

# The Impact of the EMA-EU netHTA Collaboration on Drug Development

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## List of Abbreviations

AIFA	Agenzia Italiana del Farmaco
CAVOMP	
CVZ	College voor Zorgverzekeringen(HTA,Netherlands)
DHMA	Danish Health and Medicines Authority (hosts the EUnetHTA Secretariat)
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DPBA	Dental and Pharmaceutical Benefits Agency (Sweden)
ECHTA/ECAHI	European Collaboration for Health Technology Assessment – Assessment of Health Interventions
EFPIA	
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
G-BA	Gemeinsamer Bundesausschuss (Germany)
EPAR	European public assessment report
HAS	Haute Autorité de Santé (France)
HEOR	Health Economics and Outcomes Research
HLPF	High Level Pharmaceutical Forum
HTA	Health Technology Assessment
HIS	Healthcare Improvement Scotland
JA(1,2)	Joint Action (triannual EUnetHTA projects)
MA	Marketing Authorisation
Medical Valley-EMN	Medical Valley Europäische Metropolregion Nürnberg
MHRA	Medicines and Health Care Products Regulatory Agency
MPA	Medical Products Agency (Sweden)
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NICE	National Institute for Health and Care Excellence (UK)
NIHR	National Institute for Health Research
PDCO	Paediatric Committee
PRO	Patient Reported Outcome
RCT	Randomized Controlled (Clinical) Trial
REA	Relative Effectiveness Assessment
RMP	Risk Management Plan
SA	Scientific Advice
SEED	Shaping European Early Dialogues
SmPC	Summary of product characteristics
SOC	Standard of Care
WP (1...)	Work Package (of EUnetHTA collaboration)

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## **1. Scope of the thesis**

Current drug development occurs in the field of tension between the requirements of regulatory authorities in the context of licensing and health technology assessment (HTA) bodies in the context of reimbursement and pricing. While marketing authorization is the sine qua non for market entry it is the outcome of the evaluation of a novel drug by HTA bodies that finally determines the commercial success or failure.

Whereas the regulatory field is highly harmonized in Europe, HTA assessment as a prerequisite for reimbursement decisions is still done at the national level and Europe-wide efforts for harmonization in the HTA-field are just emerging. Concurrently it was recognized that harmonization among European HTA bodies without some kind of alignment with the EMA as the central European regulatory authority would not support the goal of the whole exercise, i.e. to facilitate the access to innovative medicinal products by establishing reliable framework conditions for future drug development.

This overall goal is very ambitious. Regulators and HTA experts speak different technical languages, use different criteria for requesting and evaluating clinical data, are subjected to different legislation etc. The process of collaboration between the EMA and the European network of HTA organisations EUnetHTA started in 2010 and has led to the formulation of a 3-year work program (2013-2015) that touches almost every important aspect of drug development.

It is the goal of this thesis to give a short historical perspective of the collaboration, to elaborate the achievements so far and to provide an interim assessment of their impact on drug development. Finally the outlook given must inevitably be (cautiously) speculative since the field of collaboration between regulatory authorities and HTA bodies is still evolving, many common projects are voluntary pilots or are just moving into field testing.

The term drug development is used in its widest meaning, embracing all activities from the time of conception of a drug project until the end of all post-authorization studies. The considerations and the analysis in this thesis apply to innovative medicinal products - so called new chemical/molecular entities/ (NCEs/NMEs<sup>1</sup>). Whenever reference is made to regulatory aspects or HTA-aspects these statements relate to the European situation and especially to centrally authorized medicinal products which constitute the majority of novel medicines. Procedures and concepts from outside Europe are clearly indicated.

The field of collaboration between the EMA and EUnetHTA is not easy to grasp. EUnetHTA is a voluntary network of Health Technology Assessment Bodies (HTA-bodies) in Europe, which itself has a status as partner or observer in various other networks that directly or indirectly interact with the EMA. On the other side the EMA interacts with national HTA-bodies which at the same time are partners in the EUnetHTA collaboration, so that one can assume that these organisations feedback their experiences into the EUnetHTA network. In summary this study is based on the available information of all kinds of EMA/EUnetHTA interactions, direct collaboration, partnership in a common network, indirect interactions. It was felt that a restriction of the study to only the direct collaboration would unnecessarily simplify and distort the picture of the complex European regulatory/HTA collaborative landscape.

