate the prices of medicines, to manage their consumption or to determine their reimbursement status is adopted in a transparent manner on the basis of objective and verifiable criteria.

The proposal of an amended Transparency Directive is to be seen in the context of the Commission's efforts to reinforce the Internal Market and to generate favourable conditions for a competitive pharmaceutical industry that will provide safe, innovative and accessible medicines to European citizens.

It relates and complements a number of other recent on-going initiatives, as it is the voluntary cooperation between Member States on Health Technology Assessments, which is currently taking place in the framework of the EUnetHTA Joint Actions and to be formalised through the implementation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare.

Principles of Pharmacoeconomics

Pharmacoeconomics has been defined as the description and analysis of the cost of drug therapy to health care systems and society [17]. More specifically, pharmacoeconomic research is the process of identifying, measuring, and comparing the costs, risks, and benefits of programs, services, or therapies and determining which alternative produces the best health outcome for the resource invested.

This translates into weighing the cost of providing a therapy against the outcomes to determine which alternative yields the optimal outcome with the ultimate objective to make a decision in choosing the most cost-effective treatment option [18].

There are key basic concepts to be taken into account in a pharmacoeconomic study [19]:

- The perspective (i.e. patient, provider, payer, and society).
- The health care costs (that can be categorized as direct medical, direct nonmedical, indirect nonmedical, intangible, opportunity, and incremental costs).
- The type of method used for the analysis (i.e. cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses).

Assessing the costs and effects, that is the value of a therapy, depends heavily on the perspective of the evaluation. A pharmacoeconomic evaluation can assess the value of a product or service from single or multiple perspectives.

The costs can be categorized as:

Direct medical costs: costs incurred for medical products and services used.

Direct nonmedical costs: costs for nonmedical services that are results of illness or disease but do not involve purchasing medical services.

Indirect nonmedical costs: costs of reduced productivity (e.g. morbidity and mortality costs). They are an important source of resource consumption, especially from the perspective of the

patient. Morbidity costs are costs incurred from missing work (i.e., lost productivity), whereas mortality costs represent the years lost as a result of premature death.

Intangible costs: those of other nonfinancial outcomes of disease and medical care (e.g. pain, suffering, inconvenience, etc.).

Opportunity costs: represent the economic benefit forgone when using one therapy instead of the next best alternative therapy.

Incremental costs: represent the additional cost that a service or treatment alternative imposes over another compared with the additional effect, benefit, or outcome it provides [20].

The manner in which effects are quantified marks the distinction among pharmacoeconomic methods of analysis. Cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses are used to compare competing programs or treatment alternatives. The methods are all similar in the way they measure costs (monetary units) and different in their measurement of outcomes [20].

Cost-Minimization Analysis:

Cost-minimization analysis (CMA) involves the determination of the least costly alternative when comparing two or more treatment alternatives. With CMA, the alternatives must have an assumed or demonstrated equivalency in safety and efficacy (i.e. the two alternatives must be equivalent therapeutically). Once this equivalency in outcome is confirmed, the costs can be identified, measured, and compared in monetary units.

Cost-Benefit Analysis:

Cost-benefit analysis (CBA) is a method that allows for the identification, measurement, and comparison of the benefits and costs of a treatment alternative. The benefits realized from a treatment alternative are compared with the costs of providing it. Both the costs and the benefits are measured and converted into equivalent monetary units.

Cost-Effectiveness Analysis:

Cost-effectiveness analysis (CEA) involves comparing treatment alternatives with different safety and efficacy profiles. Cost is measured in monetary units, and outcomes are measured in terms of obtaining a specific therapeutic outcome.

The results of CEA are also expressed as a ratio, either as an average cost-effectiveness ratio (ACER) or as an incremental cost-effectiveness ratio (ICER). An ACER represents the total cost of a program or treatment alternative divided by its clinical outcome to yield a ratio representing the monetary unit cost per specific clinical outcome gained, independent of comparators.

Often clinical effectiveness is gained at an increased cost. Is the increased benefit worth the increased cost? Incremental CEA can be used to determine the additional cost and effectiveness gained when one treatment alternative is compared with the next best treatment alternative. Thus, instead of comparing the ACERs of each treatment alternative, the additional cost that a treatment alternative (A) imposes over another treatment (B) is compared with the additional effect, benefit, or outcome it provides. The ICER can be summarized as follows:

ICER= (CostA-CostB) / (Effect A – Effect B)

This formula yields the additional cost required to obtain the additional effect gained by switching from drug A to drug B.

ACER reflects the cost per benefit of a new strategy independent of other alternatives, whereas ICER renders the cost per unit of benefit when switching from one treatment strategy (that already may be in place) to another.

Cost-Utility Analysis:

Sometimes it is of interest to include a measure of patient preference or quality of life when comparing competing treatment alternatives.

Cost-utility analysis (CUA) is a method for comparing treatment alternatives that integrates patient preferences and Health Related Quality of Life (HRQOL).

CUA can compare cost, quality, and the quantity of patient-years. Cost is measured in monetary units, and the therapeutic outcome is measured in patient-weighted utilities rather than in physical units. Often the utility measurement used is a quality-adjusted life year (QALY) gained. QALY is a common measure of health status used in CUA, combining morbidity and mortality data.

QALYs represent the number of full years at full health that are valued equivalently to the number of years as experienced.

Other Elements of a Pharmacoeconomic Analysis:

The Model:

The QALY based assessment requires the quantification of the extended life expectancy and change in the Quality of Life (QoL) beyond the duration of traditional clinical trials.

To overcome the limitations associated with clinical trials, pharmacoeconomic Models are used. Models could be defined as designed structures for the flow of treatment and long-term disease prognosis. Models are used to estimate the occurrence of events, life expectancy and related costs over a time frame exceeding the duration of the clinical trials.

Frequently used Models are: Decision Tree, Markov Model and Monte Carlo Model.

Time horizon:

This is the period of time over which costs and outcomes are measured in economic evaluation.

Sensitivity Analysis:

A Model analysis is a very useful tool to estimate cost-effectiveness over a time frame that exceeds the duration of a clinical trial but it also has its limitations. The most significant one is the handling of the uncertainty around the parameters applied. That means, that the conclusions drawn from the analysis may change depending on the uncertainty of the costs and effects considered.

In order to ascertain the influence of such uncertainty, sensitivity analysis are conducted in those pharmacoeconomic analysis that use Models.

A sensitivity analysis is a way of examining if any change in results occur due to changes in the parameters applied for the Model within a certain scope.

The Clinical Trial

Introduction

In all human drugs investigations, the principles of Good Clinical Practice, concerning the protection of trial subjects need to be observed. These principles have their origins in the Declaration of Helsinki.

Once a molecule is chosen for further development, it needs to undergo the so-called pre-clinical studies prior to being tested in human subjects (i.e. the clinical trials).

Pre-clinical testing is carried out in non-human subjects in order to gather preliminary toxicity, pharmacokinetic and efficacy information. These involve in vitro and in vivo (animal experiments) testing.

The non-clinical studies to be reported in the regulatory Dossier comprise reports on pharmacology, pharmacokinetics, single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance and other toxicity studies.

This information has to be submitted to Health Authorities for evaluation [21].

Clinical trials involving new drugs are usually classified into different phases (Phase 0 to Phase IV) [22].

The clinical development proceeds over several years and during this time, in parallel, the chemical and formulation aspects of the new drug (i.e. the so-called Chemical Manufacturing Control (CMC) development) will also be undertaken.

Phase 0:

These studies are also known as first-into-human trials.

The doses employed are very small and sub therapeutic (micro dosing studies). The number of subjects is reduced, around 10 people.

As the doses used are very low, these studies do not render any information regarding safety and efficacy because the dose is too low to cause therapeutic effects.

These studies are carried out in order to collect preliminary information on the pharmacokinetic of the drug in humans, especially the oral bioavailability and half-life of the drug so that the most suitable drug candidates are selected for further development.

Phase I:

In these studies, normally a small group of healthy volunteers (20-100) is recruited.

The primary goal is to determine the safety of the drug and explore the dose ranging.

Normally, it will start administering sub therapeutic doses following with ascending doses (dose escalation studies).

In some cases, Phase I studies include patients (e.g. patients who have terminal cancer or acquired immune deficiency syndrome), as it would be unethical to test such drugs in healthy volunteers.

Phase Ia studies are defined as Single Ascending Dose studies:

A small number of participants, usually three, are administered a given dose of the drug. If no toxicity is shown, the dose is escalated and administered to a new group of subjects.

This is continued until the calculated pharmacokinetic safety levels are reached or until intolerable toxicity is observed (i.e. maximum tolerable dose (MTD)).

Phase Ib studies are defined as Multiple Ascending Dose studies:

In these studies, a group of patients receive multiple low doses of the drug. The dose is then escalated for further subjects groups until a predetermined level.

Food effect studies can also be categorized under Phase I studies:

These studies are undertaken to investigate the effects of co-administration of food on the pharmacokinetic of the drug.

These are done normally as a cross-over study, where volunteers are given two identical doses of the drug under fasting and under fed conditions.

Phase II:

The goal of these studies is to evaluate the preliminary evidence of efficacy and safety of the drug in patients, but in exceptional cases can support early approval (i.e. as a Conditional Marketing Authorisation/Exceptional Circumstances in Europe and as part of FDA Expedited Programmes in the United States).

The number of patients in these phase is around 100-300. Therapeutic doses are used. Sometimes Phase II trials are divided into:

Phase IIa: designed to assess dosing requirements.

Phase IIb: designed to assess efficacy.

They can be single-arm (non-comparative) or randomised (frequently underpowered).

An important goal of Phase II trials is to determine the dose(s) and regime for Phase III.

Phase III:

The goal of Phase III studies is to confirm the efficacy and safety of the medicinal product in a larger number of patients. Therapeutic doses are used and the number of patients is around 1000-3000 for common diseases. However, in the case of orphan diseases and also for most cancer types, the number of patients is less than 500.

Phase III trials normally constitute the pivotal clinical trials, key to prove the safety and primarily the efficacy of a drug for registration purposes.

Phase III trials are the most expensive and time-consuming trials, due to the size of patients enrolled and the duration, especially for those drugs intended to treat chronic diseases and conditions.

Phase IV:

Phase IV studies are also known as post-approval studies or post-marketing surveillance studies. That means that Phase IV begins after drug approval.

The safety surveillance is designed to detect those adverse events that due to its rarity or long-term nature could not be detected during the previous phases of the clinical trials.

They are also envisaged to assess the safety of the drug under real-world conditions of use.

Summary of Clinical trials Terms and Methodology [23[, [24]

CLINICAL ENDPOINT

It is a characteristic or variable that directly measures a therapeutic effect of a drug, an effect on how a patient feels (e.g. symptom relief), functions (e.g. improved mobility) or survives (Overall Survival (OS)).

CLINICALLY SIGNIFICANT ENDPOINT

It refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease.

CLINICAL INTERMEDIATE ENDPOINT

It refers to a clinical variable that can be measured earlier than IMM.

There are clinical endpoints that can be measured earlier than irreversible morbidity or mortality (IMM). If used, the sponsor can be required to continue existing trials into the post-marketing period in order to confirm the durability of the observed effects (e.g. continuance of the study for 2 years when only 13 months data are provided in the regulatory Dossier).

SURROGATE ENDPOINT

It is a measure that is reasonably likely to predict clinical benefit but it is not itself a measure of clinical benefit.

It could be a marker (laboratory measurement, radiographic image, other sign).

Demonstrating an effect on survival or morbidity (clinical outcome) generally requires lengthy and large trials, so an alternative is to measure an effect on other factors (like for example tumour growth or viral load instead) as surrogate points.

Assessing the predictive potential of a surrogate endpoint is very important. And a validated surrogate endpoint can be used for traditional approval.

When a surrogate endpoint is used, it must be ensured that any remaining doubts about the relationship of the effect on the surrogate to the clinical benefit are resolved by additional post-approval studies or trials.

CONFIRMATORY TRIALS

Post-marketing confirmatory trials are required to verify the anticipated effect on IMM of other clinical benefit measures used.

When a surrogate endpoint or a clinical intermediate endpoint is used, the clinical benefit has to be verified by additional post-approval confirmatory trials/studies or by longer follow-up of the same trial, which must be powered to show a difference in the clinical endpoint (requires usually more patients).

TYPES OF ENDPOINTS

Primary endpoint: It should reflect clinically relevant effects and it is selected based on the objectives of the study. The choice depends on the therapeutic indication (e.g. OS: Overall survival; PFS: Progression free survival).

Measurements relating to quality of life and health economics are further potential primary variables.

Secondary endpoint: Assess other drug effects that may or may not be related to the primary endpoint.

Endpoint PROs: Patient Reported Outcomes. Accepted for some indications (e.g. not for cancer).

Endpoint QoL: Quality of Life.

POPULATION

The sample of subjects participating in the trial who are recruited based on inclusion and exclusion criteria as determined in the protocol of the trial.

CONTROLS

In a clinical trial design, besides the test group, there could be the so-called control group(s). The patients allocated in the control groups could be administered: placebo, no treatment, a different dose or regime of the study treatment or a different active treatment (i.e. active comparator).

The placebo-controlled trial measures the “absolute” efficacy and safety of the new test drug. In contrast, an active control trial or dose comparison trial measures the effect relative to another treatment or regimen.

Note: The use of a placebo control group does not always imply that the control group is untreated. In many placebo-controlled trials, the new treatment and placebo are each added to a common standard therapy (so called add-on studies).

RANDOMIZATION

In a controlled trial, patients are randomly allocated to the different treatments under study with the objective to assure that the subject populations are similar in the test and in the control groups. It is the preferred means of assuring comparability of the groups and minimising the possibility of selection bias. It is often considered the gold standard of clinical trials.

OPEN AND BLINDED STUDIES

Blinding is a tool to reduce the risk of biased study outcomes.

In an open trial, both the researchers and participants know which treatment is being administered.

In single blind trials, participants are not aware of what treatment they are receiving and in the case of a double blind trial, researchers are also not aware.

SINGLE ARM TRIALS

Trials where there is no control group in parallel to the treatment group. It may be an important option in rare diseases with well-understood pathophysiology and a well-defined disease course.

In addition, it is important to note that time-to-event endpoints (PFS, OS) cannot be reliably measured if there is no concurrent control, so the endpoint in single-arm trials is usually overall response rate (ORR) (e.g. tumour shrinkage), where there are very large differences expected vs. the standard of care (SOC).

COMPARATIVE TRIALS

Clinical trials can be run as placebo controlled or versus an active comparator.

When the SOC is used, it is important to consider the recommendations given by scientific bodies, current clinical practice guidance, etc.

Generally, if there is an available therapy, the sponsor should compare their investigational drug to the available therapy (SOC) in clinical testing with an attempt to show superiority relating to either safety or efficacy.

ADD-ON STUDY

They are employed when the superiority of a new therapy used in combination with an available therapy is to be demonstrated vs. the monotherapy studies.

STATISTICAL POWER

It estimates the ability of a trial to detect a difference between the treatment and the control group(s). The number of subjects of the study (i.e. the sample size) has a large impact on the ability to reliably detect and measure effects of the intervention (i.e. the POWER of the study).

The larger the number of participants, the greater the statistical power but also the costs of the trial.

DIRECT VS. INDIRECT COMPARISONS

Comparisons to other therapies to demonstrate the relative effectiveness in different subgroups.

Direct comparison: Head to head within the same study.

Indirect comparison: The data taken from other studies.

Indirect comparison refers to a comparison of different health care interventions using data from separate studies, in contrast to a direct comparison within randomised controlled trials.

Indirect comparison is often used because of a lack of, or insufficient, evidence from head to head comparative trials.

INTERNAL VALIDITY (REGULATORS) VS. EXTERNAL VALIDITY (HTA)

External validity refers to the question whether results are generalizable to persons other than the population in the original study.

The only formal way to establish the external validity would be to repeat the study for that specific target population.

The target population will, by definition, differ from the study population with respect to geographical, temporal and ethnical conditions. Pondering external validity means asking the question whether these differences may influence study results. It should be assessed whether the study's conclusions can be generalized to target populations that do not meet all the eligibility criteria.

Judging the external validity of study results cannot be done by applying given eligibility criteria to a single target population. Rather, it is a complex reflection in which prior knowledge, statistical considerations, biological plausibility and eligibility criteria all have place.

HIPOTHESIS AND OBJECTIVES

HIPOTHESIS

This study departs from the hypothesis that despite recent attempts to harmonize the HTA evaluation among the European Union HTA bodies and also in relation to the regulatory framework requirements, still many discrepancies exist based not only on local economic demands but also due to scientific methodological approaches.

This situation if not solved, will make it difficult to implement the provisions of the European Directives in relation to the equity in the access to health care.

The application of a common HTA methodology in Europe could highly improve the harmonization and transparency in HTA decisions.

OBJECTIVES

The objectives of the current research are the following:

- **Analysis of the current European regulatory framework in relation to the requirements for the authorization of medicines.**
- **Analysis of the HTA methodology used by the European HTA bodies for reimbursement and financing recommendations.**
- **Analysis of the current political scenario in the European Union and the initiatives to harmonize the regulatory and HTA frameworks.**
- **Investigate the differences in requirements and methodological approaches followed for the authorisation of medicines and the HTA appraisals. Identification of key areas of discrepancies.**
- **Investigate which areas could have the potential for further harmonization respecting the current European regulations in force for the evaluation of medicines and also preserving the need to maintain local HTA requirements.**

METHODOLOGY

- **Review and analysis of the European Union pharmaceutical legislation in relation to the requirements for the authorisation of medicinal products. Expectations in relation to the quality, safety and efficacy data to be generated.**

  The research is presented in Chapter 1.

  Source of information: EUDRALEX.

- **Review and analysis of the requirements and methodology employed in the HTA evaluations by EU HTA bodies. Expectations of HTA bodies in terms of data and evidence to be generated to prove added value.**

  The research is presented in Chapter 2.

  Source of information: EUnetHTA, NICE, INAHTA.

- **Review and analysis of the current European legal framework in relation to the equity of access to healthcare.**

  The research is presented in Chapter 3.

  Source of information: Lisbon Treaty, Directive 2011/24/EU, Directive on Transparency.

- **Review and analysis of the European initiatives for collaboration and harmonization in the areas of regulatory and HTA appraisal of medicines.**

  The research is presented in Chapter 4.

  Source of information: DG-SANCO, EUnetHTA and HTAN, EMA.

- **Elaboration of a model design for the research and identification of the potential divergent criteria in methodologies and appraisals between Regulators and HTA bodies in the European Union.**

  The research is presented in Chapter 5.

- **Research study of the differences in regulatory and HTA evaluations of two centrally authorised drugs: Kalydeco and Yervoy.**

  The research is presented in Chapter 5.

  Source of information: EPARs for Kalydeco and Yervoy. HTA appraisals publicly available in English, Spanish and German for Kalydeco and Yervoy from EU HTA bodies.

  Kalydeco is indicated for the treatment of cystic fibrosis and Yervoy is indicated for the treatment of advanced melanoma.

  For this study research, these two medicinal products (Kalydeco and Yervoy) were chosen due to its specific characteristics.

  Given the indications for which they are intended (i.e. life-threatening diseases), with no equivalent pharmacological options, the chosen medicinal products for this research study offered an optimal setting for the analysis of regulatory and HTA decision elements

  Moreover, the fact that one is intended for a chronic life-threatening disease (Kalydeco) and the other for a terminal disease (Yervoy) also allowed the opportunity to investigate the impact that a prevision of long-term financing and budget considerations exert on the decision-making process of HTA bodies.

RESEARCH CHAPTERS:

CHAPTER 1:

REQUIREMENTS FOR THE AUTHORISATION OF MEDICINAL PRODUCTS IN THE EUROPEAN UNION. QUALITY, SAFETY AND EFFICACY. LEGAL AND REGULATORY FRAMEWORK.

CHAPTER 2:

HEALTH TECHNOLOGY ASSESSMENT (HTA) METHODOLOGY.

CHAPTER 3:

THE POLITICAL SCENARIO: THE NEED FOR THE DEVELOPMENT OF HARMONIZED HTA REQUIREMENTS IN THE EU.

CHAPTER 4:

EUROPEAN COLLABORATION AND HARMONIZATION REGULATORY AUTHORITIES – HTA BODIES.

CHAPTER 5:

STUDY OF THE DIFFERENCES IN THE SCOPE AND FOCUS OF THE REGULATORY AND HTA EVALUATIONS: KALYDECO AND YERVOY

CHAPTER 1: Requirements for the Authorisation of Medicinal Products in the European Union. Quality, Safety and Efficacy. Legal and Regulatory Framework.

INTRODUCTION

REGULATORY FRAMEWORK: EU HARMONIZATION

ACCELERATED ACCESS: SPECIFIC REGULATORY TOOLS

Introduction

The birth of the modern European regulatory framework for the evaluation and authorization of medicinal products comes as a result of the Thalidomide tragedy in 1962, which questioned the validity of the so far established systems for the control of medicinal products in the European Union.

Thalidomide was first marketed in 1957 in West Germany under the trade name Contergan.

Thalidomide was commercialized between 1958 and 1963 as sedative and antiemetic and afterwards it was also used against the nausea during the first three months of pregnancy.

As a sedative it became very popular as it had no side effects and it was not lethal in case of massive intake.

This medicine that had been claimed when commercialized as being completely safe, turned out to be one of the most teratogenic drugs ever put on the market.

Thalidomide caused thousands of children born with phocomelia (a congenital malformation of the limbs). Other effects included deformed eyes and hearts, deformed alimentary and urinary tracts, blindness and deafness. As a consequence of the severe malformations, many of the affected children did not survive.

In Europe, Germany and the United Kingdom were the countries more severely affected by the disaster.

This event marked a turning point in the European Union legislation of pharmaceutical products and triggered its development and way towards the unification.

In 1965, impelled by the need to promote an EU harmonization to ensure the protection of patients as well as the facilitation of the internal market of medicines, Directive 65/65 [2] was adopted by the European Community. It represented the first piece of legislation laying down the legal dispositions and rules for medicinal products in the Union.

A vast legislative development has followed the adoption of this Directive, creating a harmonized and unified framework of requirements, procedures and scientific criteria for the regulatory evaluation of medicinal products across all EU Member States.

Throughout this time, dedicated national agencies for the evaluation of medicines were established in each EU Member State and the European Medicines Agency (EMA) was created in 1993 to coordinate resources across the EU network. EMA started being operative in 1995.

The main features of this complex system are presented in this Chapter.

It is to be noted that in the EU, besides the positive regulatory evaluation on the quality, safety and efficacy of a medicinal product required for the authorization, sponsor also need to undertake negotiations on pricing and financing at national level prior to being able to commercialize the drug. National HTA bodies are normally responsible to render a recommendation in this respect.

EU Member states are confronted with the challenge of a steady rise in pharmaceutical expenditure over the last decades, a fact that has led to the adoption of increasingly innovative and complex policies to manage the consumption of medicines in the framework of public health insurance systems.

In particular, Member States' authorities have implemented a broad range of measures to control the prescription of medicinal products, to regulate their prices and to establish the conditions of their public funding. Such measures mainly aim at promoting public health for all citizens by ensuring the availability of adequate supplies of medicinal products at reasonable costs, while ensuring the financial stability of the public health insurance systems.

However, disparities in national measures may hinder or distort the internal Union trade of medicinal products and distort competition, thereby directly affecting the functioning of the Internal Market in medicinal products.

By means of the regulatory evaluation, EU or National Competent Authorities assess the quality, safety and efficacy of medicinal products, including the bioequivalence of generic

medicinal products or the biosimilarity of biosimilar medicinal products with the reference product, in the framework of marketing authorisation procedures.

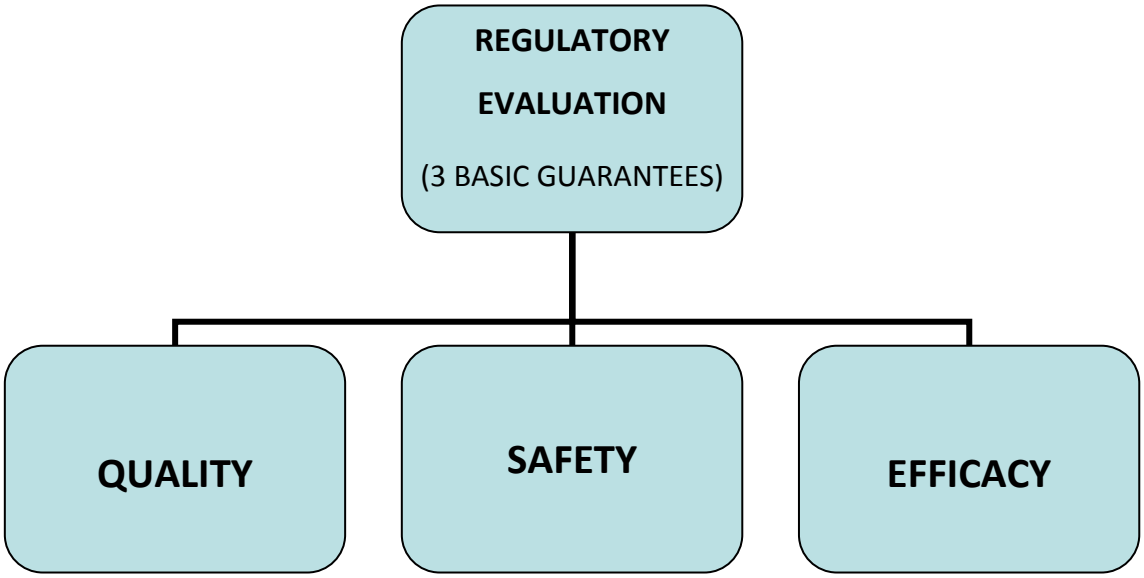

Figure 2. *Elements of the Regulatory evaluation. Source: Own elaboration.*

Therefore, it should be understandable, that during the pricing and reimbursement procedures, the Competent Authorities of the EU Member States should not re-assess the elements on which the marketing authorisation was granted by the relevant EU regulatory authorities. HTA bodies should have full access to the data used by the regulatory authorities responsible for granting the marketing authorisation of a medicinal product as well as the possibility of using or generating additional relevant data for the purpose of HTA evaluations. Further data might be needed when assessing a medicinal product in the context of its inclusion in the scope of the public health insurance system but the quality, safety and efficacy is the competence of Regulators.

In this Chapter, the foundations and main elements of the EU harmonized system for the regulatory evaluation of medicinal products is presented.

Regulatory Framework: EU Harmonization

The Pillars of the System

The legislation of the Union requires a marketing authorisation to be granted by the competent EU or national authority prior to the placement on the market of any medicinal product.

The rules in force aim to safeguard public health by ensuring that the quality, safety and efficacy of medicines are properly evaluated before these can be made available to patients in the European Union. This legislative framework also intends to facilitate trade in medicines between Member States in accordance with the principle of free movement of goods within the Union.

A large body of legislation has been developed around this principle over the last 50 years, leading to the progressive harmonisation of requirements for the granting of marketing authorisations across the EEA.

The requirements and procedures for the marketing authorisation for medicinal products for human use, as well as the rules for the constant supervision of products after they have been authorised, are primarily laid down in two legal texts which represent the core of the EU pharmaceutical legislation: Directive 2001/83/EC [25] and Regulation (EC) 726/2004 [26].

These texts additionally lay down harmonised provisions in related areas such as the manufacturing, wholesaling or advertising of medicinal products for human use.

According to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, medicinal products may be placed on the market in the Union only after they have received a marketing authorisation based on the evaluation of their quality, safety and efficacy.

The provisions of this is Directive are applicable to all medicinal products. The particulars and information required to be presented in a regulatory Dossier are indicated in Annex I of Directive 2001/83/EC (*Analytical, Pharmacological and Clinical Standards and Protocols in respect of the Testing of Medicinal Products).*

Regulation (EC) 726/2004 lays down the provisions for the centralised procedure, which is coordinated by the EMA. It supersedes Regulation 2309/93 [27] which created the centralised procedure and the European Medicines Agency.

The supranational regulatory system operates in accordance with the Community authorisation procedures (centralised, mutual recognition) which are in place since the mid-90s. The system is supported by a Community regulatory agency in charge of providing the EU institutions with scientific advice on medicinal products: the European Medicines Agency (EMA).

The Community legislation also provides for common rules for the conduct of clinical trials (the investigations in humans intended to discover or verify the effects of medicinal products before their authorisation) in the EU [28] [29].

In addition to the two main legal texts mentioned above, other numerous pieces of legislation (i.e. Directives and Regulations) have been adopted to complement and clarify the rules to be applied to certain types of medicinal products and areas, as it is the case of orphan medicinal products, paediatrics, advanced therapies, etc. All these texts are to be found in a compendia called EUDRALEX (European Union Drug Regulatory Authorities Legislation).

In this study, the legislation on orphan medicinal products has been analysed more in detail as it is relevant for the research undertaken in this Thesis dissertation.

All Community legislation in the area of medicinal products for human use is contained in Volume 1 of "The Rules Governing Medicinal Products in the European Union"[30].

Moreover, and with the purpose to facilitate the interpretation of the legislation and ensure a uniform application across the EU, numerous guidelines of regulatory and scientific nature have additionally been adopted.

A detailed explanation of the marketing authorisation procedures and other regulatory guidance intended for applicants is contained in Volume 2 (Notice to Applicants) [31].

Comprehensive scientific guidance on the quality, safety and efficacy of medicinal products is provided in Volume 3 [32].

Specific guidance on the legal requirements concerning good manufacturing practices, pharmacovigilance and clinical trials is laid down in volumes 4, 9 and 10 respectively [33] [34] [35].

THE EVALUATION PROCEDURES FOR THE AUTHORISATION OF MEDICINES IN THE EUROPEAN UNION AND THE GRANTING OF A MARKETING AUTHORISATION

The European system for the authorisation of medicinal products for human and animal use was introduced with the objective of ensuring that safe, effective and high quality medicines could quickly be made available to citizens across the European Union.

The European system offers several routes for the authorisation of medicinal products:

The Centralised Procedure: [36]

This authorisation pathway is compulsory for those products indicated in the Annex of Regulation (EC) 726/2004:

1. Medicinal products developed by means of biotechnological processes: recombinant DNA technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells; hybridoma and monoclonal antibody methods and Similar Biological ("biosimilar") medicinal products which are developed by one of the above biotechnological processes also fall under the mandatory scope of the centralised procedure.

1a. Advanced therapy medicinal product as defined in Article 2 of Regulation (EC) No 1394/2007 [37] (i.e. Gene therapy medicinal products, Somatic cell therapy medicinal products, Tissue engineered products).

2. Medicinal products for human use containing a new active substance which, on the date of entry into force of the Regulation (20 November 2005), were not authorised in the Community and for which the therapeutic indication is the treatment of any of the following diseases: Acquired immune deficiency syndrome; Cancer; Neurodegenerative disorder; Diabetes; And with effect from 20 May 2008: Auto-immune diseases and other auto-immune dysfunctions; Viral diseases;

3. Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000 [38].

There is also an optional scope of the centralised procedure that sponsors could follow if desired.

Applications for the centralised procedure are made directly to the European Medicines Agency (EMA) and lead to the granting of a European marketing authorisation by the European Commission which is binding in all Member States.

The Mutual Recognition Procedure:

It is applicable to the majority of conventional medicinal products (with the exception of those that should follow the centralised procedure). It is based on the principle of recognition of an already existing national marketing authorisation by one or more Member States.

The Decentralised Procedure:

It was introduced with the legislative review of 2004 [39], and it is also applicable to the majority of conventional medicinal products.

Through this procedure, an application for the marketing authorisation of a medicinal product is submitted simultaneously in several Member States, one of them being chosen as the "Reference Member State".

At the end of the procedure national marketing authorisations are granted in the Reference and in the Concerned Member States.

Purely national authorisations:

This process is still available for medicinal products to be marketed in one Member State only.

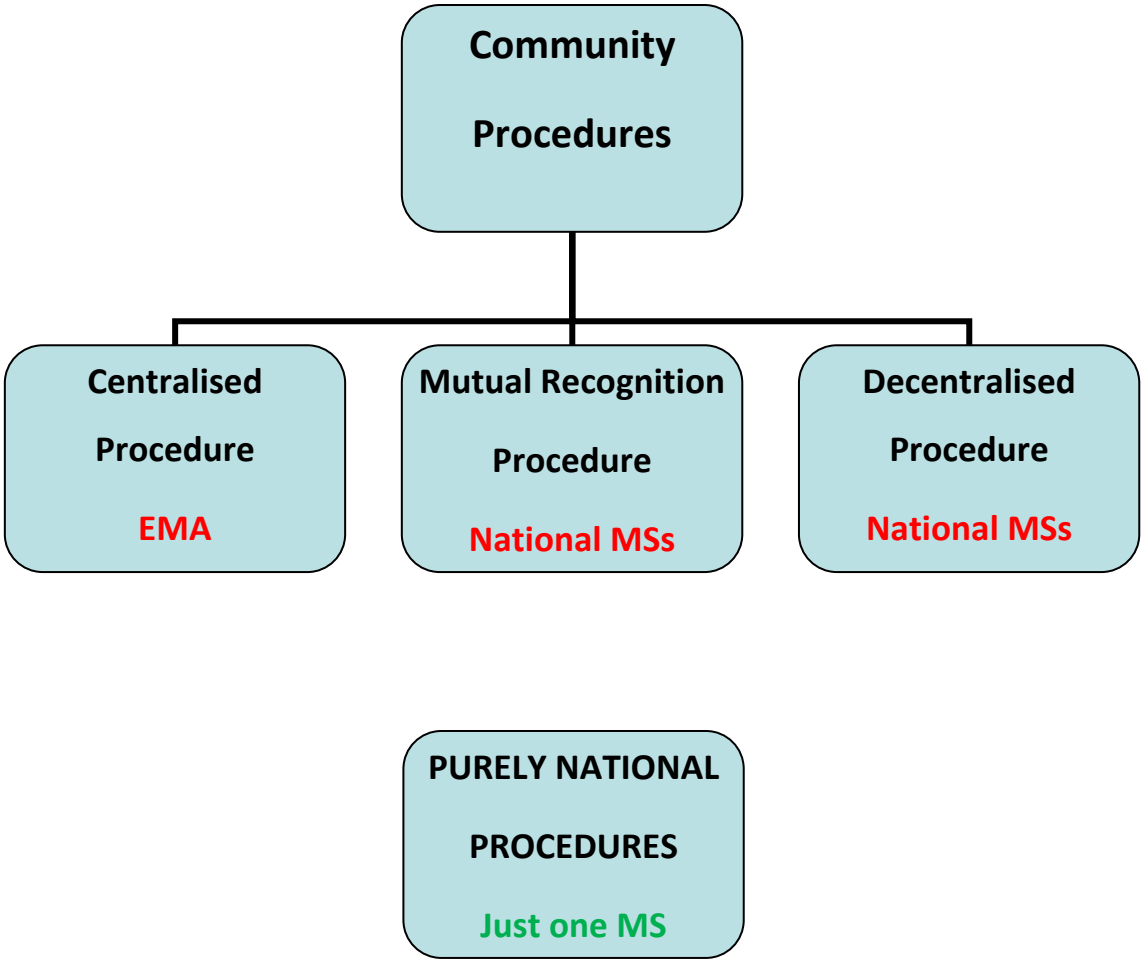

Figure 3. *Scheme of the EU regulatory authorisation procedures. Source: Own elaboration.*

The European Medicines Agency (EMA) [40]

In 1993 the European Medicines Agency (EMA) was founded with the primary task of coordinating the centralised procedure and provide scientific advice of the highest possible quality to the Community institutions on all matters relating to medicinal products for human and veterinary use.