As the field is highly dynamic it is important to note that the work presented is based on the analysis of information available by end of July 2014.

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<sup>1</sup> Generics and biosimilars are out of the scope of this work. Development and reimbursement of these medicinal products follow different rules as these drugs claim their position in health care not via innovation but via attractive pricing.

## 2. Introducing the topic

Before entering into a detailed analysis of the actual theme of the thesis – the collaboration between the EMA and EUnetHTA- it seems appropriate to

1. introduce a set of technical terms that will be used throughout this work and
2. briefly describe the “field of tension” that results from the relative position of the Regulatory Domain and the Health Technology Assessment-Domain (HTA-Domain) on the efficacy/effectiveness axis (see Fig.1 )

### 2.1 Technical terms:

<b>Efficacy</b>	“the extent to which an intervention does more good than harm under <i>ideal circumstances</i> ” [1] (emphasis by the author)
<b>Relative efficacy</b>	“the extent to which an intervention does more good than harm, under <i>ideal circumstances, compared to one or more alternative interventions</i> ” [1] (emphasis by the author)
<b>Effectiveness</b>	“the extent to which an intervention does more good than harm when provided under the <i>usual circumstances of health care practice</i> ” [1] (emphasis by the author)
<b>Relative effectiveness</b>	“the extent to which an intervention does more good than harm <i>compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice.</i> ” [1] (emphasis by the author)
<b>Health Technology Assessment (HTA)</b>	“method of <u>evidence synthesis</u> that considers evidence regarding <u>clinical effectiveness, safety, cost-effectiveness</u> and, when broadly applied, includes social, ethical, and legal aspects of the use of health technologies. .... A major use of health technology assessment is <u>informing reimbursement and coverage decisions</u> , in which case HTAs should include benefit-harm assessment and economic evaluation” [2] (emphasis added)
<b>Relative Effectiveness Assessment (REA)</b>	“The <u>purpose of a relative effectiveness assessment</u> is to <u>inform</u> health care professionals, patients and decision makers <u>about the net therapeutic benefit of an intervention compared with alternative interventions</u> . Therefore, we would position relative effectiveness assessment as a <u>specific element of a health technology assessment that focuses on the clinical implications of the intervention</u> , whereas the concept of health technology assessment is broader and can also include for example social, ethical and cost aspects”. [2] (emphasis added)

## 2.2 The efficacy / effectiveness axis as a model to visualize the fields of action of Regulatory Authorities and HTA Bodies