The Agency represents the culmination of the harmonization process achieved in the EU in the area of the regulatory evaluation of medicines and it has established itself as a world-leading agency for the evaluation of medicinal products.

The key tasks entrusted to EMA are the following:

- Provide Member States and Community institutions with the best possible scientific advice on questions about the quality, safety and efficacy of medicinal products for human and veterinary use.
- Establish a pool of multinational scientific expertise by mobilising existing national resources in order to achieve a single evaluation via the Community procedures (i.e. centralised or mutual recognition marketing authorisation procedures).
- Organise fast, transparent and efficient procedures for the authorisation, surveillance and where appropriate, withdrawal of medicinal products in the EU.
- Advise companies on the conduct of pharmaceutical research.
- Reinforce the supervision of existing medicinal products by co-ordinating national pharmacovigilance and inspection activities.
- Create databases and electronic communication facilities as necessary to promote the rational use of medicines.

Beyond the European Union: ICH/WHO Worldwide Harmonization [41]

Progressively, the different regions across the globe are developing their regulatory frameworks and systems for the evaluation of medicinal products. At the same time, the pharmaceutical industry operates more and more at an international level, doing research and marketing their products in different regions and countries. In such an environment, the need to harmonise the regulatory requirements requested by the different governments across the world is very important in order to facilitate an intelligent use of resources.

In Europe, the realisation that it was important to have an independent evaluation of medicinal products before they are allowed on the market was driven by the Thalidomide tragedy in the 1960s.

For most countries, whether or not they already had in place systems for the registration and control of medicines earlier, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products.

The divergence in technical requirements from country to country caused industry duplication of work, and waste of time and money, consumed in expensive test procedures to be carried out differently for the same purpose, in order to meet the specific requirements of each region and so be able to market new products internationally.

The urgent need to rationalise and harmonise regulation was impelled by concerns over rising costs of health care, escalation of the cost of research and development of medicines and the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need.

The harmonisation of regulatory requirements was pioneered by the European Community (EC), in the 1980s, as the EC (now the European Union), moved towards the development of a

single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonisation was feasible.

At the same time, there were bilateral discussions between Europe, Japan and the US on possibilities for harmonisation. It was, however, at the World Health Organisation (WHO) Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, that specific plans for action began to materialise.

Soon afterwards, the authorities approached the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonisation, and the International Conference of Harmonization (ICH) was conceived.

The birth of ICH took place at a meeting in April 1990, hosted by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met, primarily, to plan an International Conference.

At the first ICH Steering Committee meeting of ICH, the Terms of Reference were agreed and it was decided that the topics selected for harmonisation would be divided into safety, quality and efficacy to reflect the three criteria which are the basis for approving and authorising new medicinal products.

Since ICH's inception in 1990, the ICH process has gradually evolved. ICH's first decade saw significant progress in the development of Tripartite ICH guidelines on safety, quality and efficacy topics.

The CTD (Common Technical Document), a standardised template to provide Health Authorities with the necessary information for the evaluation of a medicinal product was also developed by the ICH.

The CTD is a harmonised structure for the Dossier to be submitted to Health Authorities for the evaluation of a medicinal product. It covers all the information (administrative and scientific aspects) which are necessary to grant a marketing authorisation.

The European Commission published the CTD format in 2000 and it was implemented in 2003 [42].

The CTD is composed of five Modules:

Module 1: Administrative information (specific requirements for each region are provided here).

Module 2: Summaries of Modules 3, 4 and 5.

Module 3: Quality.

Module 4: Pre-clinical studies.

Module 5: Clinical studies.

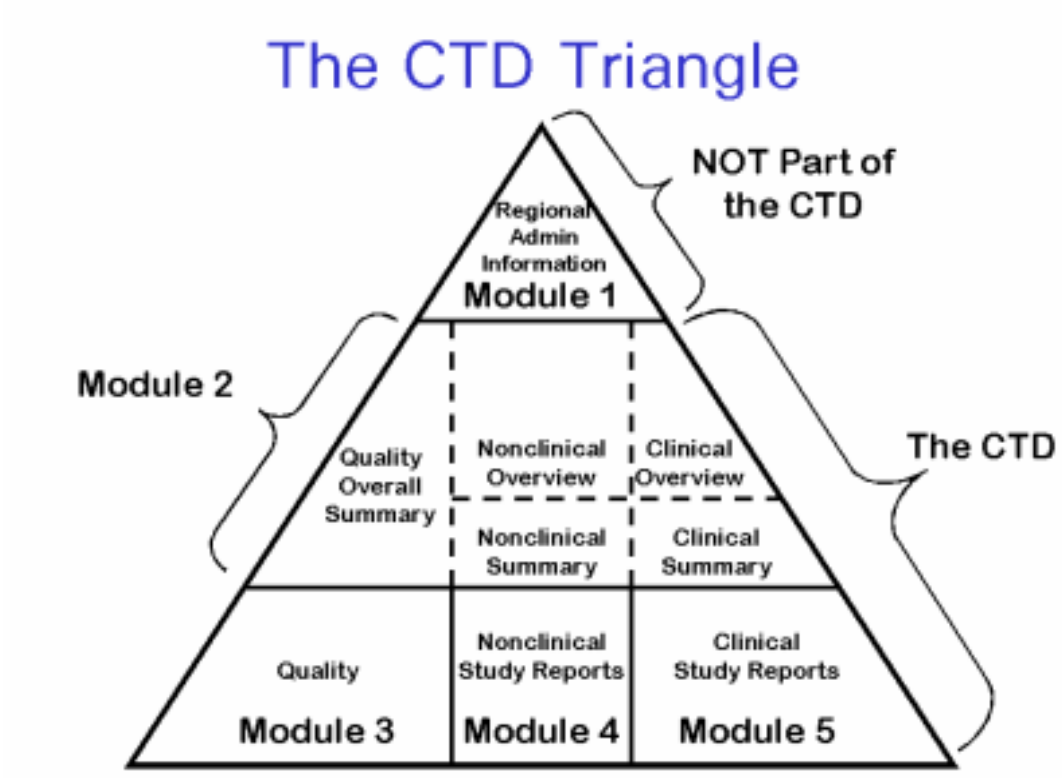

Figure 4. *The CTD Triangle. Source: ICH*

Entering into its third decade of activity, ICH's attention is now directed towards extending the benefits of harmonisation beyond the ICH regions.

Training, as well as active participation of non-ICH regions in guideline development are seen as key in order to achieve a common global regulatory network, an objective utterly desired and needed by international pharmaceutical industry.

Rare Diseases and Orphan Drugs

The European legislation for medicinal products (Regulation (EC) 726/2004) determines that all medicinal products which are indicated for rare diseases (i.e. the so-called orphan drugs) should follow the centralized procedure for the authorization of medicines.

As explained above, under the centralized procedure, the European Medicines Agency (EMA) is the scientific body responsible for performing the evaluation of these medicinal products.

The EMA provides a scientific opinion to the European Commission (EC) which will then serve as the basis for the granting of the marketing authorization.

A marketing authorization granted by the EC enjoys automatic validity in the whole European Union.

The two main pieces of legislation ruling orphan drugs are: Regulation (EC) No 141/2000 [38] and Regulation (EC) No 847/2000 [43].

In the case of orphan drugs, it is important to distinguish between the orphan designation status and the marketing authorization of an orphan medicinal product.

The orphan designation status is granted by the European Commission. It is granted early in the development of a drug and it is a competitive process. That means that more than one drug can receive orphan designation for the same condition.

It is important to note that a drug intended for the treatment of a rare disease does not necessarily need to have orphan status.

The first step for an orphan drug in order to reach the market is to be granted a centralized marketing authorisation. A drug with orphan designation status, benefits from ten years of market exclusivity in the European Union when an authorization is granted.

This is an incentive created in the framework of the European legislation for the development of these drugs. As a result, no other drug with similar structure and with the same mechanism

of action for the same indication can obtain a marketing authorisation unless it is able to break one of the derogations foreseen in the EU legislation of orphan drugs.

The second step on the way to the market, is to receive positive appraisal by each of the relevant EU HTA bodies and successful reimbursement negotiations.

In order for a medicinal product to qualify for orphan designation, a medicine must meet a number of criteria which are indicated below:

- It must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating.
- The prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development.
- No satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Applications for orphan designations are examined by the European Medicines Agency's Committee for Orphan Medicinal Products (COMP), using the network of experts that the Committee has built up.

The significant benefit is one of the criteria for orphan designation. It is defined in Regulation (EC) No 847/2000 as a *"clinically relevant advantage or a major contribution to patient care"*.

The concept of significant benefit is unique to the EU orphan legislation, and does not exist in clinical pharmacology or in any other regulatory framework.

To date 87 orphan drugs have received a marketing authorization in Europe within different therapeutic areas [44] [45].

When a designated orphan medicinal products is granted a marketing authorisation in the European Union (EU), then and a period of ten years market exclusivity is in force.

As a result, sponsor seeking authorisation for another product for the same indication as the previously authorised one should attach to the marketing authorisation application the so-called **similarity report,** addressing the possible similarity between new medicinal product under application and the orphan medicinal product(s) which have already received a marketing authorisation.

This legal requirement is set in Article 8(1) of the Orphan Regulation (EC) No 141/2000, which provides that *"…where a marketing authorisation in respect of an orphan medicinal product is granted, the Agency and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product…*".

However, point 3 of Article 8 specifies that a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if any of the three derogations indicated below are met:

- *The holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or*
- *The holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or*
- *The second applicant can establish in the application that the second medicinal product, although, similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.*

Commission Regulation (EC) No 847/2000 defines the concept of similar medicinal product and clinical superiority.

Article 3, defines similar medicinal product as a medicinal product containing a **similar active substance** or substances as contained in a currently authorised orphan medicinal product, and which is intended for the **same therapeutic indication**.

It also defines similar active substance as an identical active substance, or an active substance with the **same principal molecular structural features** (but not necessarily all of the same molecular features) and which acts via the **same mechanism**.

Based on the above mentioned definitions, the assessment of similarity between two medicinal products takes into consideration the following criteria [46] [47]:

- Principal molecular structural features
- Mechanism of action
- Therapeutic indication

If significant differences exist within one or more of these criteria, the two products will not be considered as similar and a marketing authorisation can be granted.

Where the Committee for Medicinal Products for Human Use (CHMP) concludes that the application for a marketing authorisation is not similar to an authorised orphan medicinal product or, if similar, that one of the derogations provided for in Article 8(3) of Regulation 141/2001 claimed by the applicant applies, this will not prevent the granting of the marketing authorisation/extension to the marketing authorisation, provided that the quality, safety and efficacy of the medicinal product are demonstrated.

However, if the CHMP concludes that the product which is the subject of the application for marketing authorisation is considered similar to an authorised orphan medicinal product and none of the derogations applies, the CHMP will adopt an opinion recommending the refusal of the granting of the marketing authorisation/extension to the marketing authorisation, irrespective of the demonstration of the quality, safety or efficacy of the medicinal product.

According to Commission Regulation (EC) No 847/2000, **"clinically superior"** *means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways: (1) greater efficacy than an authorised orphan medicinal product (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative efficacy claim for two different medicinal products. Direct comparative clinical trials are generally necessary, however comparisons based on other endpoints, including surrogate endpoints may be used. In any case, the methodological approach should be justified; (2) greater safety in a substantial portion of the target population(s). In some cases direct comparative clinical trials will be necessary; or (3) in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care.*

In the process of the evaluation of a designated orphan medicinal product, it is necessary to review the orphan designation at the time of marketing authorization or extension to a marketing authorization: maintenance of the orphan designation.

This enables the EMA to determine whether the medicine can maintain its status as an orphan medicine and benefit from the market exclusivity provisions.

The COMP reviews the maintenance of orphan designation based on the data available at the time and a report on the maintenance of the designation criteria, which the sponsor supplies at the same time as the application for marketing authorisation. This report includes data on:

- The current prevalence of the condition to be diagnosed, prevented or treated, or the potential return on investment.
- The current life-threatening or debilitating nature of the condition.
- The current existence of other methods for the diagnosis, prevention or treatment of the condition and if applicable, a justification of the medicine's significant benefit.

The COMP's review is carried out independently of, but in parallel to the evaluation of the marketing authorisation application by the CHMP. The COMP opinion on review of the orphan designation follows the CHMP positive opinion on marketing authorisation.

The 10 years of market exclusivity is linked to the maintenance of the orphan designation when the medicine receives a marketing authorisation for the indication concerned.

Market exclusivity is awarded by the European Commission and is specifically linked to one specific orphan designation for which a marketing authorisation has been granted.

It is also to be noted that in accordance with the legislation, orphan and non-orphan indications cannot be combined into a single marketing authorisation application.

This provision takes into account the reality that the same active substance can be both used to treat a rare disease or to treat a common disease.

An example can be found in Sildenafil, initially authorised for erectile dysfunction, and which has become one of the world's largest-selling drugs. On the 28th of October 2005, it received a separate marketing authorisation as an orphan drug for pulmonary arterial hypertension, a rare condition. Another example is ibuprofen, which is widely used and which has later been shown to be effective in treating patent ductus arteriosus, a rare condition, for which it has received marketing authorisation as an orphan. [48]

Accelerated Access: Specific Regulatory Tools

Accelerated Assessment/ Conditional Marketing Authorisation / Exceptional Circumstances Marketing Authorisation

Accelerated Assessment:

According to Articles 6(3) and 7c of Regulation (EC) No 726/2004, the maximum timeframe for the evaluation of a marketing authorisation application under the centralised procedure is 210 days, excluding clock stops when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP.

However, according to Recital 33 and Article 14(9) of Regulation (EC) No 726/2004, the applicant may request an accelerated assessment procedure (i.e. 150 days) in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, for medicinal products of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation.

Accordingly, it is possible to request an accelerated assessment procedure if it is justified that the medicinal product is expected to be of major public health interest.

There is no single definition of what constitutes major public health interest. This should be justified by the applicant of a medicinal product on a case-by-case basis. The justification should include the major benefits expected such as the introduction of a new therapy or improvement of existing alternatives to address an unmet need. In summary, its added value [49].

Conditional Marketing Authorisation:

For certain categories of medicinal products, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally required.

In such cases, it is possible for the CHMP to recommend the granting of a Conditional Marketing Authorisation (CMA), which is subject to certain specific obligations to be reviewed annually.

The legal basis for a CMA is Article 14 (7) of Regulation (EC) No 726/2004.

The provisions for the granting of such an authorisation are laid down in Regulation (EC) No 507/2006, adopted on the 29th of March 2006 [50].

The granting of a Conditional Marketing Authorisation should be restricted to situations where only the clinical part of the application dossier is not yet fully complete.

Incomplete non-clinical and/or quality data should only be accepted if duly justified and only in the case of a product intended to be used in emergency situations, in response to public health threats [51].

This may apply to medicinal products for human use that fall under Article 3(1) and (2) of Regulation (EC) No 726/2004 and fall within one of the categories set out in Article 2 and fulfils the requirement laid down in Article 4(1)(c) ("unmet medical needs will be fulfilled") of Regulation (EC) No 507/2006.

Categories:

- Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases.
- Medicinal products to be used in emergency situations, in response to public threats duly recognised either by the WHO or by the Community in the framework of Decision (EC) No 2119/98.
- Medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.

A conditional marketing authorisation may be granted where the CHMP finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.
- It is likely that the applicant will be in a position to provide the comprehensive clinical data.
- Unmet medical needs will be fulfilled.
- The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Conditional marketing authorisations are valid for one year, on a renewable basis.

The holder will be required to complete ongoing studies or to conduct new studies with a view to confirming that the risk/benefit balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

The granting of a conditional marketing authorisation will allow medicines to reach patients with unmet medical needs earlier than might otherwise be the case, and will ensure that additional data on a product are generated, submitted, assessed and acted upon marketing authorisation.

Exceptional Circumstances Marketing Authorisation

The legal basis for a marketing authorisation under Exceptional Circumstances is the Article 14 (8) of the Regulation (EC) No 726/2004, and the relevant documentation for applications in Exceptional Circumstances are laid down in Part II of Annex I of Directive 2001/83/EC.

For these products the applicant can demonstrate that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use due to the following reasons:

- The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- In the present state of scientific knowledge, comprehensive information cannot be provided, or
- It would be contrary to generally accepted principles of medical ethics to collect such information.

Consequently, the authorisation under Exceptional Circumstances is granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the Competent Authorities of any incident relating to its use

The renewal of the marketing authorisation of a medicinal product under Exceptional Circumstances follows the same rules as a standard marketing authorisation but is also subject to the fulfilment of legally binding measures called specific obligations [52].

Compassionate Use

Article 6 of Directive 2001/83/EC requires that medicinal products are authorised before they are marketed in the Community.

Unauthorised medicinal products may be available through an approved clinical trial protocol.

In addition, a treatment option for patients in the European Union suffering from a disease for which no satisfactory authorised alternative therapy exists or who cannot enter a clinical trial, may be the use of an unauthorised medicinal product in a so-called compassionate use programme.

Compassionate use programmes are intended to facilitate the availability to patients of new treatment options under development.

National compassionate use programmes, making medicinal products available either on a named patient basis or to cohorts of patients, are governed by individual Member States (MS) legislation. [53]

EMA Pilot on Adaptative Pathways

This new initiative that tries to reinforce and complement the existing regulatory tools aligning methodologies with HTA bodies is explained in detail in Chapter 4.

FDA Guideline on Expedited Programmes

Beyond the frontiers of the European Union and in order to illustrate the demands of the international pharmaceutical industry, it is of relevance to mention, that in other jurisdictions, Regulators have also understood the need to create procedures that facilitate and speed up the access to patients of innovative lifesaving new medicines.

In line with the EU existing regulatory tools and adaptative pathways pilot, the Food and Drug Administration (FDA) of the United States is also implementing measures to allow the early access of innovative medicines.

The US FDA issued in May 2014 a Guidance for industry on Expedited Programs for Serious Conditions. [54]

There are four types of expedited programmes in the FDA, each one with different criteria for admission:

- The Fast Track
- The Breakthrough Therapy
- The Accelerated Approval
- The Priority Review

The Fast Track:

This path is applicable to a drug that is intended to treat a serious condition AND non-clinical or clinical data demonstrate the potential to address unmet medical need OR

A drug that has been designated as a qualified infectious disease product.

The Breakthrough Therapy:

This path is applicable to a drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies.

The Accelerated Approval:

This path is applicable to a drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint).

The Priority Review:

This path is applicable to an application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR Any supplement that proposes a labelling change pursuant to a report on a paediatric study under 505Ab OR An application for a drug that has been designated as a qualified infectious disease product OR any application or supplement for a drug submitted with a priority review voucher

CHAPTER 2: Health Technology Assessment (HTA). Methodology.

EUROPEAN UNION NATIONAL HTA BODIES

HEALTH TECHNOLOGY ASSESSMENT (HTA)

EUROPEAN UNION NETWORK HEALTH TECHNOLOGY ASSESSMENT (EUnetHTA)

INTERNATIONAL NETWORK OF AGENCIES FOR HEALTH TECHNOLOGY ASSESSMENT (INAHTA)

European Union National HTA Bodies

Under the current legislative framework, the decisions on pricing, financing and reimbursement are within the national remit of each European Member State.

In order to aid in the decision-making process, Member States have established national HTA bodies whose role is to perform HTA evaluations and appraisals.

The landscape of HTA bodies and institutions across the EU is very diverse. Some countries have centrally established HTA bodies. Several countries also have regional agencies and some of them hospital based HTA committees in charge of financing decisions.

It is also important to note that not all European countries have the same degree of development in their HTA bodies and there is at present a lack of harmonization in the approaches and methodologies across the EU. [55]

Lessons learnt from some pilot collaborations show that HTA bodies in Europe reach different conclusions in their reports and therefore different policy decisions are adopted despite following rigorous models of assessment. [56].

Health Technology Assessment (HTA)

Health Technology Assessment (HTA) is a way of assessing the manner science and technology used in health care and disease prevention. It covers medical, social, economic, and ethical issues.

The purpose of this discipline is to provide policy-makers with objective information, so that they can formulate health policies that are safe, effective, patient focused and cost-effective.

Ideally, a HTA assessment should be transparent, unbiased, robust and systematic and firmly rooted in research and the scientific method.

HTA Methodology

When a new drug is authorized, payers (i.e. national governments, private insurance, etc.) rely on HTA assessments to ensure its cost-effectiveness and added value to the system.

HTA is a multidisciplinary process that analyses different factors and methods of evidence based medicine. The factors studied are of diverse nature: medical, social, economic and ethical. Benefits and risks will be weighed, attributing costs to these parameters [57].

The main evidence requirements for HTA appraisals related to the design of a clinical trial are the following[2]:

EVIDENCE	ELEMENTS TO BE CONSIDERED IN THE SELECTION AND DESIGN
COMPARATORS **Placebo vs. Active**	Feedback from clinicians. Identification of established management practice. Use of active comparator if feasible (mix direct/indirect comparison). Consideration of off-label use.
STUDY POPULATION **Homogeneous vs. Heterogeneous**	Feedback from clinicians. Representative of patient population in target countries. Prospective identification of biologically plausible subgroups.
ENDPOINTS **PROs, QoL, Duration of Life, etc.**	Feedback from patients. Use of measures important for patients' QoL/duration of life. Proof of surrogate-final outcome relationship.

These elements also represent the key identified areas for divergent opinions between Regulators and HTA bodies when it comes to the design of a clinical trial.

[2] Elements as defined by the SEED (Shaping European Early Dialogues for health technologies) initiatives.

Other elements considered in a HTA appraisal are the type of analysis, the perspective, the time horizon, the structure of the pharmacoeconomic model, the planned sensitivity analyses, the tools used to measure resource utilization and the discussion on the added benefit of a drug compared to the SOC and with other similar pharmacological products.

When the effectiveness of a medicine leaves some uncertainty, the opinions of HTA agencies tend to vary more as it leaves margin for higher variability in interpreting the results, the surrogate endpoints of a study and the benefit risk/ balance and relative effectiveness.

National Institute for Health and Clinical Excellence (NICE) [58]

The National Institute for Health and Clinical Excellence is a body of the National Health System (NHS) of the United Kingdom. The NICE is an independent body responsible for developing guidance, standards and information on HTA.

NICE represents at the moment, the most developed HTA body within the EU

In England and Wales, NICE produces guidance and performs HTA appraisals that are mandatory.

NICE prepares HTA appraisals on medicines using methodologies based on the most up-to-date evidence with the purpose of ensuring value for money in the NHS system, and so reduce inequalities and variation.

NICE guidance is produced for the NHS, local authorities, care providers, charities, and anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

To evaluate the clinical and cost effectiveness of a technology, NICE measures its merit **using a unit known as a Quality Adjusted Life Year or QALY**.

This is a useful way of comparing the costs and benefits of sometimes very different technologies in different conditions, by looking at the gains to quality of life and life expectancy.

This way of comparing technologies allows the understanding of the impact that introducing a new treatment will have on the ability of the NHS to maintain the services it already provides.

In its current appraisal processes, NICE advises its appraisal committees to support the use of a new drug **within a range of £20,000 to £30,000 per QALY.**

In exceptional circumstances more expensive treatments (up to about £50,000 per QALY) can be recommended, as it is the case in very specific circumstances for new drugs that are

designed to extend life at the end of life. That has been applied frequently, particularly to new cancer treatments [59].

NICE is and HTA body which is unusual in being so specific and transparent about its decision-making thresholds based on QALY. Most HTA bodies have not made publicly available the processes and thresholds they work with.

The advisory committees are able to use their discretion to support the use of a treatment at a higher cost per QALY.

The proposals on value based assessment were to regularise the decision-making process more explicitly in the methodology.

In July 2013, the Department of Health asked NICE to take into account additional terms of reference in the appraisal of new health technologies. They were intended to supplement but not replace NICE's current approach to assess the clinical and cost effectiveness of new treatments.

NICE was asked to include a simple system of weighting for burden of illness that appropriately reflects the differential value of treatments for the most serious conditions.

As a result, NICE revisited its HTA standards used. The value based assessment proposals published in March 2014, included measures to take into account more systematically and explicitly the severity of a disease, as well as the effect that diseases and conditions have on the capacity to engage in society.

The aim was to add further clarity to NICE's recommendations and enable the independent advisory committees to explore more fully the potential treatments have to improve outcomes for patients.

Another area was the agreement between NICE, NHS England and the Department of Health, on the NHS's willingness to pay for new treatments, which would take account of any special

cases, such as ultra-orphan conditions and cancer, together with a more productive sharing of risk between companies and the NHS. The aim would be to progressively reflect the value of new treatments as the knowledge of what they can offer to patients increases.

ORPHAN DRUGS

It has been acknowledged, that the standard methodologies for Health Technology Assessment needs to be tailored for orphan drugs to take into account their specificities.

Orphan drugs claim much higher prices than drugs for other non-orphan indications as they need to compensate the cost of developing a drug for a small population.

Applying the same cost-effectiveness thresholds as for other drugs would result in an automatic rejection.

The National Institute for Health and Clinical Excellence (NICE), performed a review in 2005 of the feasibility of HTA methods for the so-called “ultra-orphan” drugs.

NICE noted there would be several elements that might need to be taken special consideration such as the prevalence of the disease, the nature of the condition and the duration of the treatment.

European Union Network Health Technology Assessment (EUnetHTA)

Health Technology Assessment Network (HTAN) [60]

The European institutions are well aware of the importance of HTA cooperation, and in this respect, financial support has been directed to actions in the field of HTA through the public health programmes in the last years.

These European collaborative initiatives face the challenge of finding the right balance between progress on European cooperation in the HTA area while respecting the national remit, responsibilities and priorities that are set at this level.

The European Union has supported and financed cooperation projects in the field of health technology assessment (HTA) since 2006, beginning with the EUnetHTA project (2006-2008).

It has also financed methodological work in the field of HTA through the 7th Research Framework Programme.

The members of the HTA network shall be national authorities or bodies responsible for HTA designated by the participating Member States.

The EU cooperation on HTA has been organized in two levels:

- A **strategy level (the HTA Network (HTAN)**
- And a **scientific and technical cooperation level (EUnetHTA)**

The HTA Network will produce reflection papers on conditions to facilitate **re-use of HTA information** at national level (2014 and 2015) and on **HTA-regulatory synergies** (2015).

EUnetHTA, individual HTA bodies and EMA will try to align their position on permanent infrastructure for **parallel early dialogues.**

EUnetHTA: The Origins [61]

In 2004, the European Commission and the Council of Ministers targeted Health Technology Assessment (HTA) as "a political priority", recognising "… an urgent need for establishing a sustainable European network on HTA…"

The Commission call was answered in 2005 by a group of 35 organisations throughout Europe, led by the Danish Centre for HTA (DACEHTA) in Copenhagen (a unit in the former National Board of Health of Denmark - and the current Danish Health and Medicines Authority) which led to the activities of the EUnetHTA Project (2006-2008).

This project provided for the formation of a network of European HTA agencies in order to drive common action in the area of HTA.

The European Network for Health Technology Assessment (EUnetHTA) was established to create an effective and sustainable network for HTA across Europe.

The main goal of EUnetHTA is to promote the collaboration between European HTA organisations at European, national and regional level.

EUnetHTA is a network of government appointed organisations from EU Member States, EU-accession countries, plus European Economic Area (EEA) and European Free Trade Association (EFTA) countries and a large number of relevant regional agencies and non-for-profit organisations that produce or contribute to HTA in Europe.

Currently, EUnetHTA also performs the function of the scientific and technical cooperation Secretariat of the HTA Network.

The main objectives of the EUnetHTA initiatives are the following:

- Increase an efficient use of resources available for HTA.

- Create a system of HTA knowledge sharing.

- Promote good practice and harmonization in HTA methods and processes.

Following the 2006-2008 Project, further activities of the European Network for Health Technology Assessment were organised through establishment of the EUnetHTA Collaboration 2009, the EUnetHTA Joint Action (JA) (2010-2012) and the EUnetHTA Joint Action 2 (JA2) (2012-2015).

Further activities are expected to take place in 2016-2020.

For the detailed scope of the different EUnetHTA initiatives see Chapter 4.

HTA CORE MODEL

Undoubtedly, one of the major achievements of EUnetHTA has been the creation and put into place of the HTA Core Model, a tool that enables the production of HTA information (e.g. reports) in a consistent and harmonized way across EU HTA bodies.

It provides a methodological framework for collaborative production and sharing of HTA information. The tools consist of three main components:

- The *HTA ontology* contains an extensive list of generic questions that can be asked in an HTA appraisal. The ontology also identifies relations between the questions.
- *Methodological guidance* helps researchers in finding answers to the questions defined by the ontology.
- The *common reporting structure* provides a standard format for the output of HTA projects.

The EUnetHTA Core Model consists of nine domains to be addressed in HTA reports:

- Health Problem and current use
- Description and technical characteristics
- Safety
- Clinical effectiveness
- Costs and economic evaluation
- Ethical analysis
- Social aspects
- Organizational aspects
- Legal aspects

The core model provides a methodological guidance in order to achieve standardization of assessments across EU HTA bodies.

As some of the elements might be site specific, this core HTA model can then be adapted to local context.

Clinical evidence is considered to be non-context specific and therefore appraisals easier to share, while economic and social elements have to be tailored according to the region.

The HTA Core Model has been updated in two phases by Work Package (WP) 8 of the EUnetHTA Joint Action 2. First, a major overhaul of the Model was made in 2013, resulting in version 2.0 in which most contents were updated [62].

During 2014, the revision process continued through updating contents of the legal domain (the only domain not updated for 2.0).

Further work in 2014 included a revision of the list of HTA questions (the ontology) in some domains to remove redundant overlaps and to align the questions with those used in the rapid Relative Effectiveness Assessment (REA) model application developed within WP5.

The current HTA Core Model is version 2.1. Assessment element tables for HTA Core Model Application for Pharmaceuticals (2.1) [63].

The HTA Core Model version 3.0 is currently published as a public draft. This new version contains changes in the ontology (HTA questions) and a new social aspects domain, now called "Patient and Social Aspects" [64].

The HTA Core Model divides HTA information into standardized pieces referred to as *assessment elements*.

An assessment element defines a piece of information that is relevant for the HTA. The elements that are most likely to be useful for international sharing of information are defined as *core elements*. Each assessment element contains a question that one should consider including and answering within a specific assessment project.

The HTA Core Model organises the information within a HTA report by dividing it first into nine *domains*.

Each domain is divided into *topics*, and each topic is further divided into several *issues*. The issues are the generic questions that should be considered when assessing a health technology. The combination of a domain, topic and issue defines within the HTA Core Model an assessment element.

The relevance of the generic questions defined by the assessment elements should be evaluated within each HTA project, considering the technology that is the object of assessment as well as the project's aims and resources.

METHODOLOGICAL GUIDELINE: "Methods for Health Economic Evaluations" [65]

Their recommendations focus on the methodological challenges encountered while performing relative effectiveness assessments of pharmaceuticals and other health technologies.

The guidelines inform on what is considered a good quality of study design and conduct, less biased, reliable and applicable evidence, good reporting and synthesis of evidence and good practice of statistical data analysis in the context of HTA.

The development of the methodological guidelines was included in the work plan of the EUnetHTA JA in years 2009-2012, and is one of the objectives of the EUnetHTA JA2. The primary aim of the guidelines is to help the assessors of evidence to process, analyse and interpret the data.

Currently there is methodological guidance published in the following areas, which are to be used for the rapid relative effectiveness assessment (REA) of pharmaceuticals:

Methodological guidelines for rapid relative effectiveness assessment (REA) of Pharmaceuticals developed in WP5 of EUnetHTA JA:

- Clinical endpoints

- Composite endpoints

- Surrogate endpoints

- Safety

- Health-related quality of life

- Criteria for the choice of the most appropriate comparator(s)

- Direct and indirect comparisons

- Internal validity

- Applicability of evidence in the context of a relative effectiveness assessment

Methodological guidelines developed in WP7 SG3 of EUnetHTA JA2:

-Meta-analysis of diagnostic test accuracy studies

- Methods for health economic evaluation – A guideline based on current practices in Europe

- Internal validity of non-randomised studies (NRS) on interventions

- Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness

International Network of Agencies for Health Technology Assessment (INAHTA)

The European HTA bodies are members of the International Network of Agencies for Health Technology Assessment (INAHTA) [66].

In order to become member, the institution needs to be a non-profit organization, be dependant of a regional or national government and be at least 50% public funded.

INAHTA has a checklist for HTA appraisals and reports in order to ensure quality and standards of the evaluations.

INAHTA CHECKLIST

In the checklist, it is needed to be explicit on sources of information, literature search strategies, methods of critical appraisal, economic analysis, conflict of interest, external review and any legal, ethical or social considerations having an influence on the analysis. [67]

CHAPTER 3: The Political Scenario. The Need for the Development of Harmonized HTA Requirements in the EU

LISBON TREATY

EU DIRECTIVE 2011/24/EU ON THE APPLICATION OF PATIENTS' RIGHTS IN CROSS BORDER HEALTHCARE

DIRECTIVE ON TRANSPARENCY

Lisbon Treaty

The Lisbon Treaty [10] came into force on the 1st of December 2009. The purpose was to modernise and reform a European Union of 27 Member States that had been operating with rules designed for an EU of 15 Member States.

This Treaty modernises the EU institutions and work practices, leading to greater efficiency in the decision-making process, and increases the democratic accountability by associating the European Parliament and the national parliaments.

The Treaty of Lisbon also strengthens the social dimension of the European Union, as it recognises the social values of the Union in the founding Treaties and includes new objectives for social matters.

In this respect, the Treaty of Lisbon recognises the legal value of the Charter of Fundamental Rights of the EU [11]. As a result, the Charter becomes binding and can be cited in legal proceedings.
This recognition constitutes an advance in social matters as the Charter ensures the social rights of persons resident in EU territory as follows:

- The workers' right to information and consultation within the undertaking (Article 27 of the Charter).
- The right of bargaining and the right to strike (Article 28 of the Charter).
- The right of access to placement services (Article 29 of the Charter).
- The right of protection in the event of unjustified dismissal (Article 30 of the Charter).
- The right to fair and just working conditions (Article 31 of the Charter).
- The prohibition of child labour and the protection of young people at work (Article 32 of the Charter).
- Reconciling family and professional life (Article 33 of the Charter).
- Social security (Article 34 of the Charter).

- Healthcare (Article 35 of the Charter).

Article 35 regarding healthcare reads as follows:

"Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities".

Under this clause, in devising and implementing its policies and measures, the Union shall meet the requirements for encouraging a high level of employment and guarantee adequate social protection, fight social exclusion and also guarantee a high level of tertiary and non-tertiary based education and safeguard health as well.

The implementation of social policy at European level forms part of the shared competences between the EU and Member States.
Social policies are implemented more effectively at Member State level than at European level. In this way, and in accordance with the principle of subsidiarity, the role of the EU in this area is limited to supporting and complementing the activities of Member States.

The Treaty of Lisbon keeps this system of division of competences. In addition, it maintains the adoption of texts in accordance with the ordinary legislative procedure for the majority of social policy measures.

Even though the development and implementation of social policies remains principally the responsibility of Member States, the Treaty introduces some relevant innovations in the area of health care under Article 156 of the Treaty on the Functioning of the EU (TFEU):

"With a view to achieving the objectives of Article 151 and without prejudice to the other provisions of the Treaties, the Commission shall encourage cooperation between the Member States and facilitate the coordination of their action in all social policy fields under this chapter,

particularly in matters relating to: – employment; – labour law and working conditions; – basic and advanced vocational training; – social security; – prevention of occupational accidents and diseases; – occupational hygiene; – the right of association and collective bargaining between employers and workers. To this end, the Commission shall act in close contact with Member States by making studies, delivering opinions and arranging consultations both on problems arising at national level and on those of concern to international organizations, in particular initiatives aiming at the establishment of guidelines and indicators, the organisation of exchange of best practice, and the preparation of the necessary elements for periodic monitoring and evaluation. The European Parliament shall be kept fully informed. Before delivering the opinions provided for in this article, the Commission shall consult the Economic and Social Committee".

By virtue of this Article, the open method of coordination is institutionalised with the recognition that the Commission may undertake initiatives in order to encourage cooperation between Member States in the social domain and to facilitate the coordination of their actions. For example, these initiatives may take the form of studies or opinions with a view to establishing guidelines and indicators, and to organising the exchange of best practice with the organisation of a periodic evaluation.

Regarding the public health policy, **t**he Treaty of Lisbon maintains the previous situation where the Union's action in the field of health is largely of a coordinating, complementary and supporting nature.

The Treaty also maintains the shared competence between Member States and the EU with regards to those public health matters for which there is actual legislative competence (organs, substance of human origin, blood and veterinary and phytosanitary fields), with the inclusion in this category of a public health objective to set high standards of quality and safety for medicinal products and medical devices.

Under the Lisbon Treaty, cooperation between Member States on health services is encouraged in cross border areas. The coordination on health issues among Member States is strengthened, including the possibility of establishing guidelines and indicators, organising exchange of best practice, and preparation of periodic monitoring and evaluation, whereas actions to improve monitoring, early warning of and combating serious cross border threats to health.

EU Directive 2011/24/EU on the Application of Patients' Rights in Cross-Border Healthcare

This Directive does not only foster the right of EU patients to seek health care in countries different from their home country but it also introduces important provisions for the EU collaboration in the area of rare diseases and Health Technology Assessment (HTA).

The EU Directive 2011/24/EU on the application of patients' rights in cross-border healthcare was adopted on the 19th of January 2011 and was published in the EU's Official Journal on the 9th of March 2011. It entered into application on the 25th of October 2013 [13].

Directive 2011/24/EU establishes for the first time the right of patients in Europe to seek health care in another Member State and be reimbursed for it.

The right to health care in other Member States already existed prior to the adoption of this Directive as various EU regulations apply to unforeseen medical treatment that becomes necessary during a temporary stay abroad (Regulation No. 883/2004 on the coordination of social security systems, and the European Health Insurance Card) [68].

However, for planned care, under the existing system, a patient could apply for a prior authorisation and be reimbursed for the care. But without prior authorisation, there was no guarantee that the cost of hospital care would be met.

There were several cases during the years in the European Court of Justice, most famously the Watts case that established the principle of reimbursement for cross-border health care (Case C-372/04, Watts). [69]

Therefore, the EU legislation regarding planned cross-border health care needed to be further developed.

The Directive clarifies that patients are entitled to seek health care abroad, including for planned care, and be reimbursed for it, in principle without having to seek prior authorisation.

For non-hospital care, patients will be able to seek health care abroad without prior authorisation or other formalities, and claim reimbursement upon their return home.

In the case of hospital care, patients will be able to choose their health care provider. The new Directive covers not only public but also private health care providers.

It also establishes the patients' right to adequate information on cross-border health care, and creates national contact points to provide such information.

It also calls for European cooperation regarding mutual recognition of prescriptions made abroad.

Prescriptions issued abroad must as a rule be recognized. However, whether the medication is reimbursed is up to the Member State as the Directive does *not* affect national rules regarding pricing and reimbursement.

In the area of rare diseases, the introduction of this Directive brings important elements to make progress in the way the treatment of rare diseases can be handled in the European area:

Member States should cooperate in rare diseases through European Reference Networks (ERNs) [70], and cross-border cooperation on diagnosis and treatment of rare diseases.

It establishes a European network on eHealth and a network on Health Technology Assessment.

The Directive calls on Member States to exploit better the possibilities offered by Orphanet [71] and the existing Social Security Regulation for the referral of patients abroad for the diagnosis and for treatments which are not available in the home country.

If a patient affected or suspected to be affected, by a rare disease needs to apply for prior authorisation, a clinical evaluation may be carried out, and if no experts can be found in the home country, the Member State can request scientific advice.

The European Reference Networks bring together specialised centres and health care providers across Member States to pool resources and knowledge. This is of utmost importance in the case of rare diseases where the expertise in very specific medical domains for both diagnosis and treatment might not be available in all Member States.

At the same time, patients suffering from these particular conditions will benefit from the EU expertise and high level services of care.

The Commission will adopt specific criteria that the ERNs must fulfil, as well as criteria required from health care providers wishing to join them.

It calls for Member States to cooperate with each other on the quality and safety standards for health care, and requires Member States to publish the standards and guidelines for quality and safety that apply in their territory.

However, according to the Directive, not all healthcare is to be automatically reimbursed. The decision on which health care is reimbursed, and at what level, is entirely under the remit of the Member States.

In principle, patients are entitled to receive reimbursement for the same or similar health care, for the same amount that would have been given had the health care been provided in the home Member State. And Member States are free decide to reimburse the full costs even if they exceed the normal limit, or they may choose to reimburse certain extra costs resulting for example from disability. This is up to the Member State to decide.

The Directive also indicates that where the treatment is not part of the health care benefits in the home Member State, consideration should be given to the equivalent benefits for the patient.

Member States could refuse to reimburse the cost of health care in a country different to the affiliation country of the patient if they consider the service is not “the same or similar health care” as would have been provided in the home Member State.

Therefore, interpretation of same or similar is key to ensure that equally effective health care is reimbursed.

Other exceptions to reimbursement of cross-border health care are provided in the Directive, under the principle of “overriding reasons of general interest” such as planning requirements.

Certain cross-border health care may be subject to prior authorisation by the home Member State.

In principle, patients have the right to access cross-border health care without prior authorisation and be reimbursed for it. However, there are certain exceptions, for which Member States have the right to put in place a system of prior authorisation. They can do so only if based on the principle of “overriding reasons of general interest”.

Member States must inform the Commission about any limitations of reimbursement of cross-border health care and publish the lists. This must be limited to what is necessary and proportionate.

European Cooperation in Health Technology Assessment (HTA): European HTA Network

The Directive establishes a voluntary network for cooperation between the authorities in Member States responsible for HTA.

As per Article 15 of Directive 2011/24/EU, a voluntary network connecting the national authorities or bodies responsible for Health Technology Assessment (HTA), designated by the Member States is to be established.

The Directive provides objectives and criteria for the HTA network, whose aim will be to support the exchange of information on relative efficacy, short and long-term effectiveness of health technologies, including on the methodologies for assessment, and to avoid duplication of work.

The Directive states that the HTA network should be based on principles of good governance, including transparency, objectivity, and “appropriate stakeholder consultation”. Therefore, patient organisations have a role in this process.

Moreover, the HTA network can receive aid from the European Union in order to achieve its objectives. This support can be granted, among other things, to facilitate the consultation of stakeholders on the work of the network.

Communication with Patients' Organisations

The engagement of Patient organisations is crucial for a correct and useful implementation of the premises of the Directive.

Patients' organizations had an intense involvement and worked closely with the Commission, the EU Presidencies, and Members of the European Parliaments throughout the drafting and readings of the Directive to ensure that a patients' perspective was reflected in the text.

Patient organisations can provide feedback and advice to the Commission in raising awareness of patient communities regarding the possibilities that exist for referral abroad in cases of (suspected) rare diseases (Article 13).

This legal text, being a Directive needs to undergo the process of national transpositions in order to be fully implemented.

Many of the provisions of the Directive are optional or leave room for interpretation by Member States. How it will finally affect and how it will add value for patients depends very much on the measures finally adopted at national level in the coming years.

Directive on Transparency

Pursuant to Article 168(7) of the Treaty on the Functioning of the European Union, Member States are responsible for the organisation of their health care system and for the delivery of health services and medical care, including the allocation of resources assigned to them.

In this framework, each Member State can take measures to manage the consumption of medicines, regulate their prices or establish the conditions of their public funding.

A medicinal product authorised in accordance with EU legislation on the basis of its quality, safety and efficacy profile may therefore be subject to additional regulatory requirements at Member State level before it can be placed on the market or dispensed to patients under the public health insurance scheme.

For instance, Member States usually evaluate the cost-effectiveness of authorised medicines, or their relative efficacy as well as the short- and long-term effectiveness compared to other products in the same therapeutic class, in order to determine their price, funding and utilisation in the framework of their health insurance system.

National measures to control the funding of medicines and manage their consumption in the framework of health care systems are susceptible to create barriers to trade as they affect the capacity of pharmaceutical companies to sell their products in domestic markets.

The settled case-law of the Court of Justice of the European Union recognises the right of Member States to adopt such measures in view of promoting the financial stability of their health insurance system. However, basic conditions of procedural transparency must be met to ensure their compatibility with the rules of the Treaty

relating to the Single Market. In particular, pricing and reimbursement measures must be free of discrimination against imported medicinal products and based on objective and verifiable criteria which are independent from the origin of the products.

The Transparency Directive (Council Directive 89/105/EEC) [15], aims to ensure the transparency of measures established by EU countries to control the pricing and reimbursement of medicinal products.
It defines a series of procedural requirements designed to verify that national pricing and reimbursement decisions do not create obstacles to the pharmaceutical trade within the EU's Internal Market.

Directive 89/105/EEC codifies the minimum requirements set forth by the Court of Justice. It was adopted to enable market operators to verify that national measures regulating the pricing and reimbursement of medicines do not contravene the principle of free movement of goods. To this end, the Directive lays down a series of procedural requirements to ensure the transparency of pricing and reimbursement measures adopted by the Member States. These obligations include specific time limits for pricing and reimbursement decisions (90 days for pricing, 90 days for reimbursement or 180 days for combined pricing and reimbursement decisions).

The Directive also requires the competent national authorities to provide a statement of reasons based on objective and verifiable criteria for each of their decisions and to provide appropriate legal remedies to the applicant companies.

The Directive lies at the interface between EU responsibilities for the Internal Market and national competences in the area of public health in accordance with Article 168(7) of the Treaty on the Functioning of the European Union (TFEU).
Its provisions do not affect national policies on the setting of prices and the organisation of social security schemes, except as far as necessary to achieve transparency.

The Transparency Directive lays down three major requirements with respect to individual pricing and reimbursement decisions:

- Decisions must be made within a specific timeframe (90/180 days).
- Decisions must be communicated to the applicant and contain a statement of reasons based on objective and verifiable criteria.
- Decisions must be open to judicial appeal at national level.

Directive 89/105/EEC has never been amended since its adoption. Its provisions reflect the pharmaceutical market conditions which prevailed more than twenty years ago. However, these conditions have fundamentally changed, for instance with the emergence of generic medicines providing cheaper versions of existing products or the development of increasingly innovative (yet often expensive) research based medicinal products.

In parallel, the constant rise in public expenditure on pharmaceuticals in the last decades has encouraged Member States to devise more complex and innovative pricing and reimbursement systems over time.

Despite the historically positive impact of Directive 89/105/EEC on the Internal Market for medicines, there was evidence that it does not fully achieve its objectives in the present context:

Firstly, a gap has emerged between the provisions of the Directive, which describe the main types of pricing and reimbursement procedures established in the 1980s, and the much wider range of cost containment measures adopted nowadays by Member States.

Despite the extensive interpretation of the Directive by the Court of Justice, the implementation of its provisions in national law and the effective enforcement of its principles, in particular by the Commission, have become particularly challenging. This situation not only results in legal uncertainties but also in a reduced transparency of national pricing and reimbursement measures, which negatively affects the smooth functioning of the Internal Market to the detriment of European patients and pharmaceutical companies.

Secondly, the time limits for pricing and reimbursement decisions established by Directive 89/105/EEC are regularly exceeded by Member States. This leads to delays in the marketing of medicinal products, which in turn slows down the availability of valuable treatments for patients.

The Commission considered that pricing and reimbursement procedures should be shortened with respect to generic medicinal products. In addition, the sector inquiry showed that the interference of patent or safety related issues with pricing and reimbursement processes can significantly delay access to cheaper generic medicinal products.

After having conducted a review, the Commission proposed a new Directive to replace the longstanding Transparency Directive.
The aim is to streamline and reduce the duration of national decisions on pricing and the reimbursement of medicines.

The new Directive represents an important simplification measure and will replace the longstanding Directive from 1989 as it no longer reflects the increased complexity of pricing and reimbursement procedures in EU countries.

On the 18th of March 2013, the Commission adopted the Amended proposal for a Directive of the European Parliament and of the Council on the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems [16].

The fundamental objectives and principles of Directive 89/105/EEC remain fully valid in the new proposal. Accordingly, this initiative aims at adapting the Directive to the current pharmaceutical environment while preserving its core foundations. The overall objective of the proposal is to clarify the procedural obligations incumbent upon Member State and to ensure the effectiveness of the Directive, both in avoiding delays in pricing and reimbursement decisions and in preventing barriers to pharmaceutical trade. This is to be done without affecting national social security policies, except as far as it is necessary to achieve the transparency of national procedures and the effectiveness of the Internal Market legislation.

In spite of the difficulty to conclude on the overall cost-benefit balance of reducing the time limits with respect to originator medicines, a reduction from the current 90/180 days to 60/120 days is proposed in light of the positive impact it would have on the swift availability of innovative medicines to patients and on rewarding pharmaceutical innovation when medicines are approved for reimbursement.

However, given the complexity of the health technology assessment (HTA) procedures, it was deemed necessary to find a more differentiated approach for the time limits. Different time limits are proposed, depending on whether the medicinal products are subject to health technology assessment (90/180 days) or not (60/120 days).

Legal basis and subsidiarity:

The main objective of Directive 89/105/EEC is to facilitate the functioning of the Internal Market for medicinal products. The legal basis is therefore Article 114 of the Treaty on the Functioning of the European Union.

The existing Directive has as its underlying principle the idea of minimum interference in the organisation by Member States of their domestic social security policies.

This fundamental principle is maintained in the new proposal.

The proposed requirements to ensure timely and transparent decisions carefully balance the obligation to preserve the competences of Member States in the field of public health against the necessity to guarantee the effectiveness of the Directive in meeting its Internal Market objectives.

In order to respect the responsibilities of the Member States under the Treaty, the proposal does not provide for the approximation of national pricing and reimbursement measures, nor does it restrain the ability of Member States to freely determine the prices of medicines and the conditions of their public funding on the basis of the criteria they choose.

The proposal maintains the core principles of the existing Directive but also puts forward a comprehensive adaptation of its legal provisions based on the following key elements:

– Clarification of the scope of the Directive:

The transparency requirements apply to all pricing and reimbursement measures understood in a broad sense, including “demand side” measures to control or promote the prescription of specific medicines. Nevertheless, measures involving public procurement and voluntary contractual agreements with individual companies are excluded from the scope of the Directive in order to avoid interference with other bodies of law.

– Comprehensive coverage of national measures and legal clarity:

The provisions of the Directive are reworded in accordance with general principles (rather than on the basis of specific national procedures) and incorporate the case-law of the Court of Justice. Several key provisions are clarified and updated to avoid interpretation controversies. In particular, it is made clear that the time limits for pricing and reimbursement decisions include all procedural steps leading to the decision, including health technology assessments where applicable.

– Adaptation of the time limits for pricing and reimbursement decisions:

The time limits applicable to generic medicines are reduced to 30/60 and 15/30 days when the reference product has already been priced and included in the health insurance system. The time limits applicable to all other medicinal products are reduced to 60/120 days. However, in cases where national authorities employ health technology assessment procedures in order to assess the relative efficacy or the short- and long-term effectiveness, as an integral part of their decision-making process, the time-limits shall be 90/180 days.

– Non-interference of patent and safety issues with pricing and reimbursement procedures: The proposal clarifies that intellectual property rights should not interfere with pricing and reimbursement procedures, as is already the case for marketing authorisation procedures**. In addition, elements already assessed in the framework of the marketing authorisation process (quality, safety and efficacy, including bioequivalence) may not be reassessed in the framework of pricing and reimbursement procedures.**

– Dialogue and enforcement tools:

Different instruments are put in place to facilitate dialogue on the implementation of the Directive and to ensure its effective enforcement (consultation on draft measures at national level and pre-notification to the Commission, the creation of a remedies procedure in case of non-compliance with the time-limits related to the inclusion of medicinal products in health insurance systems).

The Union's support for cooperation on Health Technology Assessment (HTA) in accordance with Article 15 of Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare aims to optimise and coordinate HTA methodologies which should ultimately also reduce delays in pricing and reimbursement procedures of medicinal products for which Member States use HTA as part of their decision-making process.

HTA includes, in particular, information on the relative efficacy as well as on the short-term and long-term effectiveness, where appropriate, of health technologies, also taking into account broader economic and social benefits or cost-effectiveness of the assessed medicinal product, in accordance with the methodology of the Competent Authorities.

HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical aspects relating to the use of health technology in a systematic, transparent, unbiased and robust manner.

Applications to approve the price of a medicinal product or to determine its coverage by the health insurance system should not delay the placing on the market of that product beyond what is necessary.

National pricing and reimbursement measures have a clear transnational impact linked, in particular, to the potential disruption they might cause to the Internal Market for medicinal products.

The proper functioning of the Internal Market requires timely and transparent decisions to be made by Member States. However, the notion of procedural transparency is understood differently across the EU so that action by individual Member States would not provide sufficient guarantees of transparency for economic operators. Therefore the action at EU level is justified and of relevance in this area.

The main objective is to guarantee that any measure intended to regulate the prices of medicines, to manage their consumption or to determine their reimbursement status is adopted in a transparent manner on the basis of objective and verifiable criteria.

This proposal of an amended Transparency Directive is to be seen in the context of the Commission's efforts to reinforce the Internal Market and to generate favourable conditions for a competitive pharmaceutical industry to provide safe, innovative and accessible medicines to European citizens.

It relates to a number of recent or on-going initiatives, as it is the voluntary cooperation between Member States on health technology assessments, which is currently taking place in the framework of the EUnetHTA Joint Action and to be formalised through the implementation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare.

CHAPTER 4: European Collaboration and Harmonization: Regulatory Authorities-HTA Bodies.

THE PATHWAY TO COLLABORATION: DG SANCO-EC

HTA INITIATIVES: EUnetHTA

REGULATORS INITIATIVES: INTERFACE EMA-HTA

The Pathway to Collaboration: DG SANCO-EC

Since the mid-1990s, several projects supported by the European Commission have contributed to the collaboration in HTA. [72]

An important milestone has been reached in Europe in this context with the establishment of the European Union Network for HTA (EUnetHTA).

In 2004, the European Commission and the Council of the EU recognized the Health Technology Assessment as a political priority and urged for establishing a sustainable European network on HTA.

And in 2005, a group of 35 organizations throughout Europe began the activities of the EUnetHTA project.

The milestones of the project to create a sustainable and permanent HTA network in Europe are illustrated below.

Figure 5. *The European Commission's view for HTA. Source DG SANCO.*

The legal basis is provided by the cross-border health Directive. The financial support comes from the EU budget and the Member States.

The fundamental goals for the HTA network to operate is the building of trust among the concerned bodies, the establishment of common methodologies and the development of Information Technologies (IT) tools and systems to allow the interactions and exchange and the sharing of information.

There have been several phases in recent years within this overarching project as detailed below:

The EUnetHTA Project (2006-2008):

The overall strategic objective of the network was to connect public national health technology assessment (HTA) bodies, research institutions and health ministries, enabling an effective exchange of information and support to policy decisions by Member States.

Several Work Packages (WPs) were aligned with specific objectives. Each WP was entrusted to produce substantial deliverables:

WP 1: Coordination

WP 2: Communications

WP 3: Evaluation

WP 4: Common Core HTA

WP 5: Adapting HTA

WP 6: HTA and Health Policy

WP 7: New Technologies

WP 8: System to support HTA

The EUnetHTA Collaboration (2009):

The EUnetHTA Collaboration was launched in November 2008 in order to continue the work initiated during the EUnetHTA Project 2006-2008.

The EUnetHTA Collaboration was funded by the contribution of its participants.

Since 2009, the EUnetHTA Collaboration has been operating to implement the permanent collaboration on HTA in Europe.

In 2009, the EU Commission Health Programme and EU Member states decided to continue fostering the development of HTA in Europe through funding of the Joint Action on HTA.

The EUnetHTA Collaboration took an initiative in developing a proposal for the Joint Action on HTA, and since 2010, it has been implementing the EUnetHTA Joint Actions 2010-2012 and 2012-2015.

EUnetHTA JOINT ACTIONS 2010-2015 between EC and EU Member States:

A total of 38 governments appointed organizations from 27 EU Member States and Norway and a large number of regional agencies and non-for-profit organizations that produce or contribute to HTA participate are taking part.

In addition, healthcare providers and payers, patients and industry are acknowledged as stakeholders within the work carried out in the framework of the Joint Actions.

- **The EUnetHTA Joint Action (2010-2012):**

The overarching objective of the EUnetHTA Joint Action 1 (JA1) on Health Technology Assessment (HTA) including work on relative effectiveness of pharmaceuticals was to put into practice an effective and sustainable HTA collaboration in Europe by:

- Facilitating an efficient use of resources available for HTA.

- Promoting good practice in HTA methods and processes including the development of Information Technologies tools to enable the EU collaboration and sharing of information (i.e. common databases, documents repository, e-meetings facilities, etc.).
- Creating a sustainable system of HTA knowledge sharing.

The key goals of this Action are summarized below:

-Producing, publishing, storing and retrieving structured HTA information and Core HTAs (including a new application of the Core HTA Model structure).

-Improved Relative Effectiveness Assessment (REA) by identifying areas where methodological guidance is needed and by providing it, suggesting ways to integrate REA of pharmaceuticals as a special version of the HTA Core Model.

In this Action, the scope of the WPs was slightly modified compared to the initial project:

JA1 WP 1: Coordination

JA1 WP 2: Dissemination

JA1 WP 3: Evaluation

JA1 WP 4: Core HTA

JA1 WP 5: Relative Effectiveness Assessment of Pharmaceuticals

JA1 WP 6: Information Management System

JA1 WP 7: New Technologies

JA1 WP 8: Strategy and Business Model Development

- **The EUnetHTA Joint Action 2 (2012-2015):**

The general objective of the EUnetHTA Joint Action 2 (JA2) on Health Technology Assessment (HTA) is to strengthen the practical application of tools and approaches to cross-border HTA collaboration.

The activities of the EUnetHTA JA2 are supported by funding from the European Union in the framework of the Health Programme.

The second wave of the Joint Action is focused on the following aspects:

- The achievement of a better understanding for the EC and EU Member States of what could be the optimal ways to establish a sustainable structure for HTA work in the EU.
- The strengthening of the practical application of tools and approaches to cross-border HTA collaboration.
- The production of recommendations in relation to the design and management of future EU HTA cooperation.

The JA2 aims at bringing collaboration to a higher level resulting in a better understanding for the Commission and Member States of the ways to establish a sustainable structure for HTA in the EU.

Specifically, the JA2 will develop a general strategy, principles and an implementation proposal for a sustainable European HTA collaboration according to the requirements of Article 15 of the Directive for cross-border healthcare.

The defined Work Packages of this Action are as follows:

JA2 WP 1: Coordination

JA2 WP 2: Dissemination

JA2 WP 3: Evaluation

JA2 WP 4: Testing collaborative production of HTA information for national adaptation and reporting

JA2 WP 5: Applying the HTA Core Model for Rapid Assessment for national adaptation and reporting

JA2 WP 6: Information Management Infrastructure and Services (IMIS)

JA2 WP 7: Methodology development and evidence generation: Guidelines and pilots production

JA2 WP 8: Maintenance of HTA Core Model infrastructure to support shared production and sharing of HTA information

The EUnetHTA JA stakeholder Involvement Policy developed during EUnetHTA JA1 continues to apply during the EUnetHTA JA2.

As explained in Chapter 3, Directive 2011/24/EU on the application of patients' rights in cross-border healthcare was adopted in 2011.

This Directive, in its Article 15, stipulates that the Union shall support and facilitate cooperation between national authorities or bodies responsible for health technology assessment designated by the Member States.

According to the implementing Decision, and as per Art. 15 of the Directive, the HTA Network is to be supported by a scientific and technical cooperation to meet the objectives of the European cooperation on HTA.

During the meeting of the HTA Network (HTAN) in October 2013, it was confirmed that the function of the scientific and technical cooperation was to be performed by EUnetHTA until the end of Joint Action 2 (end of 2015).

This status was reflected both in the rules of procedure and the multi annual Work Programme of the HTA Network that were approved at the October 2013 meeting in Brussels.

After the completion of JA2, a subsequent appropriate mechanism of support to the scientific and technical cooperation is to be put in place by the European Commission, where EUnetHTA will consider candidating to take the scientific and technical cooperation on HTA developed from 2006 onwards.

The EUnetHTA Joint Action 1 (2010-2012) involved 24 EU countries, plus Norway and Switzerland.

The EUnetHTA Joint Action 2 (2012-2015) involves all 28 EU countries plus Norway, Switzerland, Turkey and Russia.

The organisational and governance structure of the EUnetHTA Collaboration was endorsed by the EUnetHTA Collaboration Plenary Assembly in September 2009 and has been applied in the EUnetHTA Joint Actions (2010-2012 and 2012-2015).

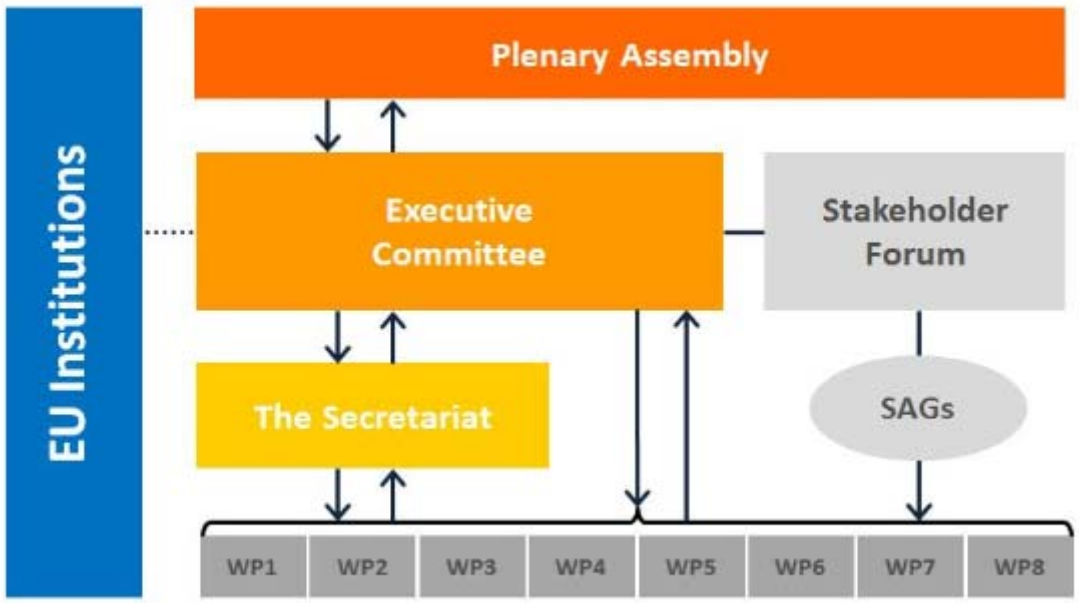

Figure 6. *EUnetHTA structure scheme: Source: EUnetHTA.*

The EUnetHTA Secretariat is held by the Danish Health and Medicines Authority.

The Plenary Assembly is comprised of the head of each of the EUnetHTA Collaboration partner organisations or a person appointed by the head (one representative per partner organisation). The Chair of the Plenary Assembly is elected by the members of the Plenary Assembly.

The Executive Committee is comprised of the representatives of the function/Work Packages lead partner organisations, the Secretariat and elected representatives from three partner organisations which do not have the function/Work Package leading responsibility (1 representative per partner organisation, the Secretariat leader and the Secretariat manager) and the Chair of the Plenary Assembly. The Chair of the Executive Committee is appointed by the members of the Executive Committee.

Stakeholder Forum is formed to ensure the transparent engagement with stakeholders and is comprised of but not limited to representatives from the European umbrella organisations representing interests of the following stakeholder groups:

1. Policymakers at regional/national/hospital level
2. Patient organisations
3. Healthcare professionals
4. Payers (statutory health insurance)
5. Industry
6. Health related media

The EUnetHTA Network Components

EUnetHTA has established links with relevant organisations, projects and initiatives in Europe and outside to enhance scientific cooperation on HTA in Europe (e.g. EMA, EFPIA, EUCERD, INAHTA, etc.).

Participation in the EUnetHTA initiatives can be done in different forms:

To become a EUnetHTA **Partner**, an organisation must be officially nominated by the Ministry of Health of their country (from EU member states, EU-accession countries, plus EEA and EFTA countries).

An organization can also apply to become **Associate** of EUnetHTA. The Executive Committee applies the following criteria to assess eligibility of an organisation to become a EUnetHTA Associate:

An applying organisation should be a public or non-profit organization and have a mandate to produce or contribute to HTA. It should have an annual budget funded at least 50% from public sources and agree to declare conflict of interest as required by the EUnetHTA policy on conflict of interest. In addition, the applying organization should agree to adhere to the EUnetHTA requirements on the participation in the EUnetHTA JA2.

Associate organizations could contribute to the activities defined in the WPs (project-based input) and/or perform general tasks that are not tied to a specific WP or project (e.g. regular provision of information to the EUnetHTA databases (POP Database, EVIDENT Database, Core HTA information)).

EUnetHTA also maintains a **Stakeholders Forum.**

Stakeholder groups are patients/consumers, industry, payers (statutory health insurance) and health care providers.

The member organisations of the EUnetHTA Stakeholder Forum are selected through an open call for expression of interest to participate in the Forum that takes place in the beginning of a Joint Action. Membership of the Forum is organisation-based.

Furthermore, EUnetHTA also launches public consultations on the documents it produces.

Examples are the public consultations launched on the HTA Core Model and the draft methodological guideline “Methods for health economic evaluations”.

As mentioned above, the key event in the process of EU HTA cooperation was the adoption of **Directive 2011/24/EU** of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare, which was published in March 2011.

Article 15 of Directive 2011/24/EU assigned the Union to support and facilitate cooperation and the exchange of information among Member States working within a voluntary network connecting national authorities responsible for health technology assessment (HTA) designated by Member States (i.e. the HTA Network).

Accordingly, an **Implementing Decision was issued on the 26th of June 2013**, providing the rules for the establishment, management and transparent functioning of this Network of national authorities or bodies responsible for health technology assessment (2013/329/EU) [73].

This Implementing Decision indicates that in order to achieve the objectives assigned by Article 15 of Directive 2011/24/EU, the HTA Network shall build on the experience gained in previous actions in the field of HTA supported by the Union and ensure relevant synergies with ongoing actions.

The members of the HTA Network shall be national authorities or bodies responsible for HTA designated by the participating Member States.

The HTA Network should also establish rules of procedure to facilitate appropriate stakeholder consultation and liaison with Union bodies, researchers and international organisations on the work of the Network.

The rules of procedure where adopted at the first HTA Network meeting, on the 16th October 2013.

The HTA Network is chaired by the Commission. The Secretariat of the HTA Network is also provided by the Commission.

It was also envisaged, that the HTA Network "shall be supported by a scientific and technical cooperation mechanism" and this function is to be performed by EUnetHTA until the end of 2015, which coincides with the finalization of the Joint Action 2.

EUnetHTA Joint Action 2 is an existing European network for HTA supported by the European Commission until October 1, 2015.

EUnetHTA, as the scientific and technical cooperation mechanism, is invited to attend the Network's meetings and its working groups, but without voting rights.

Upon request of the Commission, the European Medicines Agency may also participate in meetings of the HTA Network and its working groups.

The interaction with Regulators is promoted because while there is clearly a need to keep well separated the regulatory phase and the HTA phase, facilitating synergies and exchange of information in those areas where the need is identified is perceived as crucial.

The HTA Network may also invite European and international organisations to attend meetings as observers.

The areas of operation of HTA BODIES are the following:

The EU cooperation on HTA is now organized in two levels: a **strategy level (the HTA Network (HTAN),** with the 1st meeting held on the 16th of October 2013 and adoption of the Rules of Procedure and the Work Plan 2014-2015) **and a scientific and technical cooperation level (EUnetHTA),** to work in synergy and complementarity, with involvement of stakeholders in both strategic and scientific level:

- The HTA Network will produce reflection papers on conditions to facilitate **re-use of HTA information** at national level (2014 and 2015) and a reflection paper on synergies between **HTA and the regulatory process** (2nd half 2015).
- EUnetHTA, individual HTA bodies and EMA will try to align their position on permanent infrastructure for **parallel early dialogues.**

So, the HTA network is focused on the strategic level and The EUnetHTA at the science level.

EMA is included as third party in the HTA network (as per the Rules of Procedure).

On the strategy level, a HTAN working group has been formed to start the work on the long term strategy, formulating a clear long-term vision for EU cooperation on HTA, **(the so-called HTAN Position Paper).**

There are three immediate deliverables:

- The adoption of a long-term vision on HTA co-operation and priorities.
- Preparation of a reflection paper on HTA-regulatory synergies (2H 2015)

  (EC-funded SEED Consortium; 10 Early Dialogue pilots by mid-2015).
- Preparation of a reflection paper on facilitation and use of joint assessment (1H 2015).

Other relevant developments are collaboration with network of Competent Authorities for pricing and reimbursement.

HTA Initiatives: EUnetHTA

In recent years, the EU HTA community has directed efforts in promoting discussion to build trust and define common HTA methodologies in the framework of pilot programmes as well as in creating IT tools for the sharing of information.

The EUnetHTA Joint Action encompasses 35 organisations from 24 EU Member States.

As explained above, the EUnetHTA is developing several work packages which aim at building harmonization among HTA bodies and Regulators.

The first EUnetHTA project (2006-2008), developed a HTA Core Model for handling and sharing information. This Core Model has been further refined in subsequent actions. This is explained in detail in Chapter 2.

EUnetHTA is also developing methodological guidelines.

This Chapter will focus on the initiatives that move in the interface with regulatory authorities.

Parallel Early Dialogues

The early dialogue is a tool of paramount importance. It allows industry to anticipate and adapt the design of the clinical programmes that will ultimately lead to the generation of data to show the therapeutic value of the drug pre-authorisation and post-authorisation.

It is also a tool to identify what additional evidence might be needed beyond the marketing authorization requirements in case of recognized areas of uncertainty.

The conduct of interactions between industry and HTA bodies was started by the European Medicines Agency, with the initiative of EMA-HTA parallel Scientific Advice in 2010 as a way to pave collaboration.

Interactions have become closer and more frequent and EMA is now also regularly invited to the HTA Network meetings and to the meetings held in the European Network for Health Technology Assessment (EUnetHTA).