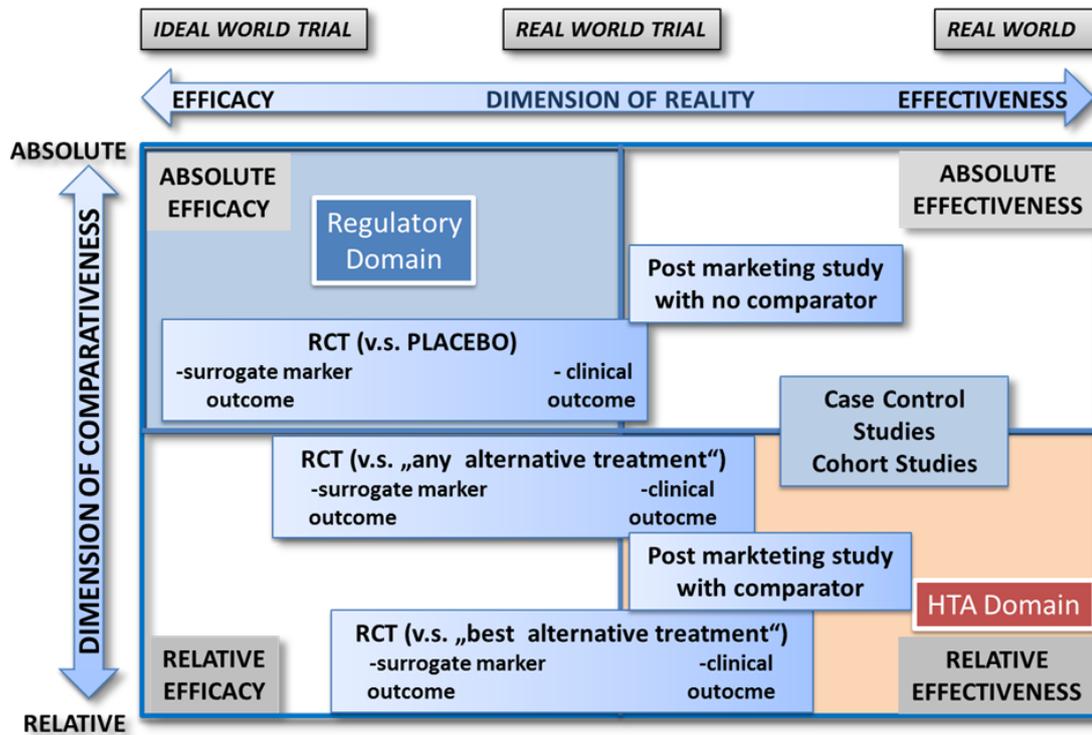


Fig.1: Regulatory Domain (Blue Quadrant) and HTA Domain (Pink Quadrant) and their respective position relative to the efficacy / effectiveness scale (Source: [3], modified by the author) The scheme is by intention idealistic, since in every day practice there is significant overlap of the two domains and the current developments in the regulatory field e.g. the new pharmacovigilance legislation with the call for post authorisation studies will certainly expand the regulatory domain towards the “the real world quadrant”.

Recital 13 of Regulation (EC) 726/2004 can be read as a general description of the Regulatory field of action in Europe in that it puts forward that “In the interest of public health, authorisation decisions under the centralized procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations.” Clinical data that form the basis for the decision about marketing authorisation in most cases originate from randomized controlled clinical trials where the medicinal product is tested against placebo or a comparator under tightly controlled conditions<sup>2</sup> The HTA Domain forms the other pole of the efficacy/effectiveness axis. Here the mandate is clearly to provide guidance for economic decisions (see definition above). For HTA /Relative Effectiveness Assessment ideally the value of a medicinal product should be demonstrated compared to standard of care under real world conditions (focus on effectiveness and external validity). Standard of care can be any medical intervention and it may vary between national health systems.

<sup>2</sup> In this context it often stressed that regulatory assessment is focused on internal validity of evidence, which means methodological rigor and minimizing bias and flaws in performing clinical studies, whereas Relative Effectiveness Assessment is concentrated on external validity which refers to the value of the presented evidence in the real world health care context [Taylor, S., & Asmundson, G. J. G. (2008). Internal and external validity in clinical research. In D. McKay (Ed.), Handbook of Research Methods in Abnormal and Clinical Psychology (pp. 23-34). Thousand Oaks, CA: Sage]

### **3. The European network of HTA bodies (EUnetHTA and HTAN)**

In Europe as in most other areas of the world the granting of the marketing authorisation and the health technology assessment (HTA) of a novel medicinal product (i.e. health technology in HTA-terminology) fall within the competence of different authorities. Whereas the regulatory path has been highly harmonized over the years e.g. by introducing the community code for medicinal products (Directive 2001/83EC), establishing a central authorisation procedure and a central regulatory authority (Regulation (EC) 726/2004), HTA as the basis for reimbursement decisions is still left to the judgment and discretion of over 30 national authorities (e.g. one national and 7 regional HTA agencies/services in Spain alone [4]). A survey over 26 European jurisdictions has highlighted the range of diversity of dedicated resources, methodologies and quality of health technology assessment and underscored the importance of efforts to establish transnational standards. [2].

Fostering innovation and commercial competitiveness of the common market, transparency of decision making, access to high quality medicines, avoidance of double work and best use of available resources are the recurrent themes of European Health Policy. Therefore it was obvious that the European Council engaged into a project focused on ways of work sharing and harmonization in the field of HTA [5].