Coinciding with the conclusion of the EUnetHTA project in 2008, the Pharmaceutical Forum, a high-level ministerial platform established by the European Commission declared that the improvement and anticipation of clinical data collection prior to the granting of a marketing authorisations (i.e. studies to be undertaken after the end of phase II clinical trials) would facilitate and accelerate the HTA process after obtaining the marketing authorisations and ultimately lead to faster decisions regarding the adoption of new products.

Early dialogues are potentially beneficial to regulatory agencies and any entity active in the field of HTA.

The conduct of early dialogues for pharmaceutical products and medical devices was included as part of the objectives of the second EUnetHTA Joint Action (October 2012 – October 2015).

In April 2013, the European Commission (Executive Agency for Health and Consumers (EAHC)), launched a call for tender concerning pilots on early dialogues between health technology

assessors and healthcare products developers during the development phase of medicinal products and medical devices.

The proposal for the **SEED Consortium** (**Shaping European Early Dialogues for health technologies) [9]** was a response to this call and was selected by the European Commission to carry out the requirements of the tender.

SEED (Shaping European Early Dialogues for health technologies) was a project financed by the European Commission for a duration of 22 months (October 2013 – August 2015).

The objective was to reduce the risk of production of data that would be inadequate to support a company's future reimbursement request.

The project is funded by the European Union in the framework of the EU Health Programme 2008-2013.

The SEED consortium is composed of 14 European HTA bodies which are also partners in EUnetHTA Joint Action 2.

The SEED programme is coordinated by HAS (France), who is the leader of the consortium and maintains the consortium Secretariat [74].

Apart from the members of SEED, other HTA bodies, representatives of health professionals, patient organisations, payers or other stakeholders may be involved as well in the early dialogues with consent of all members of the consortium.

In addition to the 14 European HTA agencies who make up the SEED consortium, other organisations may be called upon to contribute to SEED or to participate in a particular early dialogue (EMA, regulatory bodies, payers, health professionals, patients' organisations, other HTA agencies (non-members of the SEED consortium)).

SEED aims to conduct pilots on early dialogues between its member HTA agencies and developers of health products (pharmaceuticals and medical devices) whose products are currently in the development stage.

As explained above, SEED is contracted by the EAHC. The aim is to conduct a total of ten early dialogues (7 on drugs and 3 on medical devices).

Three of the seven early dialogues on pharmaceuticals will be organised in parallel with the EMA.

In addition, SEED is entrusted to prepare methodological protocols and codes of conduct.

Finally, it is also intended that recommendations for a permanent model for conducting early dialogues will be defined.

Developers may request an early dialogue with representatives of HTA bodies to discuss the development of a new pharmaceutical (chemical entity or biological product) or a new non-drug technology (e.g. medical device, diagnostic, procedure).

Generics and biosimilars are out of the scope of the early dialogues.

The pilot dialogues to be performed by SEED will be building on the experience gained from the early dialogues conducted within EUnetHTA **(EUnetHTA JA2 WP7),** serving as a basis for the development of two draft methodological protocols for drug and medical devices early dialogues.

Early dialogues allow companies developing health products to meet with European HTA bodies to present their development plan for the product in question and to ask specific questions relative to their plan.

It focuses on development strategies and not on pre-assessment of data. The advice is prospective in nature and therefore advice on on-going pivotal trials is not be accepted.

Early dialogues can be requested during the initial clinical development phase of the technology. For drugs, it should ideally be requested during the phase II to discuss the content of the planned Phase III (i.e. planned confirmatory trial(s)) and the economic rationale.

Early dialogues are restricted to one indication. However, one or more lines of treatment may be discussed within this indication.

Questions should be related to HTA in view of reimbursement and pertaining mainly to relative effectiveness, economic aspects and other areas relevant for reimbursement.

The early dialogue process is organised around the submission of a dossier followed by a plenary discussion between the company developing the product and HTA bodies who are members the SEED consortium.

The scientific contents of the early dialogues will remain strictly confidential.

The SEED programme foresees two types of early dialogue procedure: one restricted to HTA bodies and another one where also EMA can be involved.

The early dialogue meeting is a one-day meeting dedicated to one early dialogue procedure.

It is organised and hosted by the coordinator HAS, except for EMA multi-HTA advice meetings that take place at EMA premises.

The advice is not binding either for HTA bodies or for the company and does not predetermine the outcome of the assessment performed later by the individual HTA agencies.

Follow-up advice meetings with HTA bodies are not foreseen in the framework of the SEED project.

The SEED should come up with recommendation to the European Commission for a permanent structure for early dialogues from HTA bodies after having consulted EUnetHTA.

In the EUnetHTA pilots all HTA bodies draft answers to the questions from the company. These are discussed between the countries. If different opinions remain, the countries explain the different positions to the company.

The future goal is that EMA, EUnetHTA and individual HTA bodies try to align their position on permanent infrastructure for parallel early dialogues.

Under the current procedure, an interested company should send an official letter of intent to the SEED coordinator (HAS) at least 4 months in advance of the anticipated date of the start of the procedure.

Template models for the submission of information have been developed to assist companies in the provision of details regarding the development of the product and the questions to be posed to HTA bodies/EMA.

This new phase of cooperation aims at sharing common visions, increasing synergies and decreasing fragmentation.

Briefing Book Template for Pharmaceuticals to Support a Multi-HTA Early Dialogue (ED) [75]

To illustrate the items on which the early dialogues are focused, the Briefing Book Template for pharmaceuticals is reproduced below:

1. Summary

1.1. Background information on the disease

1.1.1. Overview of the disease

Relevant epidemiological data, information on natural history of the disease and evolution on treatment should be discussed.

1.1.2. Treatment options

The company should list all technologies (drugs, devices, procedures) that present relevant alternatives for the treatment of the pathology (stage, line of treatment) together with their labelling status in Europe and North America. In the case of the existence of new treatments that are in advanced phases of development, this information should be included.

1.2. Background information on the product

1.2.1. Indication

The company is asked to specify clearly the intended indication (1st line, 2nd line, 3rd line of treatment; add-on or monotherapy) of the product in development, as well as the aim of treatment (preventive, curative, palliative, symptomatic, disease modifying…). The position of the product in the treatment algorithm should be proposed. The target population of the product should be described as precisely as possible.

1.2.2. Form, route of administration, dose, dosage

Route of administration and the pharmaceutical form of the product should be described. Dose, frequency of administration and the duration of use should be discussed based on the available evidence at the stage of development.

If the administration of the product is associated with the use of a diagnostic test, a medical device or with a medical procedure, this information should be stated and adequate information given on the associated test or device.

1.2.3. Characteristics of the product

Chemical/biological product; orphan product; advanced-therapy medicinal product.

1.2.4. Mechanism of action

Pharmaco-therapeutic group should be indicated. ATC code should be given if applicable.

The mechanism of action should be described as well as key information on pharmacodynamics and pharmacokinetics.

1.3. Status of the clinical development programme

This section should contain a summary of clinical development of the product and give a clear idea of the stage of development of the product. Evidence obtained in the field of the required indication should be mentioned. Existence of trials supporting the use of the product in other indications should be mentioned for completeness.

Non-clinical development programme will be summarised if adequate (on the case by case basis).

1.3.1. Clinical development up to date

Data on efficacy and safety coming from phase I (if relevant), phase II and phase III clinical trials that are completed or ongoing should be presented. For each trial the design, doses and duration of treatment, comparator, number of subjects and description of studied population, results of the trial (or preliminary results of ongoing trials if available) and all other important information should be given. Data and results may be summarized in tables. Detailed information should be available in study reports in annexes. Cross-links to annexes are recommended.

1.3.2. Planned trials

This section should provide a comprehensive overview of all planned trials with the product in the intended indication. For the trial that is to be the subject of the Early Dialogue, a rationale and a synopsis of the protocol should be provided. The synopsis should contain key information on objectives of the trial, trial design, patient population (inclusion and exclusion criteria), comparators, endpoints (primary, secondary etc.), flowchart, follow up, methods of analysis etc. All relevant systematic information should be given at a sufficient level of detail, together with justification for the choice made and a critical discussion of key issues.

1.4. Economic aspects

If the company desires to discuss economic assessment as a part of the early dialogue, then all relevant information about the planned economic analysis should be provided.

The company should state the scope of the planned economic analysis, clearly defining the research questions.

The company should describe the main aspects of the economic analysis, in particular the type of analysis, the perspective, the time horizon, the population and the comparator(s).

An outline of the structure of the model could be provided if available. Relevant published papers could be provided as annexes to the briefing book. Expected data sources and planned sensitivity analyses should be described. Trial endpoints used to derive the model health outcome should be stated where relevant. Tools used to measure resource utilization should be described.

1.5. Regulatory status of the product

Information should be given on the marketing authorisation status of the product in other indications in EU and North America. In case the product is on the market, its reimbursement status should be given. The company should indicate whether a scientific advice has been received from other national or European institutions and provide minutes or if it is planned at any further stage. Eventually, estimated timelines for market entry may be given if this information is available.

1.6. Rationale for seeking advice

The scope of the questions and the rationale for the advice request should be elaborated.

1.7. Discussion on added benefit

The company should provide arguments supporting the added benefit of the product in the target population in comparison with the standard of care and with a pharmacologically similar product aimed to be replaced (if adequate).

2. Questions and company's positions

The company should list all questions that will be discussed during the face-to-face meeting. Any subject pertaining to relative effectiveness, economic assessment or other aspects of the development can be addressed. **Both clinical and economic areas can be covered or just one of them according to the preferences of the company**. The wording of questions should be clear and concise. Open questions are not acceptable. Given the timeframe, a high number of questions (i.e. more than 10) is not feasible to be discussed during the meeting. Questions should be ordered by area of expertise.

Each question should be followed by a separate explanation of the company's position including a comprehensive justification of the chosen approach. Each position description should not be longer than 3 pages. Cross-references to the relevant parts of the briefing document or to annexes can be included if additional detail is needed to support the argument.

All scales and scores that will be used for endpoint measurement should be presented and their validity should be commented.

2.1. Clinical questions

There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

- population
- comparator
- trial design and duration
- endpoints to support reimbursement
- Statistical issues (stratification, subgroups etc.)

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Company's position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 1.3.2 Planned trial.

2.2. Economic questions (if applicable)

There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

- population
- choice of comparator

- choice of economic model
- data used to populate the model
- time horizon and extrapolation hypothesis
- Perspective (societal, healthcare related etc.)
- utility values
- resource utilisation data

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Company's position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 1.3.2 Planned trial.

3. References

This section should contain a list of all documents referenced in the text.

4. Annexes

Any of the following documents can be attached to the briefing book, if applicable:

Referenced articles in full text versions in English

Trial protocols, summaries and reports

Relevant clinical practice guidelines

Previous scientific advice received

Regulators Initiatives: Interface EMA-HTA

Regulators are leading numerous areas of collaboration to facilitate coordination and exchange of information with HTA bodies.

HTA bodies carry out their own assessments of medicines once they have received a marketing authorisation.

In contrast to the benefit/risk assessment carried out by Regulators, HTA bodies compare the **relative effectiveness** of medicines, in order to assess their usefulness to the healthcare system in their territory. Some HTA bodies also take the **financial cost** of medicines into account, in accordance with national legislation.

The European Medicines Agency has been working closely with health-technology-assessment (HTA) bodies since 2008.

Since 2010, the Agency has been working closely with EUnetHTA, a network of government-appointed organisations from European Union Member States, the European Economic Area and accession countries and a large number of relevant regional agencies and non-for-profit organisations that produce or contribute to HTA in Europe.

The initial focus of the collaboration was a project looking into how the **information on the benefits and risks of a medicine** contained in the European Public Assessment Report (EPAR) could better address the needs of HTA bodies.

Further dialogue between the Agency and EUnetHTA has led to other areas of interaction. EUnetHTA (representing the HTA framework) and EMA (representing the Regulatory framework) are working together on several topics including:

- Provision of advice on development plans for medicines from both Regulators and HTA bodies.
- Provision of mutual input on methodological and disease-specific guidelines, evidence requirements and publication of data relevant for orphan-designated medicines.
- Collaboration on study registries.

EMA and EUnetHTA have held regular meetings, approximately twice a year since February 2010.

EMA-HTA Parallel Scientific Advice

From the side of Regulators, the European Medicines Agency (EMA) fostered the initiation of the pilot program for parallel scientific advice with HTA bodies.

The Agency offers scientific advice and protocol assistance in parallel with HTA bodies. The aim of this initiative is to allow medicine developers to gain feedback from regulators and HTA bodies at the same time, early in the development of a medicine.

This helps industry to establish the evidence that both parties will need to determine a medicine's benefit/risk balance and value.

The pilot for parallel scientific advice was launched in July 2010, covering indications such as diabetes, heart failure, lung cancer, breast cancer, pancreatic cancer, melanoma, mesothelioma, asthma, rheumatoid arthritis, multiresistant infections, food allergies, diabetic gastroparesis, Alzheimer's disease, depression, osteoporosis and three rare conditions.

This pilot main goal was to allow sponsors to obtain guidance from Regulators and HTA bodies at the same time, early in the development of a medicine to help them understand the evidence that both parties will need to determine a medicine's benefit/risk balance and value.

This program has now become a recognized initiative under the auspices of the European Commission.

Acting in its role of main European forum of discussion, bringing together Regulators and stakeholders from industry as well as from health care professionals and patients associations, EMA has also fostered workshops in relation to the EMA-HTA parallel scientific advice program with industry.

A joint EMA-HTA workshop on parallel scientific advice was held on 26 November 2013. Following the workshop, and based on the experience gained by all stakeholders, draft best practice guidance for EMA-HTA parallel scientific advice was developed and published for public consultation in May 2014. [76]

These workshop sessions are important to raise awareness and promote early dialogue and interactions among industry, regulators and HTA bodies. Also, they are meant to increase the level of participation in future collaborative programs.

The key goal of all these interactions is to understand clearly the regulatory and HTA requirements and define the scientific aspects behind the requirements. The ultimate objective is to try to establish regulatory processes that will allow dialogue between these two areas and industry in a standardized manner and at the right time during the development of a new drug.

It has been acknowledged by all stakeholders that clear guidance is necessary in order to make a rationale use of resources and this can only be achieved by a cooperative dialogue and work between Authorities and industry.

The EMA-HTA Parallel Scientific Advice procedural guidance details the timelines and actions whereby applicants can seek simultaneous feedback from Regulators and HTA bodies on their development plans. It also contains a Briefing Document Template to help companies outline the questions and rationales they want to present.

Improvement of EPARs and SmPC Documents

In October 2008, the Pharmaceutical Forum, a high-level ministerial platform for discussion between member states, EU institutions, industry, health care professionals, patients, and insurance funds, agreed on conclusions and recommendation to ensure the sustainability of the national health care systems and at the same time guarantee the competitiveness of the industry.

One of these recommendations provided a political mandate to initiate a collaboration between the EMA and EUnetHTA to improve the availability and best use of data relevant for HTA.

As a response to the recommendations from the Pharmaceutical Forum in 2008, the EMA and the EUnetHTA initiated a collaboration with the purpose to improve the contribution that the European Public Assessment Reports (EPARs) issued by the EMA can make to the **assessment of relative (comparative) effectiveness** of medicinal products, a key area for HTA bodies.

The European Medicines Agency publishes an EPAR for every medicinal product authorised through the centralised procedure in the European Union. The EPARs reflect the scientific conclusions reached by the Agency's Committee for Medicinal Products for Human Use (CHMP) at the end of the evaluation process, after deletion of commercially confidential information.

This collaboration started in February 2010 and was performed over 2 years. EUnetHTA and EMA worked together in the analysis and revision of the EPAR templates, identifying areas of improvement [77].

The scientific evidence generated during the development programme of a medicinal product can be used to estimate the benefit/risk ratio of the product (Regulatory approval) or to estimate the effectiveness of the new product as compared with existing therapies (HTA process to support decision making on price and reimbursement).

The HTA criteria can vary between countries as there are regional factors to be taken into account, but generally HTA bodies in Europe perform a relative effectiveness assessment (REA), as part of the HTA process.

The intention of the project was to make EPARs a useful tool and source of information for the preparation of REAs by HTA bodies.

As a result of the collaboration project, the templates prepared by the EMA for the writing of EPARs were revised to address better the need of information of HTA bodies.

Among other amendments of the templates, a new section was created in the "Discussion on clinical efficacy" of the assessment report, called "Design and Conduct of clinical studies".

Here, a critical discussion should be included to address the adequacy of the design of the study, the selection of the patients' population, the comparator and the choice of end points and duration of the study.

The key information needs identified led to the explicit inclusion in the EPARs of information regarding the:

- Standard treatment in the EU.

- Reasoning of the CHMP behind the final conclusions with regard to choice of comparators, endpoints and shortcomings of the data.

- Clear summary table indicating an overview of the main efficacy data from the pivotal studies.

The aspects of patient population that are crucial from a regulatory perspective are of relevance for HTA assessments and should be clearly stated not only in the EPAR but also in the approved SmPC (Summary of Product Characteristics).

In this respect, the European Medicines Agency is also developing general principles on the wording that drug makers may apply to indicate in which populations their drugs can be used. This is when to go broader or narrower in indication wording.

The indication wording initiative is being carried out by the EMA's scientific committee, the CHMP. The initiative is expected to continue throughout 2015 and potentially beyond.

The indication wording initiative will particularly focus on when the population may be broader or narrower compared to the study population investigated in the clinical trials supporting the marketing authorization application for the drug.

As well as being of relevance to drug sponsors, the initiative is also important to health technology assessment (HTA) bodies, as aspects of patient population that are important from a regulatory perspective are also of relevance for HTA assessments.

The EMA states that there are two key elements in indication wording – the study population (i.e. inclusion criteria, representativeness), and benefit/risk assessment (i.e. effect size, uncertainties, concerns in subpopulations, pharmacogenomics considerations, knowledge of mechanism of action).

Other elements can also be taken into account like factors related to disease characterization, predictability of biomarkers, etc.

The EMA discussed the indication wording initiative at a meeting with representatives from the EU Health Technology Assessment Network (EUnetHTA) in May 2015.

At the meeting, the HTA bodies underlined the important role played by the indication wording displayed on an approved drug label during the relative effectiveness evaluation of the product.

HTA bodies said that clarity is needed not only where the patient population covered by the approved indication is narrower compared to the study population, but also in cases where a "broader indication" is approved compared to the study population.

The HTA bodies said that based on the approved label and the trial data, it is important to have clarity as to why a certain indication was approved. HTA bodies want to understand why the Regulators came to a certain decision.

BENEFIT/RISK Methodologies for Regulators and Assessment Methodologies for HTA Bodies including EMA'S Effect Table

EMA benefit/risk project is being run through five Working Parties at EMA.

The main aim of the project is to improve transparency, communication and consistency of benefit/risk assessments.

EMA carried out a research project on this topic and based on this research, for which reports are available on the EMA website, **an Effect table was proposed (qualitative method) that should summarise the key issues that should be discussed for the benefit risk decision of a medicinal product.**

The Effects table was piloted with the CHMP that gave an overall positive feedback.

The effects table is designed to summarize the EMA's decision regarding the benefits and risks of a drug so that the rationale for such decisions can be communicated easily and transparently both within the regulatory system and to the public.

The EMA and the HTA bodies exchanged views and experience with the aim of determining how the EPAR could make a better contribution to the assessment of relative effectiveness

It was noted by HTA organisations that it would be helpful to have information on the precision of effect estimates in the table.

Work Package 5 of EUnetHTA Joint Actions on rapid relative effectiveness assessments, includes information from the first four domains of the HTA Core Model.

It has been acknowledged that there is no consensus at the moment on a method to quantify the benefit/risk balance. Therefore the clear presentation of data in an effects table that includes information on intervention vs comparator, the effect size of the mean outcomes and uncertainty of the evidence is regarded as very useful.

In February, 2015, the EMA's main scientific committee for human drugs, the CHMP, started including the effects table in its assessment reports at the time of its opinion on a drug and in its European public assessment reports (EPARs).

The introduction of the effects table into the routine work of the CHMP in February followed the successful completion of two pilot programs in 2103 and 2014.

This involved the construction of an effects table by the assessment teams during the evaluation procedures; collecting feedback on the difficulties in doing this and ways of improving the tables; and finally development and publication of guidance about the effects table**, which was ultimately included in the EMA Day 80 assessment report templates and guidance documents [78].**

The effects table is being included in the assessment reports of all applications for initial marketing authorization and extension of indications that have been submitted to EMA from February 2015 onwards, with the exception of generic applications.

It is to be noted that the effects table is envisaged mainly as a communication tool for the relevant stakeholders, not a as a tool to evaluate benefit/risk as such. The purpose is to provide a clear summary of the key benefit and risks elements considered during the evaluation and that are more deeply discussed in the different sections of the CHMP Assessment Report/EPAR.

The effects table summarizes the key benefits and risks of a drug by presenting a compact and consistent display of the data and uncertainties that were drivers of the CHMP's decision. See the first published EPAR containing the effects table [79].

The effects table requires that the key benefits and risks (i.e., the key "effects") are clearly identified; that the size of the effect and the statistical uncertainty are clearly described (e.g. point estimate, confidence interval); and that any other sources of uncertainty or strength of evidence are also described (e.g., multiple coherent studies, conflicting observations).

The EMA and representatives of the EU Network of HTA bodies, EUnetHTA, have agreed to revisit their experience with the effects table in May 2016.

Role of Regulators in the new Area of Adaptative Pathways

The adaptive pathways initiative (formerly known as 'adaptive licensing') is a project launched by the European Medicines Agency to try to improve timely access for patients to new medicines that are intended for serious conditions with unmet medical needs.

The adaptative pathway approach is sometimes referred to as staggered approval, progressive licensing, Medicines Adaptative Pathways (MAPs) or Medicines Adaptative Pathways to Patients (MAPPs) [80].

It is a prospectively planned process that foresees iterative phases of evidence gathering and progressive licensing adaptations of a medicinal product in two main situations:

1) An **initial approval in a well-defined patient subgroup with a high medical need** and subsequent widening of the indication to a larger patient population, this means, beginning in a restricted patient population.

2) An **early regulatory approval** (e.g. conditional approval) **possibly on the basis of surrogate endpoints** which is prospectively planned, and where **uncertainty is reduced** through the collection of **post-approval data** on the medicine's use in patients in relation to safety and efficacy. This means, refining the knowledge on the benefits and risks of the medicine during the post-authorisation phase.

The advantage of this approach is that a sponsor has the possibility to get approval and reimbursement for its medicinal product earlier and then provide further information post-approval on the benefits and risks of the medicinal product.

This approach is especially relevant for those medicinal products indicated to treat serious conditions with an unmet medical need, as it has the potential to reduce the time for approval and reimbursement and therefore reach patients much earlier than under regular procedures.

It is important to observe, that in the current EU legislation, there are already regulatory tools in place that can be used for the adaptative pathways approach.

The main ones are the following:

- The Parallel Scientific Advice (allows a sponsor a discussion with Regulators and HTA bodies on the development plans of a new drug during the early phases of development).

- The Conditional Approval Marketing Authorisation.

- The Compassionate Use.

- Patient registries and pharmacovigilance tools that allow collection of real-life data and development of the risk-management plan.

With the adaptative pathways project, EMA intends to promote early discussion among the different stakeholders involved (Regulators, HTA bodies, industry, healthcare professionals and patients' organisations, payers, researchers, etc.) to understand better the needs of each sector and propose areas for improvement that can ultimately lead to more efficient and quicker development of new promising treatments.

The interaction between Regulators and HTA bodies is crucial in this respect.

As the project progresses, and feedback is consolidated, the EC intends to examine the legal and policy aspects related to adaptive licensing, in collaboration with the EU Member States and in consultation with relevant stakeholders, as appropriate.

The regulatory pharmaceutical committee of the EC has started a reflection process on safe and timely access to medicines for patients **(STAMP)** to examine the "adaptive pathways approach" with Member States' experts.

EMA will be associated and the HTA Network will be kept informed.

EMA will provide input to the **Safe and Timely Access of Medicines to Patients expert group (STAMP) of the Pharmaceutical Committee of the EC** on the lessons learned from the case studies analysed.

The objective is to find optimized ways to combine the regulatory framework with timely access to medicines.

Pilot project

In March 2014, the EMA began inviting companies to participate in a pilot project on adaptive pathways to explore with real medicines development programmes how adaptative approaches could be implemented.

EMA changed the name of its pilot project from adaptive licensing to adaptive pathways to better reflect the idea of a life-span continuum approach from development to licensing, reimbursement and further monitoring.

The main goal of the pilot is to use concrete examples (i.e. development cases submitted by pharmaceutical companies) for an informal, non-binding early dialogue among all stakeholders and ultimately propose areas of improvement to support development of innovative medicinal products by industry.

The dialogue is confidential in nature and should in any case not be understood as a pre-assessment of the suitability of the data that are already available for an early approval. It is a discussion and exploration of the prospective development plans.

The discussions carried out in the framework of this project are not intended to replace the Scientific Advice / Protocol Assistance procedures. These are the indicated procedures for detailed discussions concerning regulatory standards and results for a medicine development program. It is also different from the EMA-HTA Parallel Scientific Advice.

The Pilot represents an opportunity for enhanced and prospective interaction with Regulators and other downstream stakeholders (HTA, patients) prior to formal regulatory interaction steps.

To qualify for the Pilot, candidate medicinal products should fulfil certain key criteria to participate in the adaptive pathways project:

- The drug is indicated for an unmet clinical need.

*- The drug should be under an **ongoing medicine-development** programme, to allow for prospective discussions on the future development plans and **prior to the initiation of confirmatory studies.***

*- Present an **iterative development plan** (i.e. either by gradual expansion of the target population (e.g. starting from a population with a high medical need or by progressive reduction of uncertainty after initial authorisation, based on surrogate endpoints).*

*- Present a plan for the monitoring of the drug in the post-approval phase (i.e. collection and use of **real-world post-authorisation data** as a complement to randomised clinical trial data).*

- Present a set of items and questions for dialogue between Regulators, HTA bodies and other relevant stakeholders.

In addition, in the information package, the sponsor of the medicine should state the following points:

. The indication of the medicine should address an unmet medical need and the clinical evidence intended to support a positive benefit/risk balance in the defined (sub)-population at the time of initial marketing authorisation.

As of December 2014, EMA had received and assessed 34 applications. Of the 34 received proposals, 6 concerned Advance Therapy Medicinal Products (ATMPS), 12 concerned orphan products, 11 came from Small and Medium Size Enterprises (SME) and 14 concerned anticancer medicinal products. Ten were selected for discussion with the applicant.

As a procedural support for the Pilot, EMA prepared a standardized template submission form to assist companies in addressing and commenting on the areas to be explored during the Pilot and the potential challenges.

These key aspects contained in the EMA submission form are reflected here as follows:

Template:

- Does the drug hold sufficient promise to address an unmet need (e.g. based on convincing mode of action, impressive preliminary animal/human data)?

- Initial indication sought.

-What evidence would support a positive benefit/risk in the defined (sub-) population at the time of initial licensing, including surrogacy of early, pharmacodynamics endpoints?

-Please comment on the compatibility with the current regulatory framework for full marketing authorisation (MA), Conditional MA or MA under Exceptional Circumstances.

-Please comment on what is the risk of failing to identify an important adverse effect based on early phase clinical trial data?

- Indication(s) subsequently sought (e.g. expansion to new indication/different subpopulation/different endpoints, or confirmation of efficacy in initial population). Highlight the possibility of iterative discussions along the progress of development.

-*What possibility there is to draw inferences from observational (non-RCT) data that are sufficiently reliable to support decision-making for regulators, payers and prescribers? Please give details on how you plan to gather Real World Data and use them to support expansion of the labelling. This is important for a good discussion in the framework of Adaptive Licensing.*

-What assurance of commitment from sponsor will there be to conduct further studies after the initial marketing authorisation. What is the feasibility of any required follow-on randomised clinical trials (RCTs) after initial Marketing Authorisation ('loss of equipoise'; lack of willingness of patients to enrol in RCT);

- What is the level of confidence that definition and control of the population through regulatory tools will be achieved (e.g. registries, PASS, PAES, conditional approval…). Please

elaborate on how this will be implemented (e.g. adequate infrastructure for registry or e-health records).

- Plan for the regulatory processes involved in drug licensing. Plan for the involvement of relevant stakeholders (HTAs, ethical committees, patients, organisations issuing clinical treatment guidelines…).

- Level of confidence that prescriber behaviour will be as anticipated (risk of large share of off-label use, can this be mitigated by collaboration with payers?).

It has to be noted that to some extent, this sort of pathway already exists in the EU pharmaceutical legislation. The Conditional Marketing Authorization (CMA) was envisaged to facilitate earlier patient access to important new medicines – Commission Regulation Nº 507/2006.

In addition, also tools like the PAES and PASS frameworks are under development.

Nevertheless, these tools prove to be not sufficient since certain strict criteria must be fulfilled in order to follow the CMA approval pathway.

In order to extend the scope of applicability of the CMA model, industry stakeholders would wish to redefine the terms of "unmet need" and "major therapeutic advantage". That would for instance allow such a model to be used for products intended to treat clearly defined groups of patients based on their genotype.

Secondly, reimbursement policies would also need to accept the need for targeted patient access and create a framework for flexible pricing and reimbursement based on evolving evidence.

And a clear alignment and agreement on what evidence will be required to bring a medicine to the market and what will be required post-launch (progressive development for a progressive licensing and a progressive reimbursement). That means, a drug regulation approach where the license is updated along with the maturity of the evidence available.

The granting of an early access needs to be accompanied by the acceptance of HTA stakeholder of the elements that allowed such early regulatory access and especially agreement on the design of data collection after the initial marketing authorization.

It is recognized by all stakeholders that unless the idea of revising decisions along the path of development is shared by different decision makers, it will be difficult to move forward.

This also involves wider inclusion of stakeholders (such as patients).

HTA bodies consider that the adaptative licensing approach might not be viable for all pharmaceuticals (e.g. large patient populations or high probability of off-label use) but more suitable for situations like new compounds or in the case of drugs with no other pharmacological alternatives, high unmet needs, severe diseases, small populations, among others.

In addition, it is perceived that the current experience from gathering data after decision making (coverage with evidence development) are not very promising.

Moreover, other aspects such as political willingness to revise decisions is for example a real-life hurdle.

The HTA bodies also support the idea that more uncertainty in the data could lead to a lower price and vice versa. Payers might be very reluctant to pay at all for a product with increased uncertainty. It is also questioned if adaptive licensing should lead to earlier licensing.

Participation in EMA pilots is at the discretion of individual HTA bodies.

Public Access to Full Study Reports

Under the procedural frameworks of the last years, it was difficult for HTA bodies to receive information produced by EMA (i.e. regulatory assessment reports), as input for their appraisals, as it was up to companies to share this information.

The problem could have been due to the fact that companies were not aware of this possibility where sponsors can inform HTA agencies during the CHMP process on a voluntary basis.

Insight in the CHMP agenda for timing purposes is a need for HTA bodies. Since EMA CHMP agendas have recently become publicly available, this point is now solved. This facilitates HTA organisations to have a quicker insight on the timing of final opinions of the CHMP.

Another request from HTA bodies to the European Commission in the framework of the interactions with Regulators, was the option to have access to CHMP information between CHMP opinion and EC decision.

In view of these identified needs, the European Medicines Agency decided to start sharing its regulatory assessment reports for drugs directly with individual health technology assessment bodies in the EU to support rapid relative effectiveness assessments (REAs) of drugs and it is working currently with the European Commission to address any legal issues that may prevent it from doing so.

This initiative raised in the context of pilots on rapid REAs which are being carried out by EUnetHTA.

EUnetHTA request was for EMA to provide individual HTA bodies with regulatory assessment reports at the time when the Agency's drug evaluation committee, the CHMP, issues its opinion (i.e. before the European Commission's decision on marketing authorization).

EMA publishes European public assessment reports (EPARs) for drugs after the Commission's decision on marketing authorization, which HTA bodies can look at.

The information on benefit/risk evaluation within the clinical section of the regulatory assessment report is particularly helpful for HTA bodies carrying out REAs.

The EMA clarified that its direct support for rapid REAs should be seen as a "transitional measure" to facilitate progress with EUnetHTA's Joint Action work program (JA2 WP5) pilots on rapid REAs.

This matter was highlighted at a joint meeting of EMA and EUnetHTA representatives in May 2015. As soon as the legal framework is agreed, the EMA will seek further information on the legal status of specific HTA organizations to establish whether they have the legal authority/capability (according to their founding act) to conclude/enter into agreements with the EMA for this sharing of information.

Other EMA-HTA Initiatives

Preparation of Disease Specific Guidelines

The objective is to set agreed criteria regarding the elements that have to be studied for drugs developed for determined therapeutic areas. EMA has the objective to prepare guidelines where HTA bodies can comment and provide feedback.

In addition, EUnetHTA members have the possibility to be directly involved in the drafting of the EMA guidelines.

EUnetHTA will also involve EMA in its work on disease specific guidelines.

EMA to Compare "Significant Benefit" Criterion for Orphan Drugs with HTA

The European Medicines Agency will be comparing whether the criterion it uses to evaluate whether an orphan drug has a significant benefit over existing treatments is lower or different to that used by HTA bodies in the EU [81] [82] [83] [84].

The comparison is being conducted in light of discussions between the EMA and representatives of the EU network of HTA bodies, EUnetHTA, which focused on the framework for orphan designation and, in particular, the significant benefit criterion at the time of marketing authorization.

EMA's orphan drugs committee (COMP) can use "major contribution to patient care" or "ease of use" as a criterion to support significant benefit and maintain the orphan status of a drug at the time of marketing authorization.

In the case of HTA bodies, however, the "ease of use" criterion is only used exceptionally and would normally require a demonstration of improved effectiveness as a result of the "ease of use".

In view of this, EMA has decided to develop further understanding regarding the similarities and differences between the regulatory significant benefit assessment and the joint REAs in terms of objective and content by performing a scientific comparison based on real-life examples of orphan drug assessments.

The EMA's scientific comparison exercise comes at a time when the European Commission is planning to review the criteria for showing that a new orphan drug product has a "significant benefit" over existing treatments.

The review is to result in the Commission updating its 2003 Communication on orphan drugs, which outlines the criteria and procedures for orphan drug designation, as well as the EU marketing authorization and market exclusivity.

The update is scheduled for the first quarter of 2016.

EMA work on New Scheme to support Drugs for Unmet Needs

The European Medicines Agency is developing a new scheme to provide better procedural support to drug sponsors that are developing drugs that have the potential to address unmet needs.

The scheme is expected to be finalized and launched at the end of 2015.

The scheme will aim to reinforce scientific and regulatory support to optimise development and enable accelerated assessment of new medicines addressing major public health needs.

The specific details for the scheme including eligibility criteria, possible procedures as well as incentives to be offered by the scheme are still under discussion.

The EMA explained the scheme at a meeting with representatives from EUnetHTA in its May 2015 meeting. At the meeting, it was pointed out that HTA bodies should also have an important role in the development of such a scheme.

United Kingdom Early Access Scheme

UK's government early access to medicines scheme (EAMS) brings a new designation which is called Promising Innovative Medicine (PIM). [85]

Under this scheme, severely ill patients with life-threatening and seriously debilitating conditions could gain access to innovative drugs under the National Health Service in England before they would normally be available, on the basis of a benefit/risk opinion from the Medicines and Healthcare Products Regulatory Agency (MHRA).

The merits of the PIM status are somehow similar to the US Breakthrough Therapy designation.

For the UK government, this is a way to facilitate an accelerated development of innovative highly needed drugs.

The scheme would be divided into 3 phases:

Stage I: PIM designation, based on early clinical data.

PIM status is open to new biological and chemical entities as well as for approved drugs in new indications. The conditions must be life-threatening or seriously debilitating, and either there must be no treatment available for that condition, or the available options are unsatisfactory.

A drug with PIM status can use the MHRA scientific advice services and the MHRA-NICE parallel scientific advice.

Stage II: Early access scientific opinion. The MHRA would issue a benefit/risk opinion, which would allow patients getting access to the drug (outside clinical trials) much earlier than normally. This opinion would be delivered on the basis of Phase II results, rather than Phase III results. If the data on quality, safety and efficacy are compelling, the opinion would be positive

and the prescribers informed. The medicinal product would be provided free of charge by the company until a centralised EU MA is granted.

Stage III:

Licensing and rapid commissioning. If the product is licensed for marketing, it will go through a standard NICE appraisal for routine NHS use on the basis of the evidence collected under the scheme and will be commissioned by NHS England through the specialised commissioning arrangements.

CHAPTER 5: Study of the Differences in the Scope and Focus of the Regulatory and HTA Evaluations: Kalydeco and Yervoy

Introduction

As explained in previous Chapters of this study, the scope and therefore the focus of the regulatory process for the authorization of medicines and the reimbursement and financing evaluations are different.

Regulators focus on the benefit/risk balance of a medicinal product and assess the quality, safety and efficacy based on the own merits of the drug in a clinical setting.

HTA bodies, also evaluate the added value of the medicine for the system. That is, the relative cost-effectiveness of the drug when compared to other available treatments. Real world data (i.e. performance of the drug in a clinical practice setting) is needed to assess the effectiveness and therefore the added value.

Both frameworks also have to deal with a certain degree of uncertainty, a challenge common to both Regulators and HTA bodies. There are different tools to try to mitigate the effects on this uncertainty in the decision-making process (i.e. PASS, PAES, Registries, etc.).

The degree of uncertainty accepted by each of the two frameworks is not necessarily the same.

The hypothesis of this study aimed at demonstrating that even in the presence of a harmonized positive opinion at EU level (i.e. EMA opinion followed by an EC decision), the factors influencing the financing decisions can still profoundly vary among the Member States due not only to economic factors but also due to methodological approaches.

The objective of this study was on the one hand to identify the elements that Regulators and HTA bodies take into account when performing their respective evaluations. And on the other hand to identify the origin of the divergent opinions among HTA bodies when confronted with the same clinical evidence.

The scope of this study will take as examples the evaluations of two centrally authorized medicinal products: Kalydeco which is indicated for cystic fibrosis and Yervoy which is indicated for melanoma.

For this study research, these two medicinal products (Kalydeco and Yervoy) were chosen due to its specific characteristics: given the indications for which they are intended (i.e. life-threatening diseases), with no equivalent pharmacological option, they offered an optimal setting for the analysis of regulatory and HTA decision elements.

Moreover, the fact that one is intended for a chronic life-threatening disease (Kalydeco) and the other for a terminal disease (Yervoy) also offered the opportunity to investigate the impact that long-term financing and budget considerations might exert on the decision making process of HTA bodies.

The new EPAR template model, including relevant elements to facilitate HTA appraisals, was introduced in November 2010. Therefore, the EPARs for Kalydeco and Yervoy, both have it incorporated.

In order to perform this research, a model for the study of the differences between the regulatory and HTA evaluations was designed.

The design of this model is described in detail below.

Model for the Study of the Differences in the Scope and Focus between the Regulatory and HTA Evaluations

DESIGN OF THE MODEL

The model was designed with the objective to enable the study of the elements that Regulators and HTA bodies take into account when performing their respective evaluations, directed to grant a marketing authorisation in the case of Regulators or to provide recommendations / decisions for financing and reimbursement in the case of HTA bodies. And also identify the origin of the divergent opinions among HTA bodies when confronted with the same clinical evidence.

This model is to be applied to the study of each individual medicinal product selected.

THE SCHEME OF THE MODEL DESIGN IS THE FOLLOWING:

- Introduction of the drug and disease of the indication
- Methodology
- Results
- Discussion
- Conclusion

INTRODUCTION OF THE DRUG AND DISEASE OF THE INDICATION

As an introduction to the analysis of each medicinal product selected, a brief description of the drug and the disease for which it is indicated is provided together with an indication of the alternative available therapies for the disease.

METHODOLOGY

Sources of Information

The following sources of information were used in the study:

- **Regulatory documents:** European Public Assessment Reports (EPARs) published by the European Medicines Agency (EMA) for the selected medicinal product.
- **Health Technology Assessment documents:** Reports publicly available in English, Spanish and German from EU HTA bodies for the selected medicinal product.

Conduct of the Research

Selection of the Elements of the Study[3]:

- The HTA Core Model Table developed by EUnetHTA was taken as the basis of the agreed methodology among EU HTA bodies[4].
- The main elements of a clinical study design.
- Key elements considered as pre-approval clinical evidence.

[3] The elements of the study were selected based on the Core Model developed by EUnetHTA, the SEED Briefing Book Guidance and the Assessment reports templates published by EMA (including the Effects Table for the evaluation of the Benefit/Risk developed by the CHMP in consultation with HTA bodies),

Day 80 assessment report templates and guidance documents, site accessed 21 July 2015, www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000337.jsp&mid=WC0b01ac0580022719#section1

[4] The HTA Core Model consists of 9 areas which represent the HTA elements to be considered for a HTA evaluation. Details are provided in Chapter 2.

Analysis:

For each of the selected medicinal products, a comparative analysis of the elements contained in the European Public Assessment Report (EPAR) and the elements contained in the HTA reports was undertaken following the 3 steps scheme described below:

1) Analysis following the HTA Core Model developed by EUnetHTA to determine the domains common to the regulatory and HTA fields. **Table A: EUnetHTA Core Model.**

2) Analysis of the study design elements which are key to accept the clinical evidence presented and which are also recognized areas frequently source of discrepancies between Regulators and HTA bodies (i.e. comparators, study population and endpoints). **Table B: Clinical Study Design.**

3) Analysis of the clinical evidence elements available pre-approval. The items considered were the benefit/risk balance, post-approval studies, degree of uncertainty and clinical added value. Study of the similarities and differences in the opinions among HTA bodies in view of the same clinical evidence which is taken from the EPAR published by the EMA. **Table C: Clinical evidence pre-approval**.

A set of Key Questions was also developed to facilitate the analysis and discussion of the results.

Figure 7. Table A: EUnetHTA Core Model

ELEMENTS	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for Pricing and Reimbursement?*
HEALTH PROBLEM AND CURRENT USE	Applicable	Applicable
DESCRIPTION AND TECHNICAL CHARACTERISTICS	Applicable	Applicable
SAFETY	Applicable	Applicable
CLINICAL EFFECTIVENESS	Not necessary for the establishment of the benefit/risk balance but could be present.	Applicable
COSTS AND ECONOMIC EVALUATION	Not applicable	Applicable
ETHICAL ANALYSIS	Not applicable	Applicable
ORGANIZATIONAL ASPECTS	Certain elements may be discussed (e.g. prescription type, prior diagnostic required, etc.)	Applicable
SOCIAL ASPECTS	Not applicable	Applicable
LEGAL ASPECTS	Not applicable	Applicable

Figure 8. Table B: Clinical Study Design

ELEMENTS	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for Pricing and Reimbursement?*
COMPARATORS **Placebo vs. Active**	PLACEBO (if ethical and feasible is preferred to measure "absolute effects"). A non-inferiority analysis (i.e. Against placebo) can be used. Sometimes Head to Head comparisons (direct comparison) are required. If an active comparator is used, then relative efficacy can be measured. Control of "false positive" errors through direct comparisons is important.	Feedback from clinicians. Identification of established management practice (like Standard of Care (SOC) therapy). Use of active comparator if feasible (mix direct/indirect comparison). Considerations of off-label use.
STUDY POPULATION **Homogeneous vs. Heterogeneous**	INTERNAL VALIDITY Balance internal (homogeneous: inclusion criteria) vs. external (heterogeneous)).	EXTERNAL VALIDITY Feedback from clinicians. Representative of patient population in target countries (heterogeneous). Prospective identification of biologically plausible subgroups. An increase in the heterogeneity improves the external validity.
ENDPOINTS (Primary clinical endpoints, PROs, QoL, Duration of Life, etc.).	Regulators are less familiar with PROs and QoL endpoints. PROs should be fully validated to be accepted by Regulators. Methodology and statistical power is very important (PIVOTAL TRIAL to	Feedback from patients: Use of measures important for patients, QoL/duration of life. Frequency of measurement is of relevance. Patient's relevant clinical endpoints to the main characteristics of the disease/condition treated. Proof of surrogate-final outcome relationship =

	measure efficacy: controlled RCT). Consistency of the effect sought.	long-term (lifetime) benefit. Longer trials to see patient's compliance. HTA less concerned about methodology and statistics

Figure 9. Table C: Clinical Evidence Pre-Approval

ELEMENTS	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for Pricing and Reimbursement?*
POSITIVE BENEFIT/RISK BALANCE (Quality, Safety and Efficacy): The 3 basic guarantees	Key factor. Pre-authorisation data based on conducted PIVOTAL clinical trials. Assessment is done based on its own merits to demonstrate therapeutic value.	Taken from regulators assessment: **Efficacy: Does it work?**
POST-APPROVAL STUDIES (Generation of additional evidence: PASS, PAES, Registries).	Required to confirm suitability of the endpoints used for clinical benefit / required to confirm safety.	Normally required: **Effectiveness data** ("real world") and not only efficacy (clinical trials). AND **Relative-cost effectiveness.**
DEGREE OF UNCERTAINTY ACCEPTED	Applicable	Applicable
CLINICAL ADDED VALUE (Relative Cost-Effectiveness): The 4th guarantee.	Economic considerations are out of the scope. Clinical added value can be part of the assessment but without entering into economic elements.	Key for HTA. Real world = effectiveness and comparative (relative) effectiveness if other available treatments. Required in order to ascertain the value for money, cost of opportunity and national budgets. Two additional questions to be answered: **Effectiveness: Does it work in clinical practice?** **Efficiency: Does it help with more efficient use of resources?**

SET OF KEY QUESTIONS FOR THE COMPARATIVE ANALYSIS

EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

(Analyses of the key questions for the EPAR)

- IS THE INFORMATION CONTAINED IN THE EPAR USEFUL FOR THE HTA APPRAISAL?

  (E.g. Sections indicating clearly if information on comparators is available).

- WHAT WERE THE KEY ELEMENTS FOR THE DECISION ON THE CLINICAL BENEFIT FOR REGULATORS?

  (E.g. Element for clinical outcome (e.g. reduction of symptoms, social element (ability to work) / subsets of population?).

- WHAT EVIDENCE WAS TAKEN AS A CONCLUSION FOR THE DECISION-MAKING?

- WHAT UNCERTAINTY WAS TOLERATED? HOW WAS IT PROPOSED TO BE MITIGATED?

- POST-AUTHORISATION COMMITMENTS? OR PRE-LAUNCH EFFECTIVENESS RESEARCH?

HEALTH TECHNOLOGY ASSESSMENT (HTA) REPORT

(Analyses of the key questions for each HTA report)

- WHAT WERE THE KEY ELEMENTS FOR THE DECISION ON THE CLINICAL BENEFIT FOR HTA BODIES?

  (E.g. Element for clinical outcome (e.g. reduction of symptoms, social element (ability to work) / subsets of population?).

  Cost-effectiveness (what was taken as cost? What was taken as effective? / Cost-utility / QALY caps / price of the medicine in the national market.

- WHAT EVIDENCE WAS TAKEN AS A CONCLUSION FOR THE DECISION-MAKING?

  HTA positive but under certain conditions for reimbursement?

  Which studies influence pricing and reimbursement? What was interpreted as uncertain about the data for evidence of effectiveness? Was this a reason for divergence between Regulators and HTA evaluations?

  Surrogate endpoints accepted? Benefit/risk balance accepted?

- WHAT UNCERTAINTY WAS TOLERATED? HOW WAS IT PROPOSED TO BE MITIGATED?

- POST-AUTHORISATION COMMITMENTS? OR PRE-LAUNCH EFFECTIVENESS RESEARCH?

- WERE PATIENTS OPINIONS TAKEN INTO ACCOUNT TO ASCERTAIN THE IMPORTANCE OF SURROGATES THAT MEASURE QoL?

RESULTS

In this section, the tables A, B and C described under the Analysis section are reflected contain a summary of the information present in the EPAR and HTA reports. The analyses is to be done for each selected medicinal product.

The following terminology is used when reporting the results in the tables:

D (element discussed in the report (i.e. EPAR/HTA)); ND (element not discussed in the report (i.e. EPAR/HTA)); NA (not applicable to the evaluation).

DISCUSSION

This section will contain a discussion analysis of the information reflected in the EPARs and HTA reports.

The discussion will focus on the elements extracted in the summary tables together with the provision of responses to the set of key questions identified for the analysis.

Special emphasis is made to the design of the clinical study (comparators, population and endpoints) as key factor to accept the clinical evidence requirements for HTA appraisals and key areas identified for divergent opinions between regulators and HTA bodies.

CONCLUSION

For each of the medicinal products selected, the conclusions of the analysis are reflected under this section.

KALYDECO

INTRODUCTION OF THE DRUG AND DISEASE OF THE INDICATION

KALYDECO

Kalydeco's active substance is ivacaftor. Ivacaftor is a selective modulator of the cystic fibrosis transmembrane conductance regulator (CFTR).

CFTR is a chloride channel present at the surface of epithelial cells in multiple organs and is responsible for the regulation of salt and water absorption and secretion.

Ivacaftor restores the function of a defective CFTR protein by increasing chloride ion transport across the CFTR chloride channel.

When the channels are defective, mucus and digestive juices can become abnormally thick. This is the cause of many of the problems of the disease. The impaired functioning of this protein is thought to be caused by mutation in different genes.

Ivacaftor increases the activity of the defective channels, normalizing the transport of ions through the channels, this way making the secretions less thick.

Kalydeco has proven activity for mutation G551D. The G551D mutation results in a defect in channel open/closed regulation (referred to as "gating mutation").

Kalydeco is recognized as being the first in a new class of medicines (CFTR potentiators) that target the cystic fibrosis CFTR and so treat the underlying cause of the disease.

Ivacaftor was designated as an orphan medicinal product in the EU on the 8th of July 2008.

On the 24th of May 2012, the Committee for Medicinal Products for Human Use (CHMP) of the EMA adopted a positive opinion, recommending the granting of a marketing authorization for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have a G551D mutation in their gene for the protein called cystic fibrosis transmembrane conductance regulator (CFTR).

On the 23rd of July 2012, the European Commission granted the EU marketing authorization to the applicant (Vertex Pharmaceuticals (UK)).

This medicine was initially only indicated for a subset of the CF patients, namely for those who have the type of faulty gene, called G551D mutation. In addition, it was only indicated for those patients aged 6 years and older.

On the 26th of June 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for Kalydeco.

The CHMP adopted a change to the indication of Kalydeco, introducing new cystic fibrosis genotypes for which the use of Kalydeco is indicated. Therefore, the full indication for Kalydeco was extended as follows:

Treatment of cystic fibrosis in patients aged 6 years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

In addition, a new warning with regard to lack of clinically relevant improvement from treatment in patients with G970R mutation in the CFTR gene was added to the product information.

Also interesting to note that in the United States, Kalydeco was granted fast track designation in May 2006 and approved in January 2012 (6 months earlier than in the EU). It was also granted breakthrough therapy designation for the treatment of CF in patients with other CFTR mutations. Ivacaftor monotherapy was the first regimen to receive breakthrough therapy designation from the FDA.

CMC Elements Described in the EPAR

Tablets 150mg.

Available Treatments

Kalydeco is recognized as being the first in a new class of medicines (CFTR potentiators) that target the cystic fibrosis CFTR and so treat the underlying cause of the disease.

The current standard treatments aim at treating the symptoms, such as chest infections, but do not remedy the underlying cause of cystic fibrosis.

Treatments can be categorized into nutritional repletion (e.g. pancreatic enzyme supplementation and nutritional supplementation), relief of airway obstruction (physiotherapy, improvement of sputum clearance, bronchodilators), treatment of infections (e.g. antibiotics), suppression of inflammation (e.g. steroids, high dose ibuprofen) and lung transplantation.

Cystic Fibrosis: An Orphan disease

According to the European Union legislation, a rare disease is a life threatening or chronically debilitating condition whose prevalence in the Union is less than five cases per 10000 inhabitants.

The European legislation for medicinal products (Regulation (EC) No 726/2004) determines that all medicinal products which are indicated for rare diseases, i.e. the so-called orphan drugs should follow the centralized procedure for the authorization of medicines.

Under the centralised procedure, the European Medicines Agency (EMA) is the scientific body responsible for performing the evaluation. The EMA provides a scientific opinion to the European Commission (EC) which will then serve as the basis for the granting of a marketing authorization which will have automatic validity in all EU member states.

The Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) is the scientific forum responsible for providing the scientific opinions on orphan designations. The designation of orphan status is granted by the European Commission upon a positive report from the above mentioned Committee.

The orphan designation status is granted early in the development of a drug and it is a competitive process. That means that more than one drug can receive orphan designation for the same condition.

In contrast, the granting of a marketing authorization for an orphan medicinal product gains the exclusivity of the EU market for ten years.

It is important to observe that a drug intended for the treatment of a rare disease does not necessarily need to have orphan status.

The first step for an orphan drug in order to reach the EU market is to be granted a centralised marketing authorisation. A drug with orphan designation status, benefits from ten years of market exclusivity in the European Union upon approval. This is an incentive created in the framework of the European legislation for the development of these drugs. No other drug with similar structure and with the same mechanism of action for the same indication can receive a marketing authorisation unless it is able to break one of the derogations foreseen in the EU legislation of orphan drugs (Regulation (EC) Nº 141/2000).

To date 88 orphan drugs have received a Marketing Authorization in Europe [86].

The second step is to receive positive appraisal by each of the relevant EU HTA bodies and successful reimbursement negotiations.

Cystic Fibrosis

Cystic fibrosis (CF) is a rare, life-shortening genetic disease which is caused by a single faulty gene. Cystic fibrosis is caused by a defective or missing CFTR protein resulting from mutations in the *CFTR* gene. Children must inherit two defective *CFTR* genes, one from each parent to have the illness.

There are more than 1,900 known mutations in the *CFTR* gene. Some of these mutations, which can be determined by a genetic, or genotyping test, lead to cystic fibrosis by creating non-working or too few CFTR protein at the cell surface.

The defective function or absence of CFTR proteins results in poor flow of salt and water into and out of the cell in a number of organs, including the lungs. This leads to the build-up of abnormally thick, sticky mucus that can cause chronic lung infections and progressive lung damage.

The underlying problem is the mutation of a gene that encodes for a chloride channel called the cystic fibrosis transmembrane conductance regulator (CFTR). This is essential for the regulation of salt and water movements across cell membranes.

It affects the cells that secrete mucus in the lungs and the cells that secrete digestive juices from glands in the gut and pancreas. These secretions become thick and block the airways and the flow of digestive juices in the gut. The lungs become clogged with thick, sticky mucus resulting in infections and inflammation (which are the main cause of morbidity and mortality) and also cause problems digesting food resulting in poor growth.

Other problems include diabetes, infertility and osteoporosis.

Cystic fibrosis is generally progressive over time as the lungs become more damaged.

Current treatments include:

- Chest physiotherapy.
- Special dietary advice, supplements and enzyme replacement therapy.
- Medical treatment to relieve bronchospasm and inflammation in the lungs, reduce viscosity of mucus in the airways or treat serious infections in the lungs.

Today, the median predicted age of survival for a person with cystic fibrosis is between 34 and 47 years, but the median age of death remains in the mid-20s [87].

It affects approximately 75,000 people in North America, Europe and Australia.

To date, 42 orphan drugs have received orphan designation for cystic fibrosis [88] and the European Medicines Agency has adopted a positive opinion for only seven drugs for cystic fibrosis. All these 7 drugs received a standard marketing authorisation.

- Bronchitol (mannitol)
- Cayston (aztreonam lisyne)
- Colobreathe (colistimethate sodium)
- Kalydeco (ivacaftor)
- Tobi Podhaler (tobramycin)
- Vantobra (tobramycin)
- Quinsair (levofloxacin)

All these authorized medicinal products have demonstrated to be of proven quality, safe and efficacious for the designated treatment. Four out of seven of these drugs have orphan designation status being Colobreathe, Vantobra and Quinsair the drugs that do not have orphan status.

From these seven cystic fibrosis drugs, just one, Kalydeco (ivacaftor), is recognized as being the first in a new class of medicines (CFTR potentiators) that target the cystic fibrosis CFTR and so treat the underlying cause of cystic fibrosis. It increases the time that activated CFTR channels remain open at the cell surface.

Colobreathe, Bronchitol and Kalydeco belong to the ATC code R: Respiratory System

Cayston, Tobi Podhaler, Quinsair and Vantobra belong to the ATC code J: General Anti-infective for systemic use.

The details are reported in the table below. **Table 1: Authorisation details of approved cystic fibrosis medicinal products.**

Figure 10. Table 1: Authorisation Details of Approved Cystic Fibrosis Medicinal Products

Medicinal Product	Active Substance	Approved Indication	Marketing Authorisation Date	Marketing Authorisation Holder
Cayston	Aztreonam	Suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 6 years and older.	21/09/2009	Gilead Sciences International Limited
Tobi Podhaler	Tobramycin	Suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in adults and children aged 6 years and older with cystic fibrosis.	20/07/2011	Novartis Europharm Limited
Colobreathe	Colistimethate sodium	Management of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 6 years and older.	13/02/2012	Foster Laboratories UK Ltd
Bronchitol	Mannitol	For the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.	13/04/2012	Pharmaxis Pharmaceuticals Limited
Kalydeco	Ivacaftor	Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene.	23/07/2012	Vertex Pharmaceuticals Limited
Vantobra	Tobramycin	Vantobra is indicated for the management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF).	18/03/2015	Pari Pharma GmbH
Quinsair	Levofloxacin	Quinsair is indicated for the management of chronic pulmonary infections due to	26/03/2015	Aptalis Pharma SAS

		Pseudomonas aeruginosa in adult patients with cystic fibrosis.		

METHODOLOGY

Sources of Information

The following sources of information were used in the study:

- **Regulatory documents:** European Public Assessment Reports (EPARs) for Kalydeco issued by the European Medicines Agency (EMA) in 2012[5] [89].

- **Health Technology Assessment documents:** Reports publicly available in English, Spanish and German from EU HTA bodies for Kalydeco. The selected reports correspond to the following HTA bodies[6] :

  - Scottish Medicines Consortium (SMC) – UK Scotland [90]
  - NHS England statement (NHS) – UK England [91]
  - AEMPS-Therapeutic Positioning Report for Spanish Government (IPT) – Spain [92]
  - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) – Germany [93]
  - National Centre for Pharmacoeconomics (NCPE) – Ireland [94]
  - Haute Autorité de Santé (HAS) – France [95]

[5] The comparative analysis performed in this study is only focused on the first indication (mutation G551D) as the available HTA reports refer exclusively to this mutation.

[6] All these HTA bodies have an advisory role but are not the ultimate decision-maker in their respective countries.

Conduct of the Research

Selection of the Elements of the Study:

- The **HTA Core Model Table developed by EUnetHTA** was taken as the basis of the agreed methodology among EU HTA bodies.
- The main elements of a **clinical study design.**
- Key elements considered as **pre-approval clinical evidence.**

Analysis:

A comparative analysis of the information contained in the EPAR and the HTA reports was undertaken following the 3 steps scheme described below:

1) Analysis following the HTA Core Model developed by EUnetHTA to determine the domains common to the regulatory and HTA fields. **The results are reflected in Table 2: EUnetHTA Core Model.**

2) Analysis of the study design elements which are frequently source of discrepancies between Regulators and HTA bodies (i.e. comparators, study population and endpoints). **The results are reflected in Table 3: Clinical Study Design.**

3) Analysis of the clinical evidence elements available pre-approval. The items considered were the benefit/risk balance, post-approval studies, degree of uncertainty and clinical added value. Study of the similarities and differences in the opinions among HTA bodies in view of the same clinical evidence which is taken from the EPAR published by the EMA[7]. **The results are reflected in Table 4: Clinical evidence pre-approval**.

[7] The clinical studies considered as sources of information were the same both in the EPAR and in the HTA reports (i.e. STRIVE, ENVISION and PERSIST). HTA bodies had more data from PERSIST study available at time of appraisal than EMA.

RESULTS

Each table contains a summary of the information present in the EPAR and HTA reports studied.

Table 2: EUnetHTA Core Model

The EUnetHTA Core Model defines the domains that HTA bodies should study for their appraisals. Not all these domains are relevant for the regulatory assessment.

The analysis showed that not all HTA reports considered all domains and also the depth and detail in which the same domains were addressed was also different.

Table 3: Clinical Study Design

The analyses showed that the clinical study design was considered appropriate in all HTA reports. No divergent opinions in this area were pointed out between Regulators and HTA bodies.

Table 4: Clinical Evidence Pre-Approval

The elements analysed under this area showed differences in opinions among the HTA bodies. The acceptance of the same degree of uncertainty regarding the long-term safety and efficacy was not equal. From the six HTA reports studied, 4 HTA bodies accepted the uncertainty present. Two bodies, the NCPE of Ireland and the SMC of Scotland did not.

The appraisal of the clinical added value (i.e. relative cost effectiveness) also varies among HTA bodies. No discussion at all is present in the French and Spanish reports. In the German report only global budget considerations are present. The English, Scottish and Irish reports address the pharmacoeconomic studies provided by the sponsor together with ICER and QALY threshold elements in addition to global budget considerations.

Figure 11. Table 2: Kalydeco - EUnetHTA Core Model[8]

ELEMENTS	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for Pricing and Reimbursement?*
HEALTH PROBLEM AND CURRENT USE	D. Main elements of the disease described.	**NHS:** D. Estimation of number of patients eligible provided (≈270). **SMC:** D. Estimation of number of patients eligible provided (≈70). **IPT:** D. Estimation of number of patients eligible provided (≈16). **NCPE:** D. Estimation of number of patients eligible provided (≈120). **HAS:** D. Estimation of number of patients eligible provided (≈74). **IQWIG:** D. Estimation of number of patients eligible provided (≈180).
DESCRIPTION AND TECHNICAL CHARACTERISTICS	D. Main elements: Indication and Posology.	**NHS:** D **SMC:** D **IPT:** D **NCPE:** D **HAS:** D **IQWIG:** D
SAFETY	D. The most frequent adverse reactions were not severe and well tolerated.	**NHS:** ND **SMC:** D. Based on EPAR. **IPT:** D. Based on EPAR. The two post-authorisation measures imposed on the MA mentioned as source of further information. **NCPE:** ND **HAS:** D. Based on EPAR. **IQWIG:** ND.
CLINICAL EFFECTIVENESS	D. Observational study imposed as a condition on the marketing authorization. Details discussed in tables 3 and 4.	**NHS:** D. Details discussed in tables 3 and 4. **SMC:** D. Details discussed in tables 3 and 4. **IPT:** D. Details discussed in tables 3 and 4. **NCPE:** D. Details discussed in tables 3 and 4. **HAS:** D. Details discussed in tables 3 and 4. **IQWIG:** ND.
COSTS AND ECONOMIC EVALUATION	NA.	**NHS:** D. Details discussed in tables 3 and 4. **SMC:** D. Details discussed in tables 3 and 4. **IPT:** ND.

[8] D (element discussed in the report (i.e EPAR/HTA)); ND (element not discussed in the report (i.e. EPAR/HTA)); NA (not applicable to the evaluation).

		NCPE: D. Details discussed in tables 3 and 4. **HAS:** ND. **IQWIG:** D. Details discussed in tables 3 and 4.
ETHICAL ANALYSIS	NA.	**NHS:** D. First drug in class. Severity of the disease. Improvement of health, reduction of hospitalizations. Indicated for children when the damage in tissues could be still slowed down. Mention to the fact that similar ultra-orphan drugs previously financed with similar ICER ranges. **SMC:** D. First drug in class. Incurable disease. **IPT:** D. First drug in class. **NCPE:** D. First drug in class. **HAS:** D. First drug in class. **IQWIG:** ND.
ORGANIZATIONAL ASPECTS	D.The medicine was authorized subject to restricted medical prescription (i.e. by specialists) and subject to genetic diagnosis of the mutation. Monitoring system by registries.	**NHS:** D. Genetic diagnosis required and sweat chloride levels controls. Prescribed by specialists. Health outcomes to be monitored by CF registries. **SMC:** D. Based on EPAR indication. **IPT:** D. Based on EPAR indication. **NCPE:** ND. **HAS:** D. Based on EPAR indication. Hospital use. **IQWIG:** ND.
SOCIAL ASPECTS	NA.	**NHS:** ND. **SMC:** ND. **IPT:** ND. **NCPE:** ND. **HAS:** ND. **IQWIG:** ND.
LEGAL ASPECTS	NA.	**NHS:** ND. **SMC:** ND. **IPT:** ND. **NCPE:** ND. **HAS:** ND. **IQWIG:** ND.

Figure 12. Table 3: Kalydeco - Clinical Study Design

ELEMENTS	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for Pricing and Reimbursement?*
COMPARATORS **Placebo vs. Active**	D. Kalydeco was compared to placebo in two Phase III pivotal trials (double-blind, randomized, multi-centre): VX08-770-102 (adults): STRIVE VX08-770-103 (children): ENVISION The SOC (i.e. pre-study medication) was continued in the patients with the exception of the inhaled hypertonic saline, which was not allowed.	**NHS:** D. Statement that 2 well conducted research studies (one in adults/one in children) placebo-controlled trials were undertaken. Only palliative treatments are currently available. **SMC:** D. Superiority over placebo showed. There are no comparators for the disease. **IPT:** D. Currently only symptomatic treatments are available. **NCPE:** ND. **HAS:** D. Currently only symptomatic treatments are available. **IQWIG:** ND.
STUDY POPULATION **Homogeneous vs. Heterogeneous**	D. Two main studies involving 219 patients with CF who had the G551D mutation in at least one allele of the CFTR gene: One of the studies was in patients >12 years old (N=167) (STRIVE). The other study involved patients between 6 and 12 years (N=52) (ENVISION). In addition, patients included had a FEV_1[9] ≥40% and a minimum body weight of 15Kg.	**NHS:** ND. **SMC:** D. The small size is acknowledged as appropriate considering the low number of patients affected by the mutation. **IPT:** D. The small size is acknowledged as appropriate considering the low number of patients affected by the mutation. **NCPE:** ND. **HAS:** D. Based on EPAR. **IQWIG:** ND.
ENDPOINTS (Primary clinical endpoints, PROs, QoL, Duration of Life, etc.).	D. The studies mentioned above had 48 weeks of duration. The main measure of efficacy was the ability to improve the pulmonary function (measured as the absolute change from baseline in percent predicted FEV_1 **after 24 weeks of treatment**). This variable was also measured at week 48. **Secondary variables:**	**NHS:** D. Improved lung function, weight gain and decrease in worsening of breathing requiring other treatments. Note is made to the absence of long-term efficacy data but it is recognized that the main indicator of cystic fibrosis, the amount of salt in sweat returns to normal values with ivacaftor treatment). Indication of the extension, non-controlled open-label study up to 96 weeks. **SMC:** D. Acknowledgement of FEV_1 as a surrogate which is the recommended primary

[9] FEV_1 is the maximum amount of air that a person can breathe out in one second.

	Other beneficial aspects: decrease rate of pulmonary exacerbations, sweat chloride concentration and increase in body weight. In addition, the change in respiratory symptoms at week 24 and 48 evaluated through the validated CFQ-R questionnaire. In the CFQ-R, patients report respiratory symptoms. It is an indicator of the symptoms on the quality of life. **PERSIST:** Study VX08-770-105 is an extension, non-controlled open-label study of studies VX08-770-102 and 103, the two pivotal trials presented for the marketing authorization application. The open-label study is up to 96 weeks (i.e. 144 weeks of treatment for those already on the drug and 96 for those initially allocated to placebo).	clinical endpoint for efficacy studies. CFQ-R mentioned. PERSIST study (up to 96 weeks) also mentioned. **IPT:** D. Based on EPAR. Indication of the extension, non-controlled open-label study up to 96 weeks (PERSIST). **NCPE:** D. Brief reference to FEV_1 as primary endpoint for Phase III clinical trials. **HAS:** D. Based on EPAR. Indication of the extension, non-controlled open-label study up to 96 weeks (PERSIST). **IQWIG:** ND.

Figure 13. Table 4: Kalydeco - Clinical Evidence Pre-Approval

ELEMENTS	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for Pricing and Reimbursement?*
POSITIVE BENEFIT/RISK BALANCE (Quality, Safety and Efficacy): The 3 basic guarantees	D. Quality: positive Safety: positive. Minor side effects. Efficacy: positive. After 24 weeks of treatment, patients aged 12 years and older who took Kalydeco had an average improvement in FEV_1 of 10.4%, compared with a reduction of 0.2% in those who took placebo. Similar results were seen in patients aged between 6 and 11 years, where Kalydeco treatment led to an improvement in FEV_1 of 12.6% compared with an improvement of 0.1% with placebo. These efficacy values were maintained at week 48.	**NHS:** D. Based on EPAR. **SMC:** D. Based on EPAR. **IPT:** D. Based on EPAR. Efficacy explicitly acknowledged. **NCPE:** ND. **HAS:** D. Based on EPAR. **IQWIG:** ND.
POST-APPROVAL STUDIES (Generation of additional evidence: PASS, PAES, Registries).	D. PASS and PAES imposed as a condition on the marketing authorisation. Real world data collection as part of these studies required.	**NHS:** D. Mention to PERSIST study. Mention that health outcomes in patients taking ivacaftor will be monitored using data from the CF registry. **SMC:** D. Long-term studies are acknowledged. **IPT:** D. The studies imposed on the MA are acknowledged and recognized as useful to clarify pending long-term safety and efficacy evidence generation. **NCPE:** ND. **HAS:** Discussed. Based on EPAR. **IQWIG:** ND.
DEGREE OF UNCERTAINTY ACCEPTED	D. EPAR indicates limited data on longer-term effects. Conditions were imposed on the MA to provide further data in this respect: From an ongoing long-term study and To conduct a five-year observational	**NHS:** D. Good evidence that ivacaftor is clinically effective although long-term safety and effectiveness data beyond 96 weeks are lacking. Monitoring of sweat chloride test required as indicators of treatment effectiveness and used as a stopping criteria for the treatment to be discontinued. **SMC:** D. The PERSIST study is acknowledged.

	study.	But long-term efficacy and safety data are considered necessary for chronic conditions and data beyond 48 weeks are limited. **IPT:** D. Absence of long-term efficacy data to prove maintenance of positive effects accepted. Monitor the efficacy in patients receiving treatment. **NCPE:** D. Absence of long-term efficacy and safety data not accepted. 96 weeks in adults and 72 in children considered limited. **HAS:** D. Absence of long-term efficacy data to prove maintenance of positive effects accepted. **IQWIG:** ND.
CLINICAL ADDED VALUE (Relative Cost-Effectiveness): The 4th guarantee.	NA.	**NHS:** D. ICER and QALY. No global budget discussion. Ivacaftor reduces need for other expensive treatments for progressive clinical deterioration and need of hospital care, including organ transplantation, which accounts for £100m annual expenditure (excluding transplantation). **SMC:** D. ICER, QALY and global budget figures provided. **IPT:** ND. **NCPE:** D. ICER, QALY and general budget considerations. Out of the accepted 45000 Euro/ QALY threshold. **HAS:** ND. **IQWIG:** Global budget discussion.