#### **3.1 A short history of HTA in Europe and the foundation of EUnetHTA**

There is broad consensus that Archibald Lemman Cochrane's monograph *Effectiveness and Efficiency: Random reflections on health services* published in 1971 was the initial intellectual landmark in the history of Evidence-Based Medicine and HTA [6]. The first HTA institution worldwide was The Office of Health Technology Assessment (OTA) founded 1976 in Washington DC [7]. The concept of HTA soon spread back to Europe (where it originated), France, Sweden and the Netherlands being the first to set up an institutional framework in the early eighties and the northern countries being pioneers in initiating first transnational collaborations [7] [8].

Between 1994 and 2002 the European Commission supported and funded several HTA projects with the goal to foster collaboration between member states (EU-ASSESS, HTA-Europe Project, ECHTA/ECAHI) [ibid]).

At the European policy level the concept of a European HTA network [5] [9] evolved mainly in the course of the process on cross border healthcare through the work and recommendations of

- *the High Level Group on Innovation and Provision of Medicines in the EU (G10,2002)*: recommendation to improve quality and sharing of data in HTA
- *Health Council (2002)*: recommendation for a HTA network as part of cross-border collaboration in health care
- *High Level Group on Health Services and Medical Care (HLG, 2004)*: recommendation to establish a sustainable HTA network and support this project by setting up a 3-year project supported by the EU Public Health Program. This was endorsed by the Council of Ministers. Subsequently the DG SANCO opened a call in 2005 for establishing such a European network on HTA.

In spring 2005 headed by the Danish Centre for HTA (DACETHTA) a task force consisting of HTA representatives from Denmark, Finland, France, Germany, Norway, Spain and United Kingdom produced a proposal for such a network. This application on behalf of thirty-five cofounding organizations and twenty four other organizations that contributed to the proposal was successful and lead to the foundation of EUnetHTA [5] (see also figure 2.). The EUnetHTA

project continued from 2006-2008. In continuation of the EUnetHTA project in 2009 the Commission opened a call on Joint Action “1” which supported the EUnetHTA collaboration from 2010-2012, this call was followed by another one on Joint Action “2” in 2011, which supports the collaboration until 2015 [9].

### 3.2 The European Health Technology Assessment Network (HTAN)

Whereas EUnetHTA is a voluntary association of organisations involved in HTA with a clear focus on scientific aspects of HTA, the so called Cross Border Directive , Directive 2011/24 EU [10] provides the legal basis for a European HTA network (HTAN) with an overall strategic mandate concerning HTA cooperation in Europa.

#### Article 15 of the Directive specifies:

“Cooperation on health technology assessment

1. The Union shall support and facilitate cooperation and the exchange of scientific information among Member States within a **voluntary network** connecting national authorities or bodies responsible for health technology assessment designated by the Member States. [...].

2. The objectives of the health technology assessment network shall be to:

(a) support cooperation between national authorities or bodies;

(b) support Member States in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy as well as on the short- and long-term effectiveness, when applicable, of health technologies and to enable an effective exchange of this information between the national authorities or bodies;

[...]

(d) avoid duplication of assessments.

[...]

4. The Commission shall, in accordance with the regulatory procedure referred to in Article 16(2), adopt the necessary measures for the establishment, management and transparent functioning of this network.

[...]

**7. Measures adopted pursuant to this Article shall not interfere with Member States’ competences in deciding on the implementation of health technology assessment conclusions and shall not harmonize any laws or regulations of the Member States and shall fully respect the responsibilities of the Member States for the organization and delivery of health services and medical care.”** [10] (Emphasis added by the author)

According to article 4 of the Cross Border Directive the Commission issued an Implementing Decision on June 26 2013. “..providing the rules for the establishment, management and transparent functioning of the Network of national authorities or bodies responsible for health technology assessment.” [11] In demarcation to the EUnetHTA collaboration that is solely focused on the scientific and technological aspects of HTA the task of the new HTA Network (HTAN) being comprised of the HTA agencies of the member states is to define a strategic multiannual work program concerning European cooperation in the HTA field.

Article 5 (2) of the Implementing Decision stipulates that “The HTA Network shall be supported by a scientific and technical cooperation and may initiate or participate in activities involving all or some of its Members, if such involvement contributes to the objectives of the HTA Network.” [11]. During the first meeting of the HTA network in Brussels in October 2013 it was confirmed that this function will be carried out by EUnetHTA until end of Joint Action 2 (end of 2015). This is also laid down in the Rules of Procedure and in the multi-annual work program of the HTA-network [12].