DISCUSSION

Cystic fibrosis is the most common, life-threatening, autosomal recessive disorder in Caucasian populations. The most common CFTR mutation is ΔF508 mutation which is present on around 67% of CF chromosomes worldwide.

In the UK, CF affects around 9000 people with a prevalence on 1.37/10000. About 7,300 people are in England**.**

The ΔF508 mutation occurs in approximately 75% of the patients with cystic fibrosis. The G551D mutation is present in around 5.7% of the patients in the UK.

From those, there are only about 320 people in England with the G551D mutation, around 270 of whom are aged 6 years and older and therefore fit the criteria for Kalydeco's approved indication.

In Scotland, around 12% of CF patients have the G551D mutation. That makes 50 patients according to the Company's estimations and 70 patients according to the Scottish Medicines Consortium experts.

In Spain around 16 CF patients have the G551D mutation. And in France around 74-80 patients.

In Ireland, 11.6% of Irish population with CF have the G551D mutation which makes a total of 113-120 patients.

In Germany the estimation is that 154-181 patients show the G551D mutation.

According to the sponsor, in total, in the European Union around 1083 patients would have the mentioned mutation.

Regulators EPAR

On the 24th of May 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive scientific opinion recommending the granting of a marketing authorization for the medicinal product Kalydeco.

The CHMP of the EMA endorsed the positive benefit/risk balance of Kalydeco.

The therapeutic indication granted was very specific: *"Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have a G551D mutation in the CFTR gene".*

In addition, Kalydeco was authorized subject to restricted medical prescription, this means only by specialized physicians and after confirmatory genotyping test: *"Kalydeco should only be prescribed by physicians with experience in the treatment of cystic fibrosis. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of the G551D mutation in at least one allele of the CFTR gene before starting the treatment".*

The design of the studies was considered adequate together with the results obtained for efficacy and safety. As it was recognized that no other alternative therapies are available, the comparison was made versus placebo.

Furthermore, and as reflected in the EPAR, the CHMP was clear regarding the lack of long-term efficacy data of the drug and in this respect imposed on the Marketing Authorisation Holder the obligation to conduct post-authorisation measures within agreed timeframes in order to mitigate the uncertainty.

These legally enforceable measures are stated in the Annex II of the Marketing Authorisation[10] for Kalydeco as follows:

Description of the condition (post-authorisation measure)	Due date
The applicant should conduct a 5-year long-term observational study with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations), according to a protocol agreed with the CHMP. The applicant should submit yearly interim analyses and the final CSR by December 2017.	December 2017
The applicant should submit the final clinical study report of the ongoing study VX08-770-105 which evaluates the long-term safety and efficacy in patients with cystic fibrosis by December 2015. **The applicant should also submit yearly interim reports within PSURs.**	December 2015

All these legally binding elements imposed by the Regulators intended to assure the use of the product in the right clinical setting. They were reflected in the scientific opinion adopted by the CHMP and translated into the corresponding marketing authorisation granted by the European Commission.

In June 2014, the EMA published that 96 weeks data from the study VX08-770-105 were made available.

[10] See EPAR for Kalydeco published by EMA.

VX08-770-105 is an open-label extension of studies VX08-770-102 and 103, the two pivotal trials presented for the marketing authorization application.

The improvement seen at week 48 of the initial study in percent predicted FEV_1 was maintained.

HTA Bodies Appraisals

NHS ENGLAND

The NHS England issued a statement on the 19th of December 2012 stating that Kalydeco would be funded by the NHS England from the 1st of January 2013 for all patients aged 6 years and over with cystic fibrosis and the G551D gene mutation, as set out in the licensed indication.

The positive statement was issued under the condition that the manufacturer provides the medicinal product with the discount agreed in the Patient Access Scheme.

Further control measures include the prescription of the drug in a specialized centre and not by the General Practitioner (GP).

Additional measures are also required in order to monitor the effectiveness of the drug during treatment (i.e. sweat chloride test or lung function criteria). These measures have the goal of mitigating the uncertainty due to the lack of long-term data.

The statement was issued by the North of England Specialised Commissioning Group (SCGs), Yorkshire and the Humber office, on behalf of the four Specialised Commissioning Groups in England. The Yorkshire and the Humber office of the North of England SCG is the national commissioning lead for cystic fibrosis and works on behalf of the four SCGs in England. A report was published in April 2013.

The review of all the available evidence on clinical effectiveness and cost-effectiveness was performed by the Clinical Priorities Advisory Group (CPAG). The CPAG was specifically established in September 2012 to consider this new treatment and provide the four SCGs in England with a single source of national advice.

NHS England informed that a rigorous assessment of the clinical and economic effectiveness of ivacaftor was performed. The health technology appraisal was undertaken by the NHS Institute for Health Research (NIHR) and a report from the national cystic fibrosis Clinical Reference Group, which is made of expert clinicians, patient representatives, and representatives from the Cystic Fibrosis Trust and NHS commissioners.

It was estimated that there are about 270 eligible patients in England to receive this treatment.

The NHS report makes explicit mention to the participation in the evaluation process of patients' organizations, namely Cystic Fibrosis Trust, the only charity in charge of cystic fibrosis in the United Kingdom (UK).

The NHS report also states that there are no other drugs dealing with the underlying cause of the disease and that the current standard of care is limited to the palliation of the symptoms. In addition, it is indicated in the report that as the illness progresses with age, more medication and more frequent hospitalizations are required. Ultimately, even lung and/or heart transplants could be required. The annual expenditure on standard care (excluding transplantation) for cystic fibrosis in England is around £100m.

The NHS report summary highlights the efficacy data extracted from the EPAR and transparently indicates the figures worked out for the incremental cost effectiveness ratio (ICER) in relation to the normally accepted QALY thresholds of the NHS. A summary of the main points of the NHS report are indicated below:

- In two pivotal randomised placebo-controlled trials (one in adults and one in children), an one open-label follow-up study, ivacaftor improved lung function measured using change in absolute % predicted Forced Expiratory Volume in 1 second (FEV_1). Both adult and children showed increase in absolute % predicted FEV_1 of around 10% when compared with the standard care. This improvement was maintained during the follow-up study (96 weeks for adults, 72 weeks for children).

- On average, adults and children treated with ivacaftor gained around 2.7Kg more than those on the placebo controlled at 48 weeks follow-up.

- Ivacaftor reduced the number of patients experiencing exacerbation when compared to the standard care. The drug also reduced the number of exacerbations requiring intravenous therapy and hospitalization.

- Sweat chloride levels, test used as diagnostic indicator for CF are normalized by ivacaftor.

- The HTA calculated the incremental cost effectiveness ratio (ICER) for ivacaftor in a number of scenarios. The threshold typically used to determine cost-effectiveness in the NHS is a £20-30,000QALY. Ivacaftor calculations of the ICER per QALY went over this figure by more than 10 times.

- Following the evaluation of the cost effectiveness for ivacaftor, NHS worked with the MAH (Vertex) to develop a Patient Access Scheme to improve the cost effectiveness of the treatment.

- At the discounted price offered, the ICER would potentially fall within the ranges financed for other ultra-orphan drugs as observed by NICE.

The NHS report concludes that Kalydeco is very expensive but acknowledged the opinion of specialist clinicians regarding the benefits for eligible patients. It was also noted that the NHS also finances other “ultra-orphan” medicines that have high opportunity cost and with incremental cost effectiveness ratios that are in a similar range as for ivacaftor.

SPANISH REPORT (IPT)

The Spanish IPT report is mainly based on the EPAR information. In addition, figures of the number of Spanish patients subject to treatment with Kalydeco are provided. It clearly acknowledges the absence of long-term efficacy and safety data and the uncertainty it brings with it. However, overall, the drug is considered and added value and a positive recommendation is given based on the clinical evidence provided.

HAS FRANCE

The French report is mainly based on the information contained in the EPAR. The drug is acknowledged as bringing a substantial improvement.. It is interesting that reference to the international situation in other EU countries is mentioned in the report.

IQWIG GERMANY

The scope of the report is restricted to an economical evaluation and budget impact to determine if the cost of the drug would be higher than 50 Million Euros.

No discussion is made on clinical evidence.

No clear recommendation is provided but just the factual figures are given.

SCOTTISH MEDICINES CONSORTIUM

The Scottish Medicines Consortium (SMC) of the NHS Scotland issued an assessment on the 7th of December 2012 were the use of Kalydeco was not recommended within NHS Scotland. Following a resubmission, on the 10th May 2013 a second assessment was published by this same body re-confirming the initial opinion of not recommending the use of Kalydeco in the authorized indication. The Patient Access Scheme submitted by the company was discussed in the second report.

The SMC recognized that clinical and statistically significant benefit for ivacaftor was proven over placebo. Evidence of substantial improvement in quality of life was provided and that there was an absence of other therapeutic options of proven benefit for cystic fibrosis patients. However, the SMC gave a negative opinion due to the high cost per QALY with the additional upwards uncertainty around the long-term trend in the FEV_1 predicted for patients maintained on ivacaftor.

However, the negative opinion of the SMC was overruled by the Scottish government, who released a new fund in order to finance Kalydeco for patients in Scotland.

NCP IRELAND

The drug was rejected in view of the high cost and the budget impact. The uncertainty left is not considered acceptable. It is not mentioned if patients associations were consulted. It leaves the possibility of financing if the price were decreased.

The Irish government finally announced that the medicine would be available to patients from the 1st of March 2013 despite the negative recommendation of the National Centre for Pharmacoeconomics. Further negotiations with the manufacturer took place which are confidential in nature.

The NHS, SCM and Spanish HTA reports state that consultation with patients' organizations took place.

A summary is provided in Table 5: Summary of key decision elements:

Figure 14. Table 5: Kalydeco - Summary of Key Decision Elements

Country	Safety & Efficacy	Uncertainty accepted	Price and budget considerations	Recommendation	Final government decision
Spain	+	YES	NO	Positive	Positive
France	+	YES	NO	Positive	Positive
Germany	+	YES	YES	Positive	Positive
England	+	YES	YES	Positive	Positive
Scotland	+	NO	YES	Negative	Positive
Ireland	+	NO	YES	Negative	Positive

From a scientific evidence point of view, the HTA reports analysed took the main clinical elements regarding safety and efficacy from the published EPAR. None of the HTA reports challenged the design of the studies nor the clinical evidence generated.

However, there was a clear difference in the way the existing degree of uncertainty was evaluated, being this aspect the key point in the justification of the negative opinions reached by the Irish and Scottish HTA bodies.

All HTA reports alluded to the presence of uncertainty regarding long term effects.

In fact, this aspect is well reflected in the EPAR. The EMA opinion noted the limited data on longer-term effects and as a result imposed conditions on the marketing authorization in this respect (provision of ongoing long-term study and the conduct of a five-year observational study).

However, while for NHS England, Spain, France and Germany this degree of uncertainty was considered acceptable and did not preclude a positive financing recommendation, for the Scottish and Irish HTA bodies this represented the scientific clinical evidence factor highlighted and emphasized in order to support the negative opinion.

From a cost-effectiveness point of view, the Irish and Scottish HTA bodies are clear regarding the non-cost-effectiveness of the treatment.

NHS England and Germany highlight the high cost of the drug but still consider it financeable due to the characteristics of the drug and the illness.

The Spanish and French HTA reports provide estimations to the number of patients eligible for the treatment in their respective countries but do not report further on cost-effectiveness elements.

Kalydeco is at the moment one of the most expensive drugs. The annual price of the drug per patient makes it difficult for some national budgets to absorb the cost [96].

The HTA reports of NHS England, SCM and Ireland indicate the fact that the public administration engaged in price negotiations with the holder Vertex Pharmaceuticals or would

be willing to do it in order to agree discounts that would facilitate the financing of this expensive treatment in their public health systems.

Nevertheless, despite the negative recommendations issued by the Scottish Medicines Consortium and the National Centre for Pharmacoeconomics of Ireland, the governments of these two countries finally decided to make the drug available, being the decision ultimately raised to the political level.

It is also to be mentioned that outside the EU, similar conclusions were reached. The Canadian Drug Expert Committee (CDEC) recommended in March 2013 ivacaftor under the condition of a substantial reduction in price to meet cost-effectiveness criteria [97]

The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia reflected in March 2014 that without a substantial price reduction or a pay for performance arrangement, ivacaftor would not be considered cost-effective ([98].

CONCLUSION

The analysis of Kalydeco shows not only the divergence in appraisals between Regulators (EMA) and EU HTA bodies but also evidences the discrepant views and recommendations reached among the different EU HTA bodies.

The analysis of the selected HTA reports shows that the methodological elements proposed by the EUnetHTA initiative have been followed to a certain extent. However, it is to be noted that not all the elements of the core model can be appreciated systematically in all the HTA reports.

The analysis of the information contained in the reports also show that different HTA bodies reach different conclusions when confronted with the same clinical evidence. The assessment of the same clinical evidence (i.e. the data generated) differs among HTA appraisals from different HTA bodies.

The CHMP endorsed a very specific indication for Kalydeco, intended for a well-defined subset of the patients' population (i.e. only those patients confirmed to have the G551D mutation) together with measures to make the product available only under restricted prescription (i.e. to be prescribed by physicians experienced in the treatment of CF).

In addition, long-term post-approval studies were imposed on the marketing authorization in order to fulfil the gap of long-term efficacy and safety data and so reduced the uncertainty.

In their HTA appraisals, England, France, and Spain explicitly acknowledged in their reports the lack of long-term efficacy data. Nevertheless, this uncertainty on the long-term efficacy of the product was not an impediment for giving a positive opinion on the use of the drug.

On the contrary, the SCM and Irish HTA bodies highlighted precisely this area of uncertainty as the main scientific argument to support its negative opinion, added to the high price of the drug.

It is to be noted, that the NHS England statement indicates clearly that the drug will only be made available under the condition that the manufacturer provides the drug with a discount agreed under the Patient Access Scheme.

It can be therefore deduced from the analysis of the Kalydeco case, that the main reason and source of divergent opinions among Regulators and HTA bodies was not the study design or the clinical evidence provided by the Company, as no HTA body challenged the design of the clinical study and 4 out of 6 HTA bodies considered the clinical evidence generated sufficient to finance the drug.

The economic cost of treatment was clearly the main driver in the evaluation.

The case of Kalydeco is especially interesting because it exemplifies the important dilemma between the scientific clinical evidence and the national budget considerations that HTA bodies face.

Kalydeco was undoubtedly and unanimously recognized at EU level by regulators on the three first basic guarantees.

However, the granting of an EU marketing authorization is not to be taken for granted as synonym of equal access to European patients. Some national HTA bodies can conclude that financing and reimbursement requirements are not met and therefore block entrance into their respective markets.

YERVOY

INTRODUCTION OF THE DRUG AND DISEASE OF THE INDICATION

YERVOY

The active substance of Yervoy is ipilimumab, an antineoplastic agent.

It is a fully human anti-CTLA-4 mononoclonal antibody (IgG1κ) produced by recombinant DNA technology in Chinese hamster ovary cells (i.e. the mammalian cell expression system).

Its mechanism of action is indirect as it acts enhancing T-cell mediated immune response.

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a negative regulator of T-cell activation. Ipilimumab acts as a T-cell potentiator that specifically blocks the inhibitory signal of CTLA-4, resulting in T-cell activation, proliferation, and lymphocyte infiltration into tumours, leading to tumour cell death.

The currently approved indication for Yervoy is the treatment of advanced (unresectable or metastatic) melanoma in adults.

The treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

The recommended posology for induction regimen is 3mg/kg administered intravenously over a 90 minutes period every 3 weeks for a total of 4 doses.

CMC Elements Described in the EPAR

Yervoy is presented as a sterile concentrate for solution for infusion (5mg/ml) for intravenous administration.

Available Treatments

Palliative treatment, consisting of systemic therapy, surgery and/or radiotherapy, is the only therapeutic option for patients with unresectable or metastatic disease.

Systemic treatment may consist of chemotherapy, and/or immunotherapy. The systemic treatments (excluding ipilimumab and vemurafenib) consist of the Interleukine-2 (IL-2) and interferon-alfa (IFNa) or chemotherapy (dacarbazine, temozolomide, fotemustine, carboplatin, paclitaxel).

At the time of Yervoy filing to EMA, only dacarbazine and vemurafenib were approved for systemic first line treatment of advanced melanoma.

However, both options had their limitations and restrictions. Dacarbazine has shown very poor clinical results and vemurafenib is only indicated for the BRAF V600 mutation-positive population.

Complete resection of isolated metastases to one anatomic site (lung, gastrointestinal tract, bone or brain) may occasionally achieve long-term survival.

Palliative radiotherapy is indicated for symptomatic relief of metastases to brain, bones and viscera.

Melanoma: A Terminal Disease

Melanoma is an aggressive form of skin cancer. Even though 95% of the tumours are found in the skin, other sites of primary extra cutaneous melanoma include ocular, mucosal, gastrointestinal, genitourinary, leptomeninges and lymph nodes.

The incidence of melanoma varies between different European countries. The estimated incidence is about 3.5 /100.000 men and 2.5/ 100.000 women per year. White populations have an approximately 10-fold greater risk of developing cutaneous melanoma than black, Asian or Hispanic populations. Approximately half the incidence is in people between the age

of 35 and 65 years, with a median age at diagnosis of 57 years. The last decades the incidence has been increased continuously. The increase in incidence affects all ages.

Patients are grouped into four prognostic categories (I-IV). If the tumour has spread beyond near-by lymph nodes, it is called advanced or metastatic melanoma which corresponds to state IV disease.

About 20% of the patients diagnosed with melanoma develop metastases and these patients have a median survival of about 7 months despite having received first line treatment.

The current first line treatments include surgery, radiotherapy and systemic treatments as explained above under the available therapies section.

Recurrent melanoma is resistant to most standard systemic therapy and no second line therapy for melanoma was established prior to ipilimumab.

To date, only 7 medicinal products have a centralized Marketing Authorization explicitly granted for the treatment of melanoma.

All these medicinal products were authorized as full marketing authorizations.

The details are reported in the table below. **Table 1': Authorisation details of approved medicinal products indicated for melanoma disease.**

Figure 15. Table 1': Authorisation Details of Approved Medicinal Products Indicated for Melanoma Disease

Medicinal Product	Active Substance	Approved Indication	Marketing Authorisation Date	Marketing Authorisation Holder
Intron A	Interferon alfa-2b	Carcinoid Tumour Hepatitis B, Chronic Hepatitis C, Chronic Leukaemia, Hairy CellLeukemia, Myelogenous, Chronic, BCR-ABL Positive Lymphoma, Follicular Melanoma Multiple Myeloma	09/03/2000	Merck Sharp and Dohme Limited
Yervoy	Ipilimumab	Melanoma	13/07/2011	Bristol-Myers Squibb Pharma EEIG
Zelboraf	Vemurafenib	Melanoma	17/02/2012	Roche Registration Ltd.
Tafinlar	Dabrafenib	Melanoma	26/08/2013	GlaxoSmithKline Trading Services Limited
Mekinist	Trametinib	Melanoma	30/06/2014	Glaxo Group Ltd
Opdivo	Nivolumab	Melanoma	19/06/2015	Bristol-Myers Squibb Pharma EEIG
Keytruda	Pembrolizumab	Melanoma	17/07/2015	Merck Sharp & Dohme Limited

Intron A is also indicated for other types of cancer and non-cancer indications.

METHODOLOGY

Sources of Information

The following sources of information were used in the study:

- **Regulatory documents**: European Public Assessment Reports (EPARs) for Yervoy issued by the European Medicines Agency (EMA) in 2011 and subsequent updates [99]

- **Health Technology Assessment documents:** Reports publicly available in English, Spanish and German from EU HTA bodies for Yervoy. The selected reports correspond to the following HTA bodies[11] (NB):

  - Scottish Medicines Consortium (SMC) – UK Scotland [100]
  - National Institute for Health and Care Excellence (NICE) – UK England [101]
  - AEMPS-Therapeutic Positioning Report for Spanish Government (IPT) – Spain [102]
  - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) – Germany [103]
  - Ludwig Boltzmann Insitute (HTA) – Austria [104]
  - Haute Autorité de Santé (HAS) – France [105]

[11] All these HTA bodies have an advisory role but are not the ultimate decision-maker in their respective countries.

Conduct of the Research

Selection of the Elements of the Study:

- The **HTA Core Model Table developed by EUnetHTA** was taken as the basis of the agreed methodology among EU HTA bodies.
- The main elements of a **clinical study design.**
- Key elements considered as **pre-approval clinical evidence.**

Analysis:

A comparative analysis of the information contained in the EPAR and the HTA reports was undertaken following the 3 steps scheme described below:

1) Analysis following the HTA Core Model developed by EUnetHTA to determine the domains common to the regulatory and HTA fields. **The results are reflected in Table 2': EUnetHTA Core Model.**

2) Analysis of the study design elements which are frequently source of discrepancies between Regulators and HTA bodies (i.e. comparators, study population and endpoints). **The results are reflected in Table 3': Clinical Study Design.**

3) Analysis of the clinical evidence elements available pre-approval. The items considered were the benefit/risk balance, post-approval studies, degree of uncertainty and clinical added value. Study of the similarities and differences in the opinions among HTA bodies in view of the same clinical evidence which is taken from the EPAR published by the EMA[12]. **The results are reflected in Table 4': Clinical evidence pre-approval.**

[12] The clinical studies considered as sources of information for the regulatory assessment of Yervoy are those provided for the first indication authorised (i.e. second line treatment) and subsequent extension of indication authorised (i.e. first line treatment) as referred in the EPAR for Yervoy. The clinical studies considered in the HTA reports are those indicated in the EPAR as follows: SMC, NICE and IQWIG (second and first line treatment are discussed). IPT, HAS (only those studies related to the second line treatment

RESULTS

Each table contains a summary of the information present in the EPAR and HTA reports studied.

Table 2': EUnetHTA Core Model

The EUnetHTA Core Model defines the domains that HTA bodies should study for their appraisals. Not all these domains are relevant for the regulatory assessment.

The analysis showed that not all HTA reports considered all domains and also the depth and detail in which the same domains were addressed was also different.

Table 3': Clinical Study Design

The analyses showed that the clinical study design was not considered completely acceptable in all HTA reports contrary to EMA's views. The choice of the comparator for the second line treatment and the first line treatment was challenged in some HTA reports.

Table 4': Clinical Evidence Pre-Approval

According to the EPAR, the ipilimumab-containing regimens demonstrated a statistically significant advantage in overall survival (OS) for the approval of the second line treatment and first line treatment.

The main safety concern was due to the immune related adverse events (irAEs) for which special risk minimization activities were put in place as part of the marketing authorization

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are discussed). LBI (EPAR studies for the second line treatment and in addition US-FDA evaluation for the first line treatment and other bibliographical sources).

granted: provision of special information brochures to health care professionals and patients and the inclusion of extensive guidance for the management of irAE in the product information.

Post-authorisation measures were also imposed on the MA in order to mitigate the uncertainty in the area of safety and efficacy of the drug, especially regarding the choice of the approved posology.

The EPAR conclusion on the benefit/risk balance of ipilimumab was positive.

The elements analysed under this area showed differences in opinions among the HTA bodies. Not all HTA reports considered acceptable the comparisons to prove added value or the degree of uncertainty regarding safety and efficacy.

Figure 16. Table 2': Yervoy - EUnetHTA Core Model[13]

ELEMENTS	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for Pricing and Reimbursement?*
HEALTH PROBLEM AND CURRENT USE	D. Main elements of the disease described.	**NICE:** D. Estimation of 1000 eligible patients. **SMC:** D. Estimation of number of eligible patients provided (≈110 a year). **IPT:** D. Estimation of incidence of the illness (5.3-5.5/100000 inhabitants and year) and age ((35-65), median 57 years). Candidate patients for the treatment a year: 215-269. **LBI:** D. No estimation of number of patients provided. **HAS:** D. Rough estimation of number of patients eligible to receive the treatment provided (≈650-1900). **IQWIG:** ND.
DESCRIPTION AND TECHNICAL CHARACTERISTICS	D. Main elements: Indication and Posology	**NICE:** D. Based on EPAR. **SMC:** D. Based on EPAR. **IPT:** D. Based on EPAR. **LBI:** D. **HAS:** D. Based on EPAR. **IQWIG:** ND.
SAFETY	D. Generally well tolerated. The most frequent adverse reactions result from increased or excessive immune activity. The majority were mild to moderate. Therapy was discontinued in 10% of patients due to adverse reactions.	**NICE:** D. Based on EPAR. **SMC:** D. Based on EPAR. **IPT:** D. Based on EPAR. **LBI:** D. **HAS:** D. Based on EPAR. **IQWIG:** ND.
CLINICAL EFFECTIVENESS	D. Elements regarding survival are integrant aspects of the evaluation. Observational studies imposed on the MA.	**NICE:** D. Details discussed in tables 3 and 4. **SMC:** D. Details discussed in tables 3 and 4. **IPT:** D. Details discussed in tables 3 and 4. **LBI:** D. Details discussed in tables 3 and 4. **HAS:** D. Details discussed in tables 3 and 4.

[13] D (element discussed in the report (i.e EPAR/HTA)); ND (element not discussed in the report (i.e. EPAR/HTA)); NA (not applicable to the evaluation).

		IQWIG: ND.
COSTS AND ECONOMIC EVALUATION	NA.	**NICE:** D. Details discussed in tables 3 and 4. **SMC:** D. Details discussed in tables 3 and 4. **IPT:** ND. **LBI:** D. Details discussed in tables 3 and 4. **HAS:** ND. **IQWIG:** ND.
ETHICAL ANALYSIS	NA.	**NICE:** D. New treatment. Severity of the disease. **SMC:** D. Novelty of the treatment. Terminal disease. **IPT:** D. Severity of the illness and absence of established second line treatments is acknowledged. **LBI:** D. Severity of the illness. **HAS:** D. Severity of the disease. Absence of alternatives. **IQWIG:** ND.
ORGANIZATIONAL ASPECTS	D. The medicine was authorized subject to restricted medical prescription (i.e. by specialists). Special monitoring of adverse reactions and additional risk minimization measures (Healthcare professional's information brochure and patient information brochure and alert card) regarding immune related adverse reactions (irARs).	**NICE:** D. Based on EPAR indication. **SMC:** D. Based on EPAR indication. **IPT:** D. Based on EPAR indication. **LBI:** ND. **HAS:** D. Based on EPAR indication. Hospital use. **IQWIG:** ND.
SOCIAL ASPECTS	NA.	**NICE:** D. No equality issues identified. **SMC:** D. As part of the patient and public involvement. **IPT:** ND. **LBI:** ND. **HAS:** ND. **IQWIG:** ND.
LEGAL ASPECTS	NA.	**NICE:** ND. **SMC:** ND. **IPT:** ND. **LBI:** ND. **HAS:** ND. **IQWIG:** ND.

Figure 17. Table 3': Yervoy - Clinical Study Design

ELEMENTS	**EPAR Information:** ***What is sought to grant a Marketing Authorization?***	**HTA Reports Information:** ***What is sought for Pricing and Reimbursement?***
COMPARATORS **Placebo vs. Active**	**FIRST INDICATION: second line treatment** D. The pivotal double-blind, randomized, multicentre Phase 3 clinical trial (MDX010-20) involved n= 676 patients with advanced (unresectable or metastatic) melanoma who had previously been treated with regimens containing one or more of the following: IL-2, dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomized in a 3:1:1 ratio to receive: 1)Ipilimumab 3mg/kg in combination with an investigational gp100 peptide vaccine (n=403). 2)Ipilimumab 3mg/kg monotherapy (n=137). 3) Investigational gp100 peptide vaccine alone (control group) (n=136). A complete induction cycle consisted of 4 doses at a dose of 3mg/kg every three weeks (induction therapy). Duration of induction phase: 12 weeks. Followed by re-induction. *Note: MDX-1379 is the experimental tumour specific peptide vaccine (gp100).* **UPDATED INDICATION: first line treatment** D.	**NICE:** D. Acceptance of second line treatment design but challenge that no direct comparison available for ipilimumab 3mg/kg monotherapy with the comparators in scope: dacarbazine for the support of the first line. **SMC:** D. Dacarbazine acknowledged as the acceptable comparator for the first line treatment indication. **IPT:** D. Based on EPAR. **LBI:** D. It questions the setting of the first line treatment study. **HAS:** D. The choice of an experimental treatment without MA is questioned for the second line treatment. **IQWIG:** D.

	Patients were randomized in a 1:1 ratio to receive dacarbazine plus ipilimumab or dacarbazine plus placebo.	
STUDY POPULATION Homogeneous vs. Heterogeneous	**FIRST INDICATION: second line treatment** D. The pivotal Phase 3 clinical trial (MDX010-20) involved n=676 patients with advanced melanoma. All patients were HLA-A2*0201 type. This HLA type supports the immune presentation of gp100. Baseline characteristics were well balanced across the 3 arms groups of the study. The median age was 57 years. **UPDATED INDICATION: first line treatment** D. Study CA184024 was a Phase 3, multi-centre, randomized, double-blind, and 2 arm study in patients with untreated Stage III (unresectable) or Stage IV melanoma. N= 500 patients. It served to extend the indications to untreated patients too.	**NICE:** D. Representative of UK patient population. **SMC:** D. Based on EPAR. **IPT:** D. Based on EPAR. **LBI:** D. **HAS:** D. Based on EPAR. **IQWIG:** D.
ENDPOINTS (Primary clinical endpoints, PROs, QoL, Duration of Life, etc.).	**FIRST INDICATION: second line treatment** D. The primary clinical endpoint was OS in the ipilimumab + gp100 group vs. the gp100 group. Key secondary endpoints were the OS in the ipilimumab+gp100 group vs. the ipilimumab monotherapy group and in the ipilimumab monotherapy group vs. the gp100 group. **Evaluation of health related Quality of Life (HRQoL) was also a secondary endpoint. But it is not discussed in detail in the**	**NHS:** D. Based on EPAR. **SMC:** D. Based on EPAR. **IPT:** D. Based on EPAR. **LBI:** D. **HAS:** D. Based on EPAR. **IQWIG:** D.

	EPAR. *Note: OS defined for each patient as the time between randomization date and death.* Assessment of tumour response was conducted at approximately week 12, after completion of the induction therapy. Duration of follow-up ranged up to 55 months. **UPDATED INDICATION: first line treatment** The primary objective of this study was to compare overall survival (OS) in patients with previously untreated stage IIIc, N3 (unresectable) or Stage IV melanoma receiving dacarbazine plus 10 mg/kg ipilimumab vs dacabazine with placebo. Secondary objectives: health-related quality of life (HRQoL) for each treatment arm.	

Figure 18. Table 4': Yervoy - Clinical Evidence Pre-Approval

ELEMENTS	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for Pricing and Reimbursement?*
POSITIVE BENEFIT/RISK BALANCE (Quality, Safety and Efficacy): The 3 basic guarantees	**FIRST INDICATION: second line treatment** D. Quality: positive Safety: positive. Special risk minimization activities in place regarding immune related adverse reactions. Efficacy: positive. For ipilimumab monotherapy, a median overall survival of 10.12 months (95%CI; 8.02-13.80) was reported whereas the observed median overall survival for gp100 monotherapy was only 6.44 months (95% CI; 5.49-8.71). **UPDATED INDICATION: first line treatment** D. All 3 basic guarantees positive. Efficacy: The indicated OS benefit of 2.1 months for ipilimumab + dacarbazine treatment in comparison to dacarbazine monotherapy is considered clinically relevant.	**NICE:** D. Based on EPAR. **SMC:** D. Based on EPAR. **IPT:** D. Based on EPAR. **LBI:** D. **HAS:** D. Based on EPAR. **IQWIG:** D.
POST-APPROVAL STUDIES (Generation of additional evidence: PASS, PAES, Registries).	**FIRST INDICATION: second line treatment** D. PASS and PAES imposed as a condition on the MA. Observational studies included as part of the Pharmacovigilance plan (CA184143). **UPDATED INDICATION: first line treatment** D. In alignment with previous indication.	**NICE:** D. Comparison of the dose 3mg/kg vs. 10 mg/kg. **SMC:** D. EPAR post-authorisation studies are acknowledged. **IPT:** ND. **LBI:** D. **HAS:** Discussed. Based on EPAR. **IQWIG:** ND.
DEGREE OF UNCERTAINTY ACCEPTED	**FIRST INDICATION: second line treatment** D. EPAR indicates need to determine the	**NICE:** D. Regarding the dose selection. **SMC:** D. Accepted with acknowledgement of post-authorisation measures imposed. **IPT:** D.

	efficacy and safety of the 10mg/kg dose vs 3mg/kg dose. EPAR indicates need to further monitor safety. EPAR indicates limited efficacy data on some patient's subpopulations. Post-marketing studies were imposed on the MA to provide further data in this respect. The medicine is also subject to additional monitoring. **UPDATED INDICATION: first line treatment** D. In alignment with previous indication.	**LBI:** D. **HAS:** D. Uncertainty limits the added value appraisal. **IQWIG:** ND.
CLINICAL ADDED VALUE (Relative Cost-Effectiveness): The 4th guarantee.	**FIRST INDICATION: second line treatment** NA. **UPDATED INDICATION: first line treatment** NA.	**NICE:** D. ICER and QALY provided. It is highlighted that no trials are available directly comparing ipilimumab 3mg/kg with the comparators in scope: dacarbazine and vemurafenib. **SMC:** D. ICER, QALY and global budget figures provided. Vemurafenib in addition to dacarbazine taken into account as comparators for the economic analyses. **IPT:** ND. **LBI:** D. Figures for total treatment cost provided. Absence of data comparing other available melanoma therapies used highlighted. **HAS:** ND. **IQWIG:** D.

DISCUSSION

Regulators EPAR

On the 19th of May 2011, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive scientific opinion recommending the granting of a marketing authorization for the medicinal product Yervoy.

The CHMP of the EMA endorsed the positive benefit/risk balance of Yervoy.

The therapeutic indication granted in 2011 was as follows: *"Yervoy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy".*

In addition, Yervoy was authorized subject to restricted medical prescription, this means only by specialized physicians.

The design of the studies was considered adequate together with the results obtained for efficacy and safety.

Overall survival (OS) advantage of ipilimumab at the recommended dose of 3mg/kg in patients with previously treated advanced (unresectable or metastatic) melanoma was demonstrated in a Phase 3 study (MDX010-20).

OS is an important objective in these patients because of the very short long-term prognosis.

The recruited patients in study MDX010-20 had been previously treated with regimens containing one or more of the following: IL-2, dacarbazine, temozolomide, fotemustine, or carboplatin.

Patients were enrolled regardless of their baseline BRAF mutation status.

For ipilimumab monotherapy, a median overall survival of 10.12 months (95%CI; 8.02-13.80) was reported whereas the observed median overall survival for gp100 monotherapy was only

6.44 months (95% CI; 5.49-8.71). No statistically significant differences in overall survival between the ipilimumab monotherapy group and the combined therapy group were observed. The median overall survival for ipilimumab plus gp100 was 10.0 months.

Long-term survival data indicated that 54 of the 403 patients in the ipilimumab plus gp100 group, 24 of the 137 patients in the ipilimumab monotherapy group, and 16 of the 136 patients in the gp100 monotherapy group remain alive for a minimum of 2 years.

The data of the secondary investigated endpoint in relation to the impact of the treatment on the quality of life are not shown in the EPAR. It is reported that the Health-related Quality of Life (HRQoL) for patients with cancer is affected negatively by the own disease progression and the side effects of the treatments administered for this condition. Most changes from baseline in HRQoL domains were “no change” or “moderate” across the three treatment groups.

As reflected in the EPAR, the CHMP was clear regarding the need to generate further safety and efficacy data under determined settings and in this respect imposed on the Marketing Authorisation Holder the obligation to conduct post-authorisation measures within agreed timeframes (Annex II conditions and Pharmacovigilance obligations).

Although efficacy was considered established for the 3 mg/kg dose, it was considered important to clarify any differences in efficacy (and safety) between 3 mg/kg and 10 mg/kg monotherapy (Study CA184169).

In addition, the CHMP requested and the company committed to conduct Study CA184143, a multinational prospective, observational study in patients with unresectable or metastatic melanoma with a final study report estimated for 2017.

The objective of CA184143, which is part of the Pharmacovigilance plan is to estimate the incidence and severity of adverse reactions; to describe the management of adverse reactions (egg, diarrhoea, colitis, hepatitis, elevated liver enzymes, hypopituitarism, hypothyroidism, rash, neurologic syndromes) and their outcomes; to describe patterns of care for adult patients receiving any therapy for unresectable or metastatic melanoma (dosing, regimen,

indication, treatment rationales, management of treatment-related adverse events, reasons for treatment termination, etc.)

As part of the Risk Management Plan of the product and to address long-term safety aspects, the proposed post-marketing study will follow the patients for a minimum of 3 years.

The legally enforceable measures stated in the Annex II of the Marketing Authorisation[14] for Yervoy are as follows:

Description	Due date
The Marketing Authorisation Holder shall perform a randomized comparison study of 3mg/kg versus 10mg/kg evaluating efficacy and safety in advanced melanoma with a survival endpoint, based on a CHMP-agreed protocol.	Final study report: 4Q 2017

Following the approval in 2011, in 2013, a variation was submitted to the EMA in order to extend the indication and also include the option to use Yervoy in patients not previously treated (i.e. as first line treatment): *"Yervoy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults".*

At the time of filing of this extension of indication, for patients with advanced melanoma without BRAF mutation, only dacarbazine was approved as first line treatment from which only a limited increase in Progression Free Survival (PFS) could be expected.

The initial marketing authorisation and indication was based on the results of the pivotal study MDX010-20 ipilimumab (3 mg/kg) where ipilimumab showed a statistically significant improvement in OS compared to gp100 vaccine (experimental vaccine), when given as second line therapy of patients with metastatic melanoma with HLA-A0201 positive status.

[14] See EPAR for Yervoy published by EMA.

Study CA184024 was a Phase 3, multi-centre, randomized, double-blind, and 2 arms study in patients with untreated Stage III (unresectable) or Stage IV melanoma. It served to extend the indications to untreated patients too. Patients were randomized in a 1:1 ratio to receive dacarbazine plus ipilimumab or dacarbazine plus placebo.

Each patient received ipilimumab (10 mg/kg or placebo) as a single dose via a 90-minute intravenous (IV) infusion. In the induction phase, ipilimumab or placebo was administered at Weeks 1, 4, 7 and 10 for a total of 4 separate doses.

The primary objective of this study was to compare overall survival (OS) in patients with previously untreated stage IIIc, N3 (unresectable) or Stage IV melanoma receiving dacarbazine plus 10 mg/kg ipilimumab vs dacabazine with placebo.

This additional study showed a statistically significant effect on OS, with a median OS with ipilimumab + dacarbazine of 11.2 months vs 9.1 months in dacarbazine monotherapy.

The primary endpoint of overall survival and secondary endpoints were considered adequate.

The results of the secondary endpoints were in line with the result of the primary endpoint and supported the increased efficacy of ipilimumab + dacarbazine treatment in comparison to dacarbazine monotherapy.

The indicated OS benefit of 2.1 months for ipilimumab + dacarbazine treatment in comparison to dacarbazine monotherapy is considered clinically relevant.

Following database lock for the main analysis, the study was amended and will continue in an extension phase, the objectives of which are to estimate survival rates at 3, 4, and 5 years for ipilimumab and to evaluate the safety profile of ipilimumab for patients in the extension phase.

Although dacarbazine has never demonstrated an OS benefit, in view of limited treatments being available, it is still commonly used in Europe as first line systemic therapy in advanced melanoma as it may achieve objective response rates of about 20%.

Therefore, showing superiority of ipilimumab in combination with dacarbazine to dacarbazine + placebo was considered an acceptable study design to prove the efficacy of ipilimumab in chemotherapy naïve patients with advanced melanoma.

Regarding the justification of the approved posology, no randomized studies comparing the efficacy of 3 mg/kg ipilimumab monotherapy with dacarbazine in previously untreated patients with advanced melanoma were provided. However, based on cross trials comparisons provided, the lower dose was proven as adequate for the extended indication.

In order to mitigate the uncertainty pre-approval, legally binding elements were imposed by the Regulators in order to assure the use of the product in the right clinical setting. They were reflected in the scientific opinion adopted by the CHMP and translated into the corresponding marketing authorisation granted by the European Commission.

HTA Bodies Appraisals

SPANISH REPORT (IPT)

The Spanish IPT report is mainly based on the EPAR information available for the first indication granted to the product (i.e. second line treatment).

In addition, figures of the number of Spanish patients, potential candidates for treatment with Yervoy, are indicated in order to provide an estimation of the impact of the inclusion of the drug on the national health system.

The drug is considered as an added value and a positive recommendation is given for the second line indication based on the clinical evidence provided.

It is to be noted that the Spanish report alludes to the fact that there are studies that would indicate the appropriateness of the use of Yervoy in a first line setting. However, being the indication not authorized in Europe at the time of the issuance date of the HTA report, the first line indication is not recommended.

HAS FRANCE

HAS France issued two reports to assess the first indication granted (i.e. second line therapy of melanoma). The first report indicated the need to re-evaluate the added benefit of the drug within one year time in order to define better the target population to receive the drug.

The French report is mainly based on the information contained in the EPAR. In addition, figures on affected patients in France are also indicated. The drug is reserved for hospital use.

The second report mentions that an application for an extension of indication is currently in progress at EMA but this is not further discussed.

Information on the licensing status in EU countries is also included in the report.

Regarding the clinical study design, the HAS report questions the choice of the comparator (gp100) as it is an experimental peptide vaccine with no MA. It is considered to act in the same order of placebo (i.e. median survival without treatment: 7 months).

It further explains that even though a difference in the overall survival was observed, the therapeutic contribution of ipilimumab is difficult to quantify given the choice of the comparator.

Yervoy is assessed as having a modest efficacy/adverse effects ratio. It even considers that the drug could have a negative impact on the quality of life based on the tolerance problems it exhibits. It is not considered to bring a benefit to public health but only a minor improvement in actual benefit.

The absence of a comparative study of ipilimumab and vemurafenib is also highlighted as a clinical weakness.

Despite this assessment, the final recommendation is positive, due to the lack of alternatives for the disease but restricting the use of the drug to a very defined population of patients (i.e. patients evading metastases with slow progression, in good general health and with life expectancy of more than three months).

IQWIG GERMANY

The aim of the report was to assess the added benefit of ipilimumab compared with dacarbazine in adult patients with advanced (unresectable or metastatic) melanoma who had not received prior therapy to treat advanced melanoma.

The HTA report is based on the dossier submitted to IQWIG by the Company.

Contrary to EMA scientific opinion, the HTA report considers that the clinical evidence provided by the company to support the benefit/risk balance of the drug in the first line indication is not adequate. The different elements are discussed and the critical points refer to the way the comparative analyses was prepared by the company to support the claim of added value over dacarbazine.

No clear recommendation is provided but just the factual data are provided in the report.

No economical evaluation is provided.

SCOTTISH MEDICINES CONSORTIUM

The HTA report of the Scottish Medicines Consortium (SMC) of the NHS Scotland already takes into consideration the extension of indication granted. This is the indication for previously untreated patients (i.e. use of Yervoy as first line treatment for melanoma).

It is explicitly stated in the report that the submission was considered under the end of life/orphan medicine process, where greater uncertainty in the economic case can be accepted.

It also indicates that the benefits of the Patient Access Scheme (PAS)[15] that improve the cost-effectiveness of ipilimumab were taken into account, being the advice subject to the maintenance of these economic conditions. Data of the economical evaluation are provided.

Patients and health care professional's views were taken into account to assess the added value of ipilimumab, as an end of life and orphan equivalent medicine. The social benefits of the use of ipilimumab (e.g. increase in survival return to employment, emotional and economic benefits) are highlighted.

Regarding the assessment of the clinical evidence, it was reflected in the HTA report that the efficacy of the approved dose for the first line indication (i.e. 3mg/kg) was limited to two retrospective single-arm observational studies. In this respect, reference to the post-approval measures imposed on the MA to mitigate uncertainty are acknowledged.

The absence of a comparative study of ipilimumab and vemurafenib is also highlighted as a clinical weakness.

[15] A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug. Under a PAS, a confidential discount is given on the price of the medicine. A Patient Access Scheme Assessment Group (PASAG) was established under the auspices of NHS Scotland. The PASAG operates independently of the SMC in order to maintain the integrity and independence of the assessment process of the SMC.

Nevertheless, a substantial improvement in the quality of life and the absence of other treatments of proven benefit resulted in a final positive recommendation.

NICE ENGLAND

The NICE HTA reports considered both the initial indication granted (i.e. second line therapy) and the extension of indication approved (i.e. first line therapy).

In the summary of appraisal, most of the EUnetHTA Core Model Table domains can be recognized.

Regarding the evidence for clinical effectiveness, it is highlighted that there were no trials directly comparing ipilimumab 3mg/kg monotherapy with the comparators in scope: dacarbazine and vemurafenib.

NICE also questioned the methodological approach of the company to prove added value and questioned some of the assumption made by the company like for instance regarding the equivalence of the 3mg/kg dose and the 10mg/kg dose or that ipilimumab plus dacarbazine was equivalent to ipilimumab alone . However, it was considered acceptable and the 3 months extension of life an added benefit.

A cost effectiveness evaluation (ICER, QALY) is provided and considered adequate for a life-extending end-of-life treatment.

The final appraisal determination is that the drug is recommended only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme (confidential discount).

The NICE report concludes with two recommendations: one to investigate further to establish the optimal treatment sequence for vemurafenib and ipilimumab in patients with BRAF V600 mutation-positive melanoma and another one to determine if concomitant dacarbazine enhances the clinical effectiveness of ipilimumab (relative effectiveness of ipilimumab as first line or second line therapy).

LBI AUSTRIA

The HTA report from LBI substantially differs in scope and format to the other HTA reports analysed. It has the form of an informative document about Yervoy and the treatment of melanoma disease. Not only the studies evaluated by EMA and described in the EPAR are taken into account but also the studies reported in the US-FDA evaluation of the drug and other bibliographical references.

The report focuses on the use of Yervoy as first line treatment, despite the fact that this indication was not authorized in Europe at the time the report was issued. In this respect, the available data from study CA184024 are discussed. The fact that in the US the drug is authorized for both first and second line treatments is also discussed.

The estimated costs of the drug are presented but without giving overall budget figures for the country.

The report is critical regarding the clinical study design for the first line indication. It is questioned why ipilimumab was tested in combination with dacarbazine and not alone.

The absence of comparative efficacy data and other available treatments for the first line treatment such as IL-2 and vemurafenib is also highlighted.

The uncertainty regarding the proposed dose is also highlighted despite the post-authorization measures imposed. The impact on price is also considered.

Contrary to EMA scientific opinion, the HTA report considers that the benefit/risk balance of the drug is not positive (i.e. gain of only 2.1 months OS with a considerable increase in toxicities) and in addition not justified by the high cost. The use of ipilimumab in commercial setting is not endorsed. Enrolment in clinical trials is indicated.

A summary is provided in **Table 5': Summary of key decision elements.**

Figure 19. Table 5': Yervoy - Summary of Key Decision Elements

Country	Safety & Efficacy	Uncertainty accepted	Price and budget considerations	Recommendation	Final government decision
Spain	+	YES	NO	Positive	Positive
France	+	YES	NO	Positive	Positive
Germany	-	NO	NO	Negative	Positive
England	+	YES	YES	Positive	Positive
Scotland	+	YES	YES	Positive	Positive
Austria	-	NO	YES	Negative	Positive

The analysis of Yervoy shows that from a scientific evidence point of view, all the HTA reports analysed took the main clinical elements regarding safety and efficacy from the published EPAR.

Regarding the benefit/risk ratio, NICE clearly acknowledges the adverse reactions caused by Yervoy but considers a positive benefit/risk ratio in line with EMA evaluation. HAS considered that the drug could even have a negative impact on the QoL due to tolerance problems but accepted it based on lack of alternatives. The SMC on the contrary, appraises the drug as exerting a positive impact on the QoL.

Very interestingly, IQWIG and LIB challenged the positive benefit/risk balance of the drug overruling EMA's opinion in this respect.

The main areas of discrepancy between EMA and HTA bodies are the choice of comparator and the clinical evidence pre-approval. Moreover, even among HTA bodies there are divergent opinions in this respect.

Even with the acknowledgment of some weaknesses (especially in relation to the choice of the comparator), the clinical design setting was accepted in most HTA reports (NICE, SMC, HAS, IPT) but was not accepted by others (LBI, IQWIG).

The acceptance of uncertainty is another focus of discrepancies. In some HTA reports, a discussion is provided regarding the existence of uncertainty and the post-authorisation measures to mitigate it. IPT, SMC and NICE clearly identify it but accept it. HAS identifies it as an aspect that limits the added value of the medicine. LIB does not accept it.

The appraisal of the clinical added value (i.e. relative cost-effectiveness) also varies among HTA bodies. No discussion at all is present in the French and Spanish reports. The German report considers the data provided unsuitable to reach conclusions. The Austrian HTA report precludes a positive recommendation based on deficiencies in this area.

On the contrary, the SMC and NICE reports highlight the methodological weaknesses incurred by the company but still considers it acceptable under the setting of an end of life drug.

Nevertheless, despite the negative recommendations issued by the German and Austrian HTA bodies, the governments of these two countries finally decided to make the drug available, being the decision ultimately raised to the political level.

CONCLUSION

The analysis of Yervoy shows not only the divergence in appraisals between Regulators (EMA) and EU HTA bodies but also evidences the discrepant views and recommendations that the different EU HTA bodies can reach in the presence of the same clinical evidence.

The analysis of the selected HTA reports shows that the methodological elements proposed by the EUnetHTA initiative have been followed to a certain extent. However, it is to be noted that not all the elements of the Core Model can be appreciated systematically in all the HTA reports.

It is acknowledged at present that discrepant views currently exist regarding the cost-effectiveness evaluation among HTA bodies as reflected in the Yervoy analysis. This can be due to many factors: different methodologies, different QALY limits accepted or budget considerations or discrepant views as to what is considered a substantial clinical benefit.

Some HTA reports challenged the clinical trials design (choice of comparator and posology). The choice of comparator is an area which is a frequent source of divergences.

In addition, the degree of uncertainty to be accepted differed among HTA bodies.

However, what is a very interesting outcome from the analysis of Yervoy is how some HTA bodies can even challenge the positive benefit/risk balance of a medicine, even when this aspect has been positively endorsed by the EMA.

Regarding price considerations, it is to be noted, that NICE and the SMC indicate clearly that the drug will only be made available under the condition that the manufacturer provides the drug with a discount agreed under the respective Patient Access Schemes. This is the evidence of the importance of the price and budget considerations for some HTA bodies' appraisals.

It can be therefore deduced from the analysis of the Yervoy case, that discrepant views regarding the clinical study design, considerations as to what is assessed as a substantial clinical benefit and added value remain together with differences in methodological considerations in the cost-effectiveness analysis.

All these factors together with price considerations lead to the different opinions among EU HTA bodies despite being confronted with the same clinical evidence.

THESIS DISCUSSION

Where are we now?

The Science

On-Going Work: The Creation of a Common European Policy. The Establishment of a Standardized Process Joining Regulatory and HTA Evaluations

What does the Analysis tell us? EPARs vs. HTA Appraisals for the Centrally Authorized Medicinal Products Kalydeco and Yervoy

Where are we now?

From the methodological review of the Regulators and HTA bodies' frameworks, it is to be acknowledged that Regulators and HTA bodies work under different remits and therefore the scope of the evaluation they perform on medicines is not the same.

However, this can turn out to be very frustrating for pharmaceutical companies when the same evidence gained during clinical programmes leads to different appraisals and decisions.

It is also difficult to accept for the civil society and the patients'organisations, especially in view of the recent legislative efforts to guarantee an equity in the access to health care in the European Union.

In Europe, considerable efforts have been made during the past 20 years towards the harmonization of scientific criteria in relation to the evaluation of the quality, safety and efficacy of medicines.

The creation of the European Medicines Agency (EMA) in 1993 and the beginning of its activities in 1995 represented a key milestone in this process. It provided a forum for meetings and discussions among European Union Regulators and acted as the single voice of Europe to interact with third countries and international organizations outside Europe.

In contrast, the European Health Technology Assessment network (HTAN) has increased its interactions and collaboration only in recent years and therefore it still has a long way to walk in this process of mutual understanding, trust building and harmonization of methodologies, criteria and processes.

The European Commission is fully committed to incentivize this initiative and has set a comprehensive plan to pave the way to collaboration as Europe realizes it cannot continue with 28 opinions in the framework of HTA science.

As the scope of the evaluations is different, the areas of assessment necessarily differ between Regulators and HTA bodies:

- Regulators focus on the quality, safety and efficacy of medicinal products (i.e. the so-called three basic guarantees) and it is expected that the information contained in the registration Dossiers is assessed based solely on the drug's own merits.

- HTA bodies' evaluation focus on clinical and cost-effectiveness and comparative (relative) effectiveness (i.e. the so-called fourth guarantee), being the main core principles: the value for money, national budgets and the cost of opportunity.

Public Institutions Views

There is a clear wish and effort to move towards a more harmonized system to enable the development of well-defined and targeted clinical programmes and this way speed up the access of innovative medicines to patients.

EMA has been the lead of the parallel scientific advice program that started as a pilot in 2010.

The aim of the program was to evolve towards a system where parallel Regulators-HTA advice becomes a standard procedure.

It is acknowledged that it is not possible to erase any sort of discrepant views between regulators and HTA assessments since the objectives and purpose of each type of evaluation are different. But nevertheless, the initiation of a dialogue as early as possible plays a key role in mitigating areas of discrepancies. Moreover, it can solve future problems and avoid waste of resources by advising companies on the right strategy to follow in the planning of their clinical trials. Numerous initiatives are currently on-going working on different areas.

Tremendously important is the reduction of the time invested in the development of a new drug. Identifying the needs of the two areas in an early dialogue would facilitate industry to meet both at the same time as opposed to in sequence as traditionally done. Knowing in advance and with certainty the expected requirements would allow industry to anticipate and adapt the clinical plans to demonstrate the therapeutic value of a medicine and the generation of data post-marketing authorization.

The intention of public institutions is to facilitate an earlier, better and more efficient planning, reducing time and costs and de-risking the success of programs by avoiding different decisions in view of the same evidence.

Industry Views

The current interest on this topic is enormous since it has important and direct implications in the costs and time invested in the development of new medicines and the predictability of successful outcomes both for the granting of marketing authorizations and positive financing and reimbursement opinions from HTA bodies.

In the European Union, governments are the key buyers of medicines, since the majority of European countries have either national healthcare systems or regulate somehow the compulsory private healthcare policies.

The perspective of the industry has dramatically evolved in the last two decades. Twenty years ago industry did not see the need to enter into dialogue with Regulators. Nowadays these interactions are frequent, sought and reciprocally productive. A good example is the International Conference of Harmonization (ICH) forum.

Ten years ago industry also did not seek interactions with HTA bodies and did not think of bringing Regulators and HTA bodies together.

But the environment has changed and nowadays more research is needed, and therefore more collaboration with different external parties becomes necessary to plan ahead.

Historically, industry took a stepwise approach, getting regulatory advice and approval of medicines in one wave, patients' organization involvement in a second one and finally payers' discussions. Now the objective is to carry out all these discussions in parallel and initiate the dialogue as early as possible in the development of drugs.

Patients Views

In the case of orphan drugs, those drugs indicated for the treatment of rare diseases, or in the case of end of life diseases, the alignment between regulators and HTA is even more urgently needed.

Nowadays, many factors exert pressure on decision-makers (economic and demographic factors, impact on healthcare budgets, growing investors' expectations, society sustainability and values, stratified therapies, etc.).

In view of patients' organizations, Regulators should take a flexible approach and become partners of successful development of new medicines by ensuring industry visible, predictable and consistent scientific opinions.

Generation of evidence should be a continuum along the product's lifecycle and a more flexible approach of Regulators and HTA bodies would be desirable.

In this respect, as explained in Chapter 4, Regulators and industry are studying the possibility to develop an evaluation process for medicines which is progressive in the level of requirements demanded, the so-called Adaptive Pathways. This would allow earlier patients' access to medicines in high medical need situations.

The key message is that early dialogue and harmonization is needed among the different decision-maker stakeholders (Regulators, HTA bodies, payers) as well as medical experts to help establish the potential and reality of a given product, the uncertainties and possible pathways to generate additional evidence, not to forget the patients' organizations who can play a crucial role in informing on the reality of the medical needs.

The Science

The key goal is to define clear guidance so that the scientific information needs of HTA bodies and Regulators can be commonly addressed by industry in clinical development programmes.

Regulators Views

In terms of the criteria and requirements in the evaluation of medicines in respect of quality, safety and efficacy, which are science driven, a high degree of harmonization is already achieved at European Union level.

A well-defined, transparent and predictable core of legislation is publicly available together with numerous supportive explanatory documents to help understand the provisions and requirements laid down in the Directives and Regulations.

A vast set of scientific guidelines covering the areas of quality, safety and efficacy is also publicly available and subject to periodic revision and public consultation. These guidance provides industry with a transparent view of the common acceptable standards which are required in Europe for the authorization of medicinal products.

The European Medicines Agency also exerts a crucial role in the alignment and harmonization among EU national authorities and provides the forum of discussion among all relevant stakeholders (i.e. Regulators, pharmaceutical industry and patients & health care professional's' organisations). And also through the numerous interactions with international organisations and authorities of third countries.

Beyond the EU frontiers, the highly regulated regions of the ICH (Europe, United States, Japan and also Canada and Switzerland) are uniting efforts to issue common scientific guidelines and harmonize their Pharmacopoeias.

Regulators worldwide are aware of the globalization of the pharmaceutical industry. Products are not developed for single countries or regions and the present situation is that industry is faced with the challenge to having to meet the different requirements set by the different regulatory authorities of each country or region.

It is clear that a higher degree of alignment should be feasible and highly desirable worldwide.

In this respect, the WHO is a crucial actor and should also play a proactive role in this area, trying to embark regulatory authorities of developing countries into dialogue, exchange and education programmes. Meeting their specific needs is key while at the same time ensuring that a harmonization worldwide can be preserved to the higher extent possible. Requirements should be realistic and achievable.

The European legislation sets out the conditions for the approval of a medicinal product. For Regulators, in the clinical area, a medicinal product should have a positive benefit/risk balance. In order to assess this, randomized, controlled clinical trials are necessary and compliance with Good Clinical Practice (GCP) requirements should be fulfilled.

Regulators have tools where the added value of a medicine is actually evaluated to qualify the entrance into certain procedures like the qualification for the accelerated assessment, CMA and EC MA, determination of the significant benefit of orphan drugs. The way of evaluating such aspects needs to be aligned with HTA expectations.

In terms of methodological aspects, in order to assess the value of an intervention, Regulators focus on the quality of the drug and the robust design of the clinical trials presented to assess the safety/efficacy balance.

HTAs Views

In the field of Health Technology Assessment, financing and reimbursement requirements' decisions heavily depend on economic and social factors which are context-specific and have a local nature. As a consequence, a certain degree of harmonization in this respect is only feasible nowadays to a certain extent.

In terms of methodological aspects, in order to assess the value of an intervention, HTA bodies focus on:

Efficacy: Does the medicinal product work?

Effectiveness: Does the medicinal product work in clinical practice?

Efficiency: Does the medicinal product help with more efficient use of resources?

The main areas of evidence key for HTA are:

The population.

The comparators.

The endpoints of the trial.

The uncertainty on the long-term effects.

For the choice of the population, the crucial factors identified for a good planning of a clinical trial are: information gathered from clinicians, ensure representativeness of patient population in target countries and prospectively identify biologically plausible subgroups.

For the choice of comparators: information obtained from communication with clinicians, identification of established management practice and standards of care (SOC), the use of active comparator and if possible mix direct/indirect comparison and also the consideration of the off-label use.

The indirect comparisons to other therapies (i.e. to demonstrate relative effectiveness in different subgroups) are sometimes complicated by issues with access to comparator data.

In relation to the endpoints: it is important to talk to patients, use measures important for patients' QoL/duration of life (frequency of measurement matters) and the demonstration of the relationship of the surrogate point chosen to the final outcome.

Companies are expected to show the value of their product with evidence based on robust and good quality data.

This is the basis to justify positive opinions on financing and negotiation of prices. A lot of these data can be generated within the clinical trials, but the design of the studies has to be thought and planned ahead.

Currently, due to the lack of harmonization, it is difficult for companies to meet all requirements from different EU HTA bodies.

The key identified areas where HTA bodies and Regulators have divergent opinions are the following:

- Comparators: placebo vs. active; different standards of care in different countries; different views on standard care, comparators, off-label use.
- Study populations: homogeneous vs. heterogeneous.
- Endpoints: PROs, QoL.
- Uncertainty aspects.

On-Going Work: The Creation of a Common European Policy. The Establishment of a Standardized Process Joining Regulatory and HTA Evaluations

Driven by the Directive EU 2011/24

Directive EU 2011/24 on the application of patients' rights in cross-border healthcare is the clear proof of the commitment the European institutions have made towards the improvement in the equality of healthcare access across the EU countries.

The Directive provides a legal basis for enhanced European cooperation in key areas of healthcare (Health Technology Assessment, eHealth, rare diseases, and healthcare quality and safety standards).

The sharing of knowledge and identification and transfer of best practices across Europe is incentivised. The purpose is that it will gradually lead to improved access to healthcare, and to a better safety and quality of care throughout Europe.

In addition, it creates a legal framework for the patients' right to seek healthcare in another Member State than their Member State of affiliation, and to be reimbursed for it **what ultimately should foster the harmonization in the standards and appraisals in the HTA area.**

It is also a provision of the Directive that prescriptions should be recognized among Member States. It does not imply that it has an impact on pricing and reimbursement policies, which remain under the national remit in each Member State. **However, it is fair to predict that this practice together with the sharing of knowledge and good medical practices will all lead to a**

progressive harmonization of the medicines that are available on the markets of the different EU Member States.

The Directive provides objectives and criteria for the HTA network. The aim will be to support the exchange of information on relative efficacy, short and long-term effectiveness of health technologies, including the methodologies for assessment, and ultimately also to avoid duplication of work.

Rare diseases:

The Directive contains very promising provisions regarding rare diseases.

Some patients might see themselves in the need to seek health care out of their country of affiliation due to lack of expert diagnostic or treatment options.

The Commission is devoted to support the Member States in cooperating with each other to develop better capacity for the diagnosis and treatment of rare diseases. The main tool for this purpose will be European Reference Networks (ERNs).

Reference networks already exist in some disease areas, but the Directive gives them a legal basis and a specific focus on rare diseases.

Europe Working to find a Link: European HTA-Regulators Projects

In 2004, the European Commission and the Council of the EU recognized the Health Technology Assessment as a political priority and urged for establishing a sustainable European network on HTA.

In 2005, a group of 35 organizations throughout Europe began the activities of the EUnetHTA project.

The objective was to create a sustainable and permanent HTA network in Europe with the fundamental goals to build trust among the concerned bodies, the establishment of common methodologies and the development of Information Technologies (IT) tools and systems to allow the interactions and exchange and sharing of information.

Currently, several work packages are being developed by the HTA network in the framework of different Joint Actions.

A key tool which is being developed and optimized is the HTA Core Model table, which has been subject of study in this Thesis.

It should serve as a template for HTA bodies to carry out their evaluations and this way achieve an operational harmonization among EU HTA bodies.

Another of the most relevant tools whose aim is to facilitate and promote interactions with industry stakeholders is the Early Dialogues and the SEED programme.

The intention in future to try to establish a process for permanent Early Dialogue.

This tool is envisaged to provide advice to industry for the planning of clinical trials programmes. The intention of holding an Early Dialogue is to set the scope of feasible programs and de-risk designs. Ideallly they should be conducted pre-Phase III but for some cases, also with option for pre-Phase II. The idea is to run them prior to the conduct of confirmatory trials to ensure all needs are met.

In those cases where a bridge between HTA and regulatory requirements is not possible, early dialogue can also serve to identify how the additional data can be generated.

An ideal situation should lead to the establishment of common procedures, timelines and packages that allow for time for discussions between regulators, HTA and industry

The issuance of clear guidelines defining the processes mentioned above is one key goal. In addition, these guidance should be subject to periodic consultation in order to allow for continuous updates that might be required as science and needs evolve.

EUnetHTA represents the forum of collaboration for HTA bodies in Europe.

It provides an independent, science based platform for HTA bodies to exchange HTA information and develop HTA methodologies.

EUnetHTA work strives to achieve efficient, best evidence, harmonized and transparent methodologies in HTA appraisals with the mission to contribute to the sustainability of health systems in Europe while respecting the principle of subsidiarity of the European Union.

In 2010, EUnetHTA and EMA started their collaboration in the form of exchange information and discussion on topics of common interest. The cooperation started with a project to improve the European Public Assessment Reports (EPARs), **as a tool to contribute to the relative effectiveness assessments to be performed by HTA bodies.**

The collaboration between the European Medicines Agency and EUnetHTA addresses one of the recommendations made by the Pharmaceutical Forum (to improve the availability and best use of data relevant to relative effectiveness assessment).

The Pharmaceutical Forum is a high-level platform for discussion made up of Ministers from all European Member States. Representatives of the European Parliament, the pharmaceutical industry, health care professionals, patients and insurance funds, discuss and work on how to

improve the performance of the pharmaceutical industry in terms of its competitiveness and contribution to social and public health objectives.

The European Medicines Agency publishes an EPAR for every medicinal product authorised through the centralised procedure in the European Union. The EPARs reflect the scientific conclusions reached by the Agency's Committee for Medicinal Products for Human Use (CHMP) at the end of the evaluation process, after deletion of commercially confidential information.

The EPAR project was followed by cooperation in other areas: databases for post-licensing studies, significant benefit for orphan medicinal products, EUnetHTA's rapid model for Relative Effectiveness Assessment of Pharmaceuticals (possibilities to streamline the timelines of rapid pilots with EMA assessments), early scientific advice, EMA-HTA parallel scientific advice, regulatory and HTA methodological guidelines, Adaptative Pathways etc.

Currently, meetings between the EUnetHTA and EMA representatives are held twice a year. In addition, EMA participates as observer in relevant activities of the EUnetHTA Joint Actions.

In an effort to increase awareness and transparency, EMA is in charge of preparing guidance on EMA-HTA parallel scientific advice.

Work is also on-going in the preparation of disease-specific guidelines to set agreed criteria.

What does the Analysis tell us? EPARs vs. HTA Appraisals for the Centrally Authorized Medicinal Products Kalydeco and Yervoy

The research performed on Kalydeco and Yervoy confirms the initial hypothesis that despite the last years program directed to harmonize the HTA evaluations among the European Union HTA bodies and also in relation to the regulatory framework requirements, still many discrepancies exist based not only on local economic demands but also due to scientific methodological approaches.

KALYDECO AND YERVOY ANALYSIS

As explained in detail in Chapter 5, the main differences observed between Regulators and HTA bodies in their appraisals, relate to the acceptance of the uncertainty regarding long-term effects of the medicinal product and the acceptance of the appropriateness of the measures imposed in this respect by Regulators in order to mitigate it.

This uncertainty was the main point of discrepancy for Kalydeco.

Regarding the analysis of Yervoy, some elements of the clinical study design were challenged by HTA bodies despite EMA positive views, like the comparator or the approved posology.

A very important finding from the analysis of Yervoy is that some HTA bodies might even challenge the Benefit/Risk balance of a medicinal product endorsed at European level by the EMA. This is contrary to the provisions of the Directive on Transparency.

From the analysis of Yervoy, it can also be observed that there are also differences among HTA bodies regarding what is considered an improvement in the quality of life of a patient or even what is a clinically relevant added value.

The processes for the consultation of patients' organisations in the elaboration of the appraisals is also not equivalent among HTA bodies.

Another important key point of divergence among HTA bodies is the detail of the economic evaluations performed (i.e. relative cost-effectiveness assessments).

Regarding all these aspects, the harmonization of guidance and standards among HTA bodies and with Regulators would have a very positive impact in terms of predictability of the clinical evidence to be accepted.

Nevertheless, the example of Kalydeco also evidences that the solution to EU inequalities in access to health is not be solved solely with the achievement of a harmonized EU HTA framework, as it is clear that the clinical evidence can be overruled by price and budget considerations.

The price of the medicine turns out to be a key factor. The existence of a Patients Access Scheme or negotiations with governments regarding price reductions can revert an opinion from negative to positive.

Some HTA bodies make explicit reference to the different treatment certain drugs have (i.e. orphan drugs and end-of life drugs), where higher QALY prices can be accepted like NICE or the SMC, which would be in line with the Regulators approach in terms of granting a higher degree of flexibility. Nevertheless within certain budget limits and restrictions too.

From the study of Kalydeco and Yervoy it can be questioned if the price of the drug does not exert an influence on the degree of uncertainty in the clinical evidence tolerated by HTA bodies.

The message to note from this study is that despite being recognized for the three first basic guarantees at European level, not all medicines necessarily become available to European patients in an equity manner.

The quick availability or presence at all of a determined medicine on the market of a given European country will depend on the national HTA assessments.

If European HTA bodies find that a medicine does not meet the requirements for financing and reimbursement, the entrance into the market could be blocked and subsequently the availability of the medicinal product to patients on those countries.

Therefore, the accessibility of a certain medicinal product in a certain country depends on the strategy of the laboratory and the decision taken by national health authorities concerning reimbursement.

The sponsor's strategy plays a role and is under the scope of market access which is not part of the scope of this Thesis. Governments have a limited influence over the laboratory decisions.

It is however under the remit of governmental bodies to ensure harmonized and transparent HTA assessments.

In this respect, the achievement of harmonized EU HTA methodologies and processes would clearly have a positive impact.

THESIS CONCLUSIONS

This research study allowed to verify the departing hypothesis that despite last years' attempts to harmonize the HTA evaluation among the European Union HTA bodies and also in relation to the regulatory framework requirements, still many discrepancies exist based not only on local economic demands but also due to scientific methodological approaches.

The research also allowed to identify areas that could be better harmonized to bridge the current existing gap between Regulators and HTA bodies, while respecting the current legal frameworks under which each of the two areas operates.