Since its foundation in 2013 the HTA Network has held two meetings and is currently in the process of working on a draft strategy with the aim to develop a vision for long-term HTA-cooperation in the EU [ibid.]



Fig.2: Time-line for the establishing EUnetHTA and the European HTA Network and the mode of future interaction between EUnetHTA and the European HTA Network as envisioned by EUnetHTA (Source [13])

### 3.3 The Organizational Framework of EUnetHTA [14] [15] [16]

#### 3.3.1 EUnetHTA Participants

**Partners:** Consisting of

- The **Founding Partners** of the EUnetHTA Collaboration (25 organisations from 13 Member States, Norway and Switzerland (eg. DIMDI and IQWIG for Germany, NETSCC for United Kingdom)
- Other publicly funded HTA organisations from EU member states, EEA and EFTA, nominated by their Ministries of Health (e.g. NICE for United Kingdom)

Partners become **Lead Partners** by leading one of the work packages of the collaboration. Their obligations are: organization and management of the respective work package. They have access to tools and information generated by the collaboration. Their participation is voluntary and they can resign any time.

**Associates:** Consisting of

- Non-profit HTA-organisations willing to actively contribute to the scientific work of EUnetHTA (e.g. G-BA and Medical Valley EMN for Germany, HIS for Scotland). They participate in EUnetHTA at their own expense.

Their obligation is to actively participate in the activities of the collaboration. They may resign any time and they can participate in the Plenary Assembly without having a voting right.

### 3.3.2 EUnetHTA Governance: (see Fig.3)

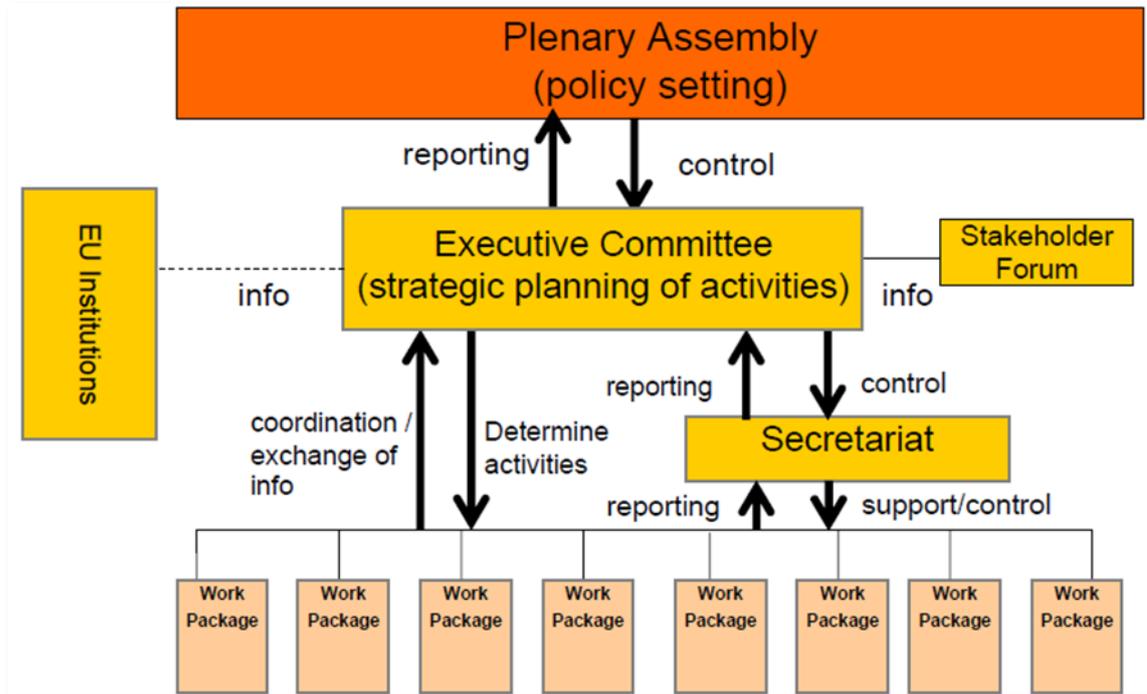


Fig.3: The Organizational Framework of EUnetHTA, Source: [17]

#### Plenary Assembly

- Members are the Heads (or person nominated by the head) of the Partner Organisations, Chair is appointed by Plenary members

The Assembly makes strategic decisions e.g. on work packages, work plans, budget, composition and involvement of stakeholder forum etc..

#### Executive Committee

- Members are representatives from the Lead Partners (1/Lead), the Secretariat Leader and Manager, three representatives from non-Lead Partners, Chair is appointed by Committee members.

It is an executive body responsible for proposing strategies, work plans etc., implementation of the agreed policy and management of the collaborations and it has the right of proposal for composition of stakeholder forum.

#### Secretariat

It has a purely administrative role and is hosted by the Danish Health and Medicines Authority (DHMA).

#### Stakeholder Forum

- Consists of European umbrella organisations (max. 4 per peer group) representing
  - 1. Policymakers at regional/national/hospital level
  - 2. Patient organisations
  - 3. Healthcare professionals
  - 4. Payers (statutory health insurance)
  - 5. Industry
  - 6. Health related media

Stakeholder representatives can participate in Joint Action, have the status of observers and commenters, provide advice and give input by bringing forward themes and concerns.

### 3.4 The EUnetHTA work plans

EUnetHTA is taking forward the recommendations of the High Level Pharmaceutical Forum (HLPF) [18] with respect to the implementation of good practice principles of relative effectiveness assessment<sup>3</sup> (REA) and promotion of exchange of information related to REA among Member States. While leaving the autonomy of Member States with respect to pricing and reimbursement decisions untouched the HLPF stressed the need for improvement in the quality of the scientific assessment of the relative effectiveness by consolidation of methodology, best use of available data, improvement in the way of generation of data by early dialogue between industry and national authorities and establishment of ways of optimal exchange of data. All these activities should happen under the umbrella of an already existing network. Finally EUnetHTA took over the role of this hub for transnational HTA collaboration in the sense of the HLPF recommendations. The work of the EUnetHTA collaboration is being performed within the framework of so called Joint Actions, a term to underscore the collaborative nature of interaction between the European Commission and the Member states. Joint Action 1 (JA1) took place from 2010-2012, Joint Action 2, building on the results of JA1 lasts from 2013-2015.

JA1 and JA2 have the same structure of 8 Work Packages (WPs), WP4, 5, and 7 being focused on the scientific output):

Work Package (WP)	Tasks [17] [19]
WP1	Coordination: Strategic Planning, Reports, Organisation of Meetings
WP2	Dissemination: Communication, Trainings
WP3	Evaluation: Achievement of working goals, quality assurance
<b>WP4</b>	<b><u>Core HTA Model:</u></b> <b>Online tool, testing and performing pilot core HTAs, application in national context</b>
<b>WP5</b>	<b><u>Relative Effectiveness Assessment of Pharmaceuticals:</u></b> <b>Tools for rapid and full REA, testing and performing pilots, application in national context</b>
WP6	Information Management System (IMS)
<b>WP7</b>	<b><u>New Technologies:</u> Additional Evidence Generation, Early Dialogs</b>
WP8	Strategy and Business Model Development

The objectives of JA1 were:

- “1. Development of a general strategy and a business model for sustainable European collaboration on HTA
2. Development of HTA tools and methods

<sup>3</sup> The HLPF, composed of the European Commission, the 27 Member States, three representatives from the European Parliament, EFTA representatives and key stakeholders from the public and private health care sectors, endorsed the following definition of relative effectiveness:” Relative effectiveness can be defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice.” (Core Principles on relative effectiveness, online available at: [http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea\\_principles\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf), accessed 12-06-2014) Relative effectiveness assessment of a health technology is the starting point for health economic assessments like cost-effectiveness analysis (Phillips, C.: What is cost-effectiveness analysis, online available at: <http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/Cost-effect.pdf>, accessed 12-06-2014)

3. Application and field testing of developed tools and methods” [17]

Scientifically the main effort during JA1 was concentrated on refinement, adaptation (e.g. to the needs of rapid REA) and initial testing of the HTA Core Model (see below), a tool developed during the EUnetHTA Project (2006-2008). In addition a series of general scientific guidelines was developed and a pilot set of two Scientific Advice procedures (called Early Dialogues) were performed. [20]

Objectives of JA2 are [19]:

1. “..Test the capacity of national HTA bodies to produce structured core HTA information (full core/rapid HTAs) together and apply it in national context ...” [ibid.]