Otherwise, if the current situation of disharmony if not solved, it will be difficult to implement the provisions of the European Directives in relation to the equity in the access to health care.

The pharmaceutical industry would also benefit importantly from an increased harmonization and transparency in requirements, making it possible an optimization in the use of resources dedicated to the research and innovation of new medicinal products.

The application of a common HTA methodology in Europe could also highly improve the harmonization and transparency in HTA decisions. And this way, provide EU HTA bodies' recommendations and governments' final decisions on financing with more transparency and legitimacy towards the patients and general public.

The achievement of common methodological and scientific standards, guidance, processes and ways for patients' organisations involvement in the decision-making process would have a very positive impact on the system.

Nevertheless, increased transparency as to what each government is able/willing to pay for each treatment is also crucial as the price proves to play a key role in final decisions. The pharmaceutical industry also needs to be made aware of what are the price caps and thresholds governments are capable to finance so that they also recognize the role they have in making innovative treatments available to patients at a fair price.

The Regulatory framework in the EU could be harmonized thanks to the fact that the evaluations in this area are science driven, without economic underlying aspects. Regulators initiated this process more than two decades ago.

The harmonization model at HTA level is still in an early development phase. It is exciting and promising times for HTA bodies who should embrace this opportunity with enthusiasms and responsibility. Learn from the Regulators experience and apply those learnings that are useful for their areas at the same time that align with regulatory requirements.

Driven by a political mandate of the EC and the Council of Europe, the EU Member States have started the path to HTA and Regulators-HTA harmonization.

It has to be acknowledged that all stakeholders are on a learning curve so there is a long and challenging way ahead. But the chances of achieving a great success are very high. The European system proved in the past with the regulatory experience to be a fantastic network for cooperation and high level professionalism.

The financing and reimbursement decisions are within the national remit of EU Member States and therefore it is more complicated to be harmonized at EU level than the regulatory requirements for the approval of medicines.

However, a potential future solution to be explored could be the creation of a centre EU HTA body responsible to provide the non-context specific elements of HTA appraisals or otherwise the establishment of a mutual recognition procedure among HTA bodies similar to what operates in the regulatory area.

The ultimate goal is in any case that the European cooperation between HTA agencies evolves from project-based initiatives via Joint Actions and research projects into a permanent mechanism of cooperation. Models like the one operated by the European Medicines Agency in the field of Regulators could be an example.

The task of this HTA Secretariat should be facilitating cooperation. The scientific work would continue to be performed by national HTA bodies, as it is today under the EUnetHTA model.

The strategic objectives of the EUnetHTA JA2 are moving towards that direction:

-By strengthening the practical application of tools and approaches to cross-border HTA collaboration.

-By bringing collaboration to a higher level resulting in better understanding for the Commission and Member States of the ways to establish a sustainable structure for HTA in the EU.

-By developing a general strategy, principles and an implementation proposal for a sustainable European HTA collaboration according to the requirements of Article 15 of the Directive for cross-border healthcare.

Pharmaceutical industry has a lot of expectations in this process. Nowadays, industry is facing global challenges in the development of new medicines. When non-scientific regional criteria create inefficiency in the system, the whole of the society loses valuable assets. Financing has unavoidably a regional focus but a way needs to be found to match it with the global focus pharmaceutical industry has today.

The challenge that the HTA network faces now is how to harmonize this from its inception to avoid the long process of bringing together well established regional practices.

Even when it has to be acknowledged that regionalisms are unavoidable and they will persist to a certain extent, Europe could be now the lead in a process to achieve clearer guidance for companies in a field of extreme uncertainty.

There is a need for a common core model, collaboration and exchange of information among European countries and transparency towards industry.

Clear guidelines have a positive influence on responsible prescriber's behaviour, patients get guidance for an informed choice, and public health infrastructures benefit from harmonized approaches too. The efficiency of the medicine development process could be enormously improved by better incorporating real-life clinical data into drug development and appropriate guidance is needed in this area.

The European Network for HTA (EUnetHTA) can contribute to the creation of an established and agreed core model and to the connection of the European HTA bodies, avoiding duplication of work and ensuring consistency in the evaluations of evidence based data.

For this purpose, HTA bodies need to build trust among them and need to work in a harmonized way that enables the effective exchange of information, using the same methodology and assessment templates for the HTA appraisals.

It has to be born in mind that despite attempts for harmonization, a margin of variability will always exist. Policy decisions differ across the different countries whether to include the medicines as part of the services and whether or not to finance them. And some countries could even decide to include and reimburse medicines despite lack of definite conclusions in HTA reports. This way, the differences in national contexts will unavoidably lead to different prices of medicines in the different markets.

However, it should be at least ensured that clinical evidence has the same appraisal in the different regions.

The Conclusions on the clinical data related to safety and efficacy should be easily readable from the EMA EPARs for use by HTA bodies. And in fact, in the HTA Core Model, it is considered that the clinical evidence is not context specific.

However, the present study research proves that HTA bodies reach different conclusions when confronted with the same clinical evidence.

The goal of an increased collaboration would be to share high quality and systematic reports while respecting the regional specificities of the regional contexts and the national competences in the areas of pricing and reimbursement.

The aim is to move towards a system that allows the reduction in development times and enables the optimization in the use of resources. Ideally, regulatory evaluation and HTA principles should strive to achieve common parameters for clinical trials.

In the last two decades, regulatory agencies have enormously increased the level of harmonization, communication and transparency in relation to their assessment processes.

The goal now is to achieve the same degree of collaboration for the HTA process and its outcomes and find a common path where both evaluations meet and align.

We are currently witnessing the creation of the pillars of the future system for the operation of an EU HTA network in the same way as it already occurred with the EU regulatory network.

In the competitive environment where pharmaceutical industry moves nowadays and where the ultimate success or failure of one project heavily influences the possibilities for financial support for other projects in the development pipeline, it is of utmost importance to ensure that companies have at their disposal accurate information on what are the requirements for the authorization and financing of drugs so that they can plan accordingly from early stages in the development.

Regulators and HTA bodies are aware of this reality and willing to engage in a transparent and productive dialogue with industry in order to ensure predictability and facilitate as much as possible patient's early access to new medicines. Collaboration and communication is a key factor in achieving an understanding of requirements and ultimately the planning of clinical programs that generate the needed data and evidence to address both regulators and HTA bodies' expectations.

Industry could enormously benefit from a standardized process with a core of common data requirements that could still be supplemented if needed by region specific requirements. Here is the value of collaboration and exchange to establish a core model of methods to be used in HTA.

KALYDECO AND YERVOY

One of the first conclusions derived from the analysis of Kalydeco and Yervoy is that the EUnetHTA Core Model is still not yet fully implemented by EU HTA bodies.

Kalydeco and Yervoy would have in principle an absolute added value into the health care systems, as no other alternatives were available for these life-threatening diseases (chronic and terminal respectively). Both medicines cover a recognized unmet medical need even though Yervoy does not have orphan designation status as such in the EU.

However, some HTA appraisals were negative in this respect. Not only economic considerations were raised by some HTA bodies as drivers for the negative evaluations but also the clinical evidence generated. This point is hardly justifiable as the clinical evidence is considered to be non-context specific. However, some HTA bodies emphasized certain aspects of the clinical data generated in order to support their negative opinions.

It is also clear from the study that the existence of price reductions or a PAS is crucial for the positive opinion of certain HTA bodies. HTA bodies are willing to accept higher degrees of uncertainty for serious conditions treatments but not at any price.

Kalydeco

Analysing the case of Kalydeco in the light of the adaptative pathways approach launched by EMA, we can easily recognized that many of the elements described for an ideal candidate drug for such approach were actually met by Kalydeco. Kalydeco first sought indication was intended for a well-defined and restricted population of patients.

Compelling efficacy data were provided at the time of approval and conditions for the further generation of clinical evidence (efficacy and safety) long-term were imposed on the marketing authorization granted.

The pack of clinical data was considered sufficient and Kalydeco received a standard marketing authorization.

Kalydeco addressed a high unmet medical need, a situation that opens the possibility to justify a higher degree of uncertainty at the time of initial authorisation, in contrast to therapeutic areas with authorized treatment options available.

In spite of this clear regulatory view, it was precisely the lack of clinical evidence the argument raised by the HTA bodies that concluded against a financing decision.

Regarding the status of Kalydeco outside Europe, the US Food and Drug Administration (FDA) provided a lot of support to Kalydeco. The first authorization was granted for the G511D mutation in January 2012. It was granted priority review, and approval was received 3 months later. It was considered an excellent example of personalized medicine, where drugs are targeted to treat patients with a specific genetic makeup [106].

In January 2013, the FDA granted Kalydeco the first two breakthrough therapy designations: one for Kalydeco monotherapy for other CFTR mutations that culminated for approval in February 2014 for the extended indications and a second for the combination regimen of VX-809 and Kalydeco [107].

Yervoy

The study of the Yervoy case illustrates further aspects:

The standards applied for the evaluation of what is an added benefit, an improvement of quality of life and even a positive risk/balance are not fully harmonized among HTA bodies.

Some HTA bodies even challenged EMA scientific opinion in this respect.

The scope of assessment of some HTA bodies could go beyond the approved indications in the EU and beyond the evaluation of the data provided in the EPAR discussion.

The promotion of dialogue between Regulators and HTA bodies is a way of improving harmonization of standards and transparency in relation to the clinical evidence generation requirements that companies will need to meet to get approval and reimbursement for the medicines.

Nevertheless, cases like Kalydeco and Yervoy evidence that there are overriding economic factors that could ultimately determine the final decisions of a HTA body.

Orphan Diseases: Are the Patients fairly treated? Can the same Methodology be applied? Is there Equity within the EU?

THE CHALLENGES OF THE ECONOMICAL EVALUATION OF ORPHAN DRUGS

Increasing pressures on health care budgets are driving to a model where the use of economic evaluation in financing and reimbursement decisions is becoming a key factor.

The European Union has embarked in the challenging project of trying to harmonize the HTA practices among its Member States and align the HTA and the regulatory evaluation requirements as much as possible. However, at present, differences in the standards used among the EU countries remain in the HTA area.

These variations in evidence requirements among different countries for the purposes of financing and reimbursement is more dramatic in the case of orphan drugs, where on some occasions, no other equivalent therapeutic options at the disposal of these patients are left available.

The uncertainty about data support, high price and often lifelong treatment are the cause of payers' reluctance to finance these drugs.

Nevertheless, it is questionable if the same QALY thresholds should be applied to orphan diseases, which are by definition life-threatening and with a low prevalence.

The research reveals that some HTA bodies actually apply different standards, allowing more uncertainty and higher prices (with a limit).

Many stakeholders from different angles are discussing the current European framework for rare diseases. While acknowledging the success of the regulation established in 2000 as the boost for the development of orphan drugs, it is also pointed out that some areas need to be improved and an evolution of the system is also required.

Orphan drugs usually have high prices that cause their inability to meet the thresholds of cost-effectiveness established by some HTA bodies.

It has been discussed if HTA methodologies would need to be tailored for orphan drugs, taking into account the rarity of the disease, the small population benefiting from the drug, the seriousness of the condition, the unmet medical need and the lack of availability of other alternatives.

In the absence of this special HTA treatment, patients bear the risk that access to the novel treatments will be blocked.

Some agencies already have more lenient views towards these medicines and take special measures for orphan drugs. An example it the exemption from having to present an additional benefit dossier [108].

Even if due to the higher prices, orphan drugs do not meet the current standards of cost-effectiveness, it also needs to be taken into consideration that due to the reduced population affected by these conditions, the percentage of the overall drug budget they account for is small [109].

Patients can only benefit from the drugs if they get access to them. At the same time, it is a legitimate question from governments, what is the added value the new medicines will bring to this population. Not all orphan drugs have the same degree of novelty and/or efficiency.

There are certain elements that should be assessed in the HTA appraisals for orphan drugs such as:

- The rarity of the disease.
- The severity of the disease.
- The level of research undertaken to receive a marketing authorization as an orphan.
- The level of uncertainty.

- The manufacturing complexity of the product.

- The follow-up measures imposed.

- The availability of alternatives for the treatment of the condition.

- Other indications also granted to the same substance.

All these elements are considered already not only by HTA bodies, but also by Regulators in a formal or informal way when making the decisions on the merits of a medicine.

The future objective would be the establishment of transparent criteria for the HTA assessment of orphan drugs in the EU as it is a crucial point that will need to be solved in the future[110] [111]|112].

Companies need a climate of regulatory certainty and a transparent decision-making process in order to invest in the development of orphan drugs. At the same time, governments have the legitimate right to ensure that the treatments they will pay for will certainly bring a benefit to their patients. Resource allocation in national healthcare budgets is a constant pressure, especially in economic crisis times where austerity measures are spread over all areas.

When after a first rejection at the time of reimbursement negotiations, a reversal of decision is taken by a government as a result of patients organizations and public pressure, the reputation of the system is also put at stake. This is not a beneficial climate either for companies or for public institutions.

It is clear that the current HTA methodologies employed need to be tailored for orphan drugs given their peculiarities.

The currently used thresholds for cost-effectiveness cannot be met by these drugs if applied. The criteria to be chosen against which these drugs are to be evaluated is not harmonized at EU level though.

The EU institutions are currently revisiting the existing legal provisions and looking into ways to provide more flexibility for the development of drugs for unmet medical needs. The FDA procedures for expedited programmes could serve as an example.

The EMA-HTA has launched a platform to assess viability of such approaches in the EU and allow novel medicines to reach patients without the HTA bodies acting as a bottleneck.

This is definitely an exciting and challenging topic that will need thorough debate in future.

Market Access to Orphan Drugs

The granting of a marketing authorisation for an orphan drug blocks the market during ten years unless another drug can fulfil one of the derogations stated in the legislation.

That means that if no financing is granted and no commercialization takes place in certain countries, those patients will be deprived from the drug of that Marketing Authorisation Holder and also other potential drugs for the same indication.

HTA bodies would be limiting enormously the options of treatment for these patients.

Rare diseases patients' organizations also claim for alternative regulatory options that allow a quick access to novel treatments. They defend the approach that evidence generation should be a continuum throughout the product life cycle and advocates for more regulatory flexibility for progressive patient' access to new drugs in the line of the adaptative pathways initiative commenced by EMA or the expedited programmes offered by FDA.

It is claimed that regulatory flexibility is needed to help the development of these therapies and early dialogue plays also a key role in this respect.

The use of surrogate endpoints and the generation of data post-authorisation should also be acceptable.

In addition, there are currently tools in place that should be better used like the conditional marketing authorization / exceptional circumstances frameworks and the use of Patients Access Schemes.

It is clear to patients' organization as well as to industry that this regulatory flexibility should be established as a clear policy, constituting part of the regulatory framework and not just be reduced to an informal approach to be used on a case-by-case basis.

Companies need predictability in the guidance provided by the institutions and the delivery of consistent scientific opinions.

It is also a desire that the guidelines issued by the regulatory agencies of the two biggest regions (i.e. EMA in the EU and FDA in the US) align as much as possible, since the development of new drugs is undertaken in a global environment.

As a final conclusion, it has to be remarked that Regulators in the EU have achieved an enormous degree of harmonization and cooperation. This process that started more than 20 years ago now proves the benefits of a European cooperation.

The EU HTA network is currently undergoing a similar process.

In the last two decades, regulatory agencies have enormously increased the level of harmonization, communication and transparency in relation to their assessment processes.

The HTA bodies in Europe are now working to achieve the same degree of harmonization and collaboration for HTA processes and find a common path where both evaluations meet and align.

However, the local focus that the financing perspective has cannot be obviated and as a result, different national conclusions can arise from the same clinical evidence. Some of them could be due to the selection of different factors for the analysis or the outcome of the importance and interpretation given based on local specificities and values or on national cost-effectiveness thresholds and budget's restrictions.

The present study research reveals that on occasions, the decisions on financing are not mainly driven by clinical evidence but on price caps and general budget considerations. And divergent decisions among HTA bodies would also heavily be explained by these economic factors.

In such a situation, will the disharmony among European countries be solved if a common core HTA method and efficient sharing of data were established among HTA bodies?

To a certain extent it can positively influence and reassure public institutions with the legitimacy and transparency of their decisions.

Regulators and HTA bodies are aware of the need to provide pharmaceutical companies with clear guidelines for the development of new medicines and are willing to engage in a transparent and productive dialogue with industry in order to ensure predictability and facilitate as much as possible patient's early access to new medicines.

A disharmony in this area would also raise controversy across patients' organizations as it seems unjustifiable that in the framework of the European Union Equity, not all patients enjoy the same degree of health protection.

The Directive calls for Member States to cooperate in the establishment of quality standards.

Disharmony in appraisals across Europe would lead patients to question and exert pressure on their governments if certain treatments are reimbursed in some countries but not in others, especially for serious conditions where no other alternatives exist.

Even though the European Directives make it clear the national remit of financing decisions, it is crucial that public institutions build a harmonized system and make transparent the underlying causes of their decisions.

As a final conclusion of these study, the identified areas of opportunity and strategies for the future could be the following:

- Acceptance by EU HTA bodies of the scientific opinions and decisions made by Regulators in their area of competency. It is not justifiable that the decisions made by a legally recognized competent institution at EU level regarding the Risk/Benefit balance are not automatically endorsed by HTA bodies.

- Establishment of common, clear and transparent methodological guidance and processes among EU HTA bodies and where needed, involving Regulators (especially regarding the degree of uncertainty and the mitigating measures to be accepted).

- Clear definition of the scope of HTA appraisals together with explicit indication of the clinical evidence (i.e. studies) taken into account for the evaluation.

- Creation of a EU HTA Institution responsible for the appraisal of non-context specific elements, in order to ensure the same decision in view of the same clinical evidence or otherwise the establishment of a procedure for the mutual recognition of appraisals among EU HTA bodies.

- Higher and more transparent involvement of patients' organisations in the consultation of relevant endpoints and the decision making process.

- Increased transparency regarding the price that governments are willing to pay for a treatment.

However, in this subject of access and equity, not only Regulators should be seen as the only responsible party. Industry also has a responsible role to play.

Regulators and HTA bodies are taking important steps and efforts to harmonize criteria and are willing to embark in a transparent dialogue with industry to facilitate the development of new drugs. But at the same time, sponsors of the new medicines also need to be aware of the European governments' obligation to assure the sustainability and equity in their health systems.

It is key to engage industry in the responsibility they also bear in making medicines available to patients at reasonable prices that allow the return of investment and at the same time allows for the sustainability of the EU healthcare systems.

BIBLIOGRAPHY

[1] Lembit Rägo, Budiono Santoso (2008): "Drug Regulation: History, Present and Future. Chapter 6". *Drug Benefits and Risks: International Textbook of Clinical Pharmacology*, revised 2nd edition. Edited by C.J. van Boxtel, B. Santoso and I.R. Edwards. IOS Press and Uppsala Monitoring Centre.

[2] Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products. *OJ 22, 9.2.1965, p. 369–373 (DE, FR, IT, NL). English special edition: Series I Volume 1965-1966 P. 20 – 24.*

[3] European Federation of Pharmaceutical Industries and Associations EFPIA (2014): "The Pharmaceutical Industry in Figures", http://www.efpia.eu/uploads/Figures_2014_Final.pdf

[4] European Network of Health Technology Assessment (EUnetHTA). http://www.eunethta.eu/ (last accessed October 2015).

[5] European Network of Health Technology Assessment (EunetHTA). HTA Core Model. http://www.eunethta.eu/hta-core-model (last accessed October 2015).

[6] Michael Berntgen, Anne Gourvil, Mira Pavlovic, Wim Goettsch, Hans-Georg Eichler, Finn Børlum Kristensen (2014): "Improving the Contribution of Regulatory Assessment Reports to Health Technology Assessments—A Collaboration between the European Medicines Agency and the European network for Health Technology Assessment", *ELSEVIER,* 17, 634-641.

[7] European Medicines Agency (EMA) HTA collaboration. http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000476.jsp&mid=WC0b01ac0580236a57 (last accessed October 2015).

[8] European Medicines Agency (EMA). Workshop of HTA. November 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/06/event_detail_000721.jsp&mid=WC0b01ac058004d5c3

[9] Shaping European Early Dialogue (SEED). http://www.earlydialogues.eu/ (last accessed October 2015).

[10] Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community, signed at Lisbon, 13 December 2007. *Official Journal of the European Union, C 306, 17 December 2007.*

[11] Charter of Fundamental Rights of the European Union (2000 /C 364 /01). *Official Journal of the European Communities, C 364, 18 December 2000.*

[12] Consolidated version of the Treaty on the Functioning of the European Union. *Official Journal of the European Union, C 326, 26 October 2012.*

[13] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. *OJ L 88, 4.4.2011, p. 45–65.*

[14] Orphanet (The portal for rare diseases and orphan drugs). http://www.orpha.net/consor/cgi-bin/index.php (last accessed October 2015).

[15] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems. *OJ No L 40 of 11. 2. 1989 p. 8.*

[16] Amended proposal for a Directive of the European Parliament and of the Council on the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems. */* COM/2013/0168 final/2 - 2012/0035 (COD) */.*

[17] Townsend RJ (1987): "Post-marketing drug research and development", *Ann Pharmacother,* 21, 134–136.

[18] Cam Donaldson and Karen Gerard (2005): *Economics of Health Care Financing. The Visible Hand*. Palgrave MacMillan.

[19] Folland, Goodman, Stano. Pearson (2007): *The Economics of Health and Health Care*. 5th Edition. New Jersey: Pearson Prentice Hall.

[20] Joseph T. DiPiro, Robert L. Talbert, Gary C. Yee, Gary R. Matzke, Barbara G. Wells, L. Michael Posey (2011): *Pharmacotherapy: A Pathophysiologic Approach, 8e,* McGraw-Hill Education, LLC.

[21] International Conference of Harmonization (ICH) Module 4. http://www.ich.org/products/ctd.html. (last accessed October 2015).

[22] General Considerations for Clinical Trials E8 (ICH Harmonised Tripartite Guideline). Current Step 4 version dated 17 July 1997.

[23] Statistical Principles for Clinical Trials E9 (ICH Harmonised Tripartite Guideline). Current Step 4 version dated 5 February 1998.

[24] Choice of Control Group and Related Issues in Clinical Trials E10 (ICH Harmonised Tripartite Guideline). Current Step 4 version dated 20 July 2000.

[25] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. *OJ L 311, 28.11.2001, p. 67.*

[26] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. *OJ L 136, 30.4.2004, p. 1–33.*

[27] Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. *OJ No L 214 of 24. 8. 1993, p. 1.*

[28] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *OJ L 121, 1.5.2001, p. 34.*

[29] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. *OJ L 158, 27.5.2014, p. 1–76.*

[30] EudraLex Volume 1: Pharmaceutical Legislation Medicinal Products for Human Use. http://ec.europa.eu/health/documents/eudralex/index_en.htm. (last accessed October 2015).

[31] EudraLex Volume 2: Pharmaceutical Legislation Notice to applicants and regulatory guidelines medicinal products for human use. http://ec.europa.eu/health/documents/eudralex/index_en.htm. (last accessed October 2015).

[32] EudraLex Volume 3: Scientific guidelines for medicinal products for human use. http://ec.europa.eu/health/documents/eudralex/index_en.htm. (last accessed October 2015).

[33] EudraLex Volume 4: Good manufacturing practice (GMP) Guidelines. http://ec.europa.eu/health/documents/eudralex/index_en.htm. (last accessed October 2015).

[34] EudraLex Volume 9: Pharmacovigilance guidelines. http://ec.europa.eu/health/documents/eudralex/index_en.htm. (last accessed October 2015).

[35] EudraLex Volume 10: Clinical trials guidelines. http://ec.europa.eu/health/documents/eudralex/index_en.htm. (last accessed October 2015).

[36] European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure. http://www.ema.europa.eu/ema/ (last accessed October 2015).

[37] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *OJ L 324, 10.12.2007, p. 121–137.*

[38] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. *OJ L 18, 22.1.2000, p. 1.*

[39] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. *OJ L136, 30.4.2004, p. 34.*

[40] European Medicines Agency http://www.ema.europa.eu/ema/ (last accessed October 2015).

[41] International Conference of Harmonisation (ICH) http://www.ich.org/home.html (last accessed October 2015).

[42] Amended by Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. *OJ L159, 27.6.2003, p.46.*

[43] Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'. *OJ L 103, 28.4.2000, p. 5–8.*

[44] EMA Orphans Drugs. http://www.ema.europa.eu/ema/ (last accessed October 2015).

[45] Community Registry Orphan Medicinal Products Designations. http://ec.europa.eu/health/documents/community-register/html/orphreg.htm (last accessed October 2015).

[46] EC Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000 on assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity (2008/C 242/08). *Brussels, 19.9.2008 C (2008) 4077 final.*

[47] EMA Pre-Submission Guidance "What is the procedure and timetable for assessment of similarity and, where applicable, derogation report vis-à-vis authorised orphan medicinal products?" http://www.ema.europa.eu/ema. (last accessed October 2015).

[48] Simoens S, Picavet E, Cassiman D, Dooms M (2012): "What price do we pay for Re purposing medicines for rare diseases?"*, Brit Med J.*

[49] Guideline on the procedure for accelerated assessment pursuant to article 14 (9) of Regulation (EC) No 726/2004. *EMEA/419127/05*.

[50] Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. *Official Journal L 92, 30/3/2006 p. 6 – 9.*

[51] Draft Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004. *EMA/CHMP/509951/2006, Rev.1 3 Committee for Medicinal Products for Human Use. 23 July 2015.*

[52] Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to Article 14 (8) of Regulation (EC) No 726/2004. *EMEA/357981/2005.*

London, 15 December 2005.

[53] Guideline on compassionate use of medicinal products, pursuant to article 83 of Regulation (EC) No 726/2004. *Doc. Ref: EMEA/27170/2006. London, 19 July 2007.*

[54] Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics

U.S. Department of Health and Human Services Food and Drug Administration Centre for Drug Evaluation and Research (CDER) Centre for Biologics Evaluation and Research (CBER) May 2014 Procedural.

[55] International Society for Pharmacoeconomics and outcomes research. ISPOR http://www.ispor.org/ (last accessed October 2015).

[56] Kristensen FB, Gerhardus A (2010): "Health technology assessments: what do differing conclusions tell us?" *BMJ, 341:c5236.*

[57] Fundación Gaspar Casal (2008): *Eficiencia y Medicamentos: Revisión de las Guías de Evaluación Económica. La Cuarta Garantía.*Barcelona, Sanofi-Aventis.

[58] National Institute for Health and Clinical Excellence NICE. https://www.nice.org.uk/ (last accessed October 2015).

[59] National Institute for Health and Clinical Excellence (NICE): Appraising Orphan Drugs. http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf (DRAFT v3).

[59] NICE calls for a new approach to managing the entry of drugs into the NHS. NICE Press release 18th September 2014.

[60] European Commission – Health Technology Assessment. http://ec.europa.eu/health/technology_assessment/policy/index_en.htm (last accessed October 2015).

[61] European Network Health Technology Assessment EUnetHTA www.eunethta.eu (last accessed October 2015).

[62] HTA Core Table version 2.0 http://meka.thl.fi/htacore/model/AE-tables-pharma-2.0.pdf

[63] HTA Core Table version 2.1 http://meka.thl.fi/htacore/ViewApplication.aspx?id=17128

[64] HTA Core Table version 3.0 http://meka.thl.fi/htacore/BrowseModel.aspx

[65] HTA Methodological Guidelines. http://www.eunethta.eu/eunethta-guidelines (last accessed October 2015).

[66] International Network of Agencies for Health Technology Assessment. Members. INAHTA www.inahta.org/Members/ (last accessed October 2015).

[67] International Network of Agencies for Health Technology Assessment. HTA checklist. www.inahta.org/HTA/Checklist (last accessed October 2015).

[68] Regulation (EC) No 883/2004of the European Parliament and of the Council of 29 April 2004 on the coordination of social security systems. *OJ L 166, 30.4.2004, p. 1–123.*

[69] C-372/04 Yvonne Watts / Bedford Primary Care Trust, Secretary of State for Health, judgment of 16.5.2006 Social policy: Patient mobility – Medical expenses incurred in another Member State http://ec.europa.eu/dgs/legal_service/arrets/04c372_en.pdf

[70] European networks of reference for rare diseases. http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf/index_en.htm (last accessed October 2015).

[71] Orphanet. http://www.orpha.net/consor/cgi-bin/index.php (last accessed October 2015).

[72] DG SANCO – HTA. http://ec.europa.eu/health/technology_assessment/policy/index_en.htm (last accessed October 2015).

[73] COMMISSION IMPLEMENTING DECISION of 26 June 2013 providing the rules for the establishment, management and transparent functioning of the Network of national authorities or bodies responsible for health technology assessment (2013/329/EU). *OJ L 175, 27/06/2013, p.71.*

[74] HAS – SEED Secretariat. http://www.earlydialogues.eu/has/ (last accessed October 2015).

[75] Briefing Book Template for an Early Dialogue. http://www.earlydialogues.eu/has/?page_id=311 (last accessed October 2015).

[76] Best Practice Guidance for Pilot EMA HTA Parallel Scientific Advice Procedures. *EMA/109608/2014 Human Medicines Development and Evaluation. 7 May 2014.*

[77] Berntgen M, Gourvil A, Pavlovic M, Goettsch W, Eichler HG, Kristensen FB (2014):

"Improving the contribution of regulatory assessment reports to health technology assessments--a collaboration between the European Medicines Agency and the European network for Health Technology Assessment". *Value Health*, 17(5):634-41.

[78] Day 80 assessment report templates and guidance documents. www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000337.jsp&mid=WC0b01ac0580022719#section1 (last accessed 21 July 2015).

[79] Assessment report: Lenvima (EMA/250082/2015), 26 March 2015. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003727/WC500188676.pdf

[80] H-G Eichler, LG Baird, R Barker, B Bloechl-Daum, F Børlum-Kristensen, J Brown, R Chua, S Del Signore, U Dugan, J Ferguson, S Garner, W Goettsch, J Haigh, P Honig, A Hoos, P Huckle, T Kondo, Y Le Cam, H Leufkens, R Lim, C Longson, M Lumpkin, J Maraganore, B O'Rourke, K Oye, E Pezalla, F Pignatti, J Raine, G Rasi, T Salmonson, D Samaha, S Schneeweiss, PD Siviero, M Skinner, JR Teagarden, T Tominaga MR Trusheim,S Tunis,TF Unger, S Vamvakas and G Hirsch (2015): "From adaptive licensing to adaptive pathways: Delivering a flexible life-span

approach to bring new drugs to patients". *Clinical Pharmacology & Therapeutics*, 97: 234–246. doi: 10.1002/cpt.59.

[81] 1. Minutes of EMA/EUnetHTA meeting held on 8 May 2015 (EMA/353327/2015), published online 30 June 2015. www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/07/WC500189013.pdf

[82] EUnetHTA JA2 WP5 - Applying the HTA Core Model for Rapid Assessment for national adaptation and reporting. www.eunethta.eu/activities/EUnetHTA%20Joint%20Action%202%20(2012-15)/ja2-wp5-applying-hta-core-model-rapid-assessment-nation (last accessed July 2015).

[83] Ian Schofield (2015): "Action on 'weaknesses and challenges' in EU orphan drug system could lead to tougher designation requirements". *Scrip Regulatory Affairs*.

[84] Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products. *OJ, 29 July 2015, C-178 (2-8)*.

[85] MHRA. https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency (last accessed October 2015).

[86] European Medicines Agency. Find Medicine. Human Medicines. EPARs. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 (last accessed October 2015).

[87] M Donatello Salvatore, Roberto Buzzetti, Ermanno Baldo, Maria Lucia Furnari, Vincenzina Lucidi, Daniela Manunza, Italo Marinelli, Barbara Messore, Anna Silvia Neri, Valeria Raia, Gianni Mastella (2012): "An overview of international literature from cystic fibrosis registries", Part 4:Update 201. *ELSEVIER. Journal of Cystic Fibrosis* 11. P.480–4931.

[88] Register of designated orphan medicinal products. DG SANCO. http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm (last accessed October 2015).

[89] Kalydeco (ivacaftor). European Public Assessment Report. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002494/human_med_001575.jsp&mid=WC0b01ac058001d124

[90] - Scottish Medicines Consortium (SMC): Ivacaftor 150mg film-coated tablets (Kalydeco). SMC Nº (827/12). 7 December 2012 and 10 May 2013.

[91] Clinical Commissioning Policy: Ivacaftor for cystic fibrosis (G551D gene)). April 2013. Reference: NHSCB//A01/P/a.

[92] Informe de Posicionamiento Terapéutico de Ivacaftor (Kalydeco). 18 June 2014.

[93] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG)-Berichte-Nr. 143. Ivacaftor. 30 October 2012.

[94] National Centre for Pharmacoeconomics (NCPE). Ireland. Cost-effectiveness of Ivacaftor (Kalydeco) for the treatment of cystic fibrosis in patients age 6 years an older who have the G551D mutation. January 2013.

[95] Haute Autorité Santé. Transparency Committee. Opinion 7 November 2012. Kalydeco.

[96] Deborah Cohen, James Raftery (2014): "Paying twice: question over high cost of cystic fibrosis drug developed with charitable funding", *BMJ 348:g1445.*

[97] Final CDEC Recommendation. Ivacaftor. CDEC Meeting – February 20, 2013. Notice of CDEC Final Recommendation – March 22, 2013.

[98] Public Summary Document. Ivacaftor. March 2014 PBAC Meeting.

[99] Yervoy (ipilimumab). European Public Assessment Report. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002213/human_med_001465.jsp&mid=WC0b01ac058001d124

[100] - Scottish Medicines Consortium (SMC): ipilimumab 5mg/ml concentrate for solution for infusion (Yervoy). SMC Nº (997/14). 10 October 2014.

[101] National Institute for Health and Care Excellence. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (December 2012) & Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (May 2014).

[102] Informe de Posicionamiento Terapéutico de ipilimumab (Yervoy). 22 Febrero 2013.

[103] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG)-Commission No. A13-44. Ipilimumab (new therapeutic indication). 13 March 2014.

[104] Horizon Scanning in Oncology. Ipilimumab (Yervoy) for the first-line therapy of advanced/metastatic cutaneous melanoma. Ludwig Boltzmann Institute (HTA) – Austria (Jun 2012).

[105] Haute Autorité Santé. Transparency Committee. Opinion 14 December 2011 and 6 November 2013. Yervoy.

[106] FDA. News Release.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm

[107] FDA Kalydeco Overview.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=KALYDECO

[108] German AMNOG. E.g., exemption from standard economic evaluation in Belgium and the Netherlands; German AMNOG, which exempts orphan drugs with sales of less than 50 million Euros per year from being subject to an "additional benefit" dossier. http://www.english.g-ba.de/benefitassessment/information.

[109] Hughes-Wilson et al. (2012): "Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments?" *Orphanet Journal of Rare Diseases,* 7:74.

[110] Gaining Reimbursement of Orphan Products in Europe: Challenges due to wide variations in evidence requirements and processes (ISPOR 15th Annual European Congress, 3-7 November 2012, Berlin, Germany).

[111] Michael F Drummond (2008): "Challenges in the economic evaluation of orphan drugs", *Eurohealth,* Vol 14 No 2.

[112] Susan R.Forda, Richard Bergström, Magda Chlebus, Richard Barker and Peter Hongaard Andersen (2013): "Priorities for improving drug research, development and regulation", *Nature Reviews. Drug Discovery*, Volume 12.