Deliverables :

WP4: at least 3 full Core HTAs, generation of national HTA using the Core Model, transfer of existing Core HTAs into national reports

WP5: at least 14 rapid REAs collaboratively produced(Strand A: 10 for drugs and Strand B: 4 for non-drug technology Transfer of rapid HTA into approximately 20 national reports for drugs and approximately 10 national reports for technologies

2. “...Implement, pilot and further develop models and tools as well as production processes to support collaborative production of core HTA information ...”[ibid.]

Deliverables: WP7: Templates for manufacturers of health technologies for submission of information to support HTA reports and REAs. Early Dialogues (3 on drugs and 1 for medical devices) and disease specific guidelines.

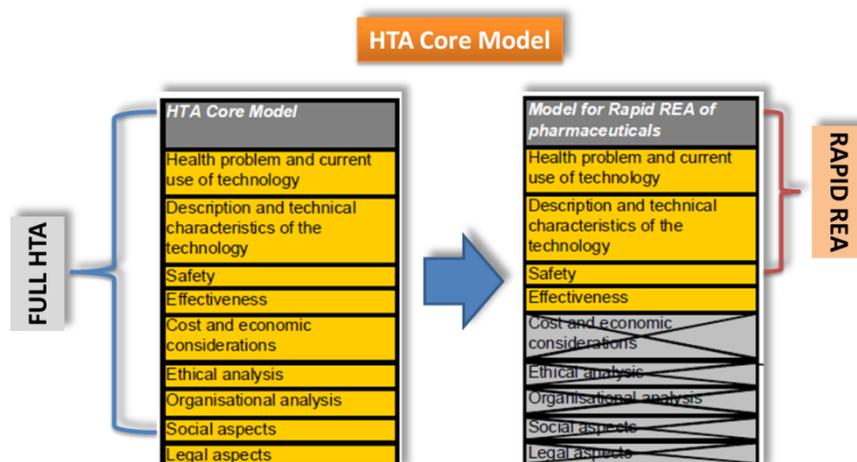
“...Develop and test a methodological basis for European cooperation on HTA including guidelines for distinct methodological issues and quality improvement of evidence generation for HTA.”[ibid.]

Deliverables: WP7: Guidelines on methodological issues, guidelines, position paper and pilots on additional evidence generation.

The HTA Core Model [21](refined and field tested during JA1, used for preparing collaborative HTAs for national adoption during JA2): As is it is the main tool for HTA used in EUnetHTA it shall be briefly described: The HTA Core Model is a methodological framework that has been developed to define the elements (organized in so-called domains) to be considered in a health technology assessment (HTA). Its purpose is to facilitate standardised reporting in order to enable collaborative production and sharing of HTA information.

The model consists of three main components

- The so called HTA-Ontology: Collection of questions that a HTA should answer
- Methodological Guidance
- Reporting Structure



Source: [22]

Fig.4: The HTA Core Model with its 9 Modules (for the purpose of EUnetHTA the modul “cost and economic considerations” is not used, for rapid REA only the first 4 Modules are applied)

#### 4. History and scope of the EMA-EUnetHTA collaboration

The collaboration between the EMA and EUnetHTA started in 2010 (see Fig.5) [23]. The political mandate came from a recommendation of the High Level Pharmaceutical Forum (HLPF) concerning an improvement of the quality and use of available data pertinent to relative effectiveness assessment (REA) [18]. The starting point in February 2010 was a project on the improvement of the presentation of data in the European assessment report (EPAR) as suggested by the HLPF. It was also agreed to work on a road map for the exploration of other possible areas of collaboration.

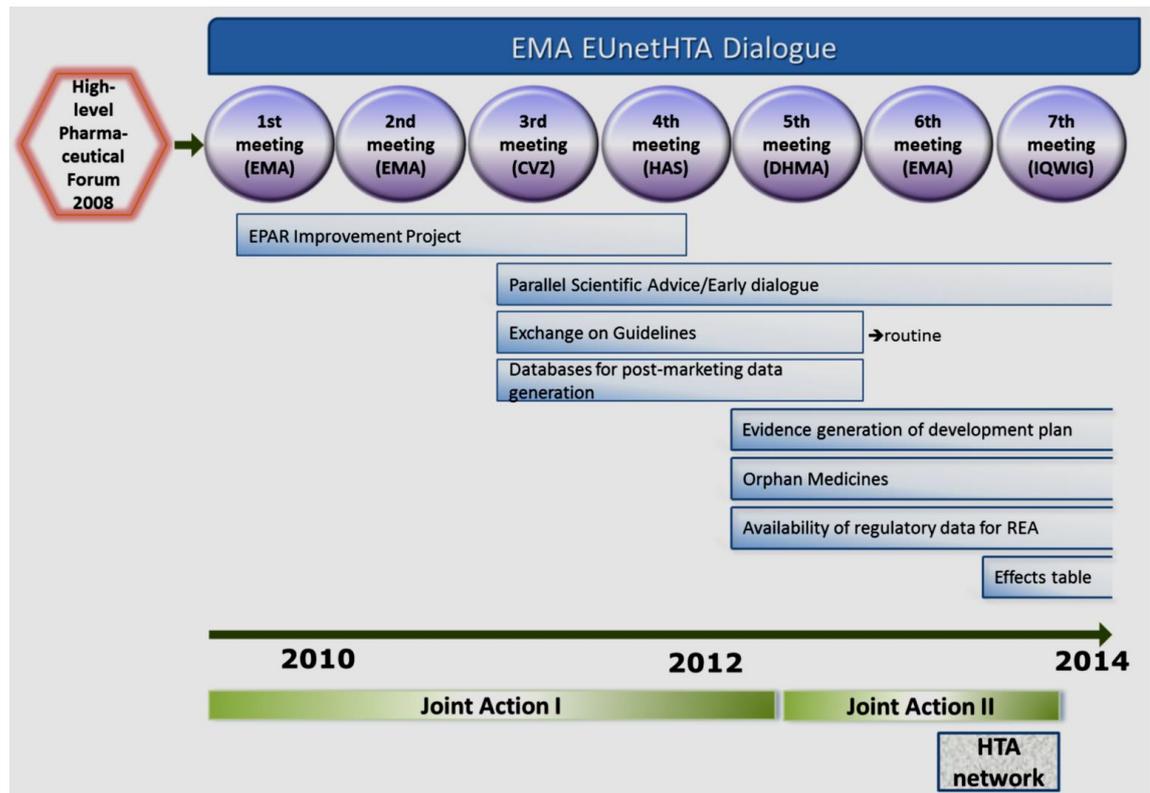


Fig.5: Temporal evolution of the EMA-EUnetHTA collaboration and its relation to the working plans of JA1 and JA2. The acronyms in parenthesis represent the names of the organisations hosting the different EMA-EUnetHTA meetings. Source: [24] In May 2014 the 8<sup>th</sup> meeting has taken place in London, the next meeting being planned for December 2014 [25].

Between 2010 and 2013 the collaboration extended to topics such as guidelines, parallel scientific advice, post-authorisation evidence generation etc. [25]. In the meanwhile the various topics of the collaboration address all aspects of the life cycle of a medicinal product (see Fig.6). In November 2013 a three year work plan (2013-15) was published for the EMA-EUnetHTA collaboration with the following areas being the main fields of activity:

***“Areas of collaboration***

- Scientific advice/early dialogue involving regulators and HTAs.
- Scientific and methodological guideline development.
- Post-licensing (post-authorisation) data generation.
- Availability of clinical study data.
- Orphan medicinal products.
- Cooperation in pilot projects.
- Cooperation in specific pilot projects of EUnetHTA JA2.
- Conferences, workshops and seminars / meetings.” [26]

## Elements of EMA/EUnetHTA dialogue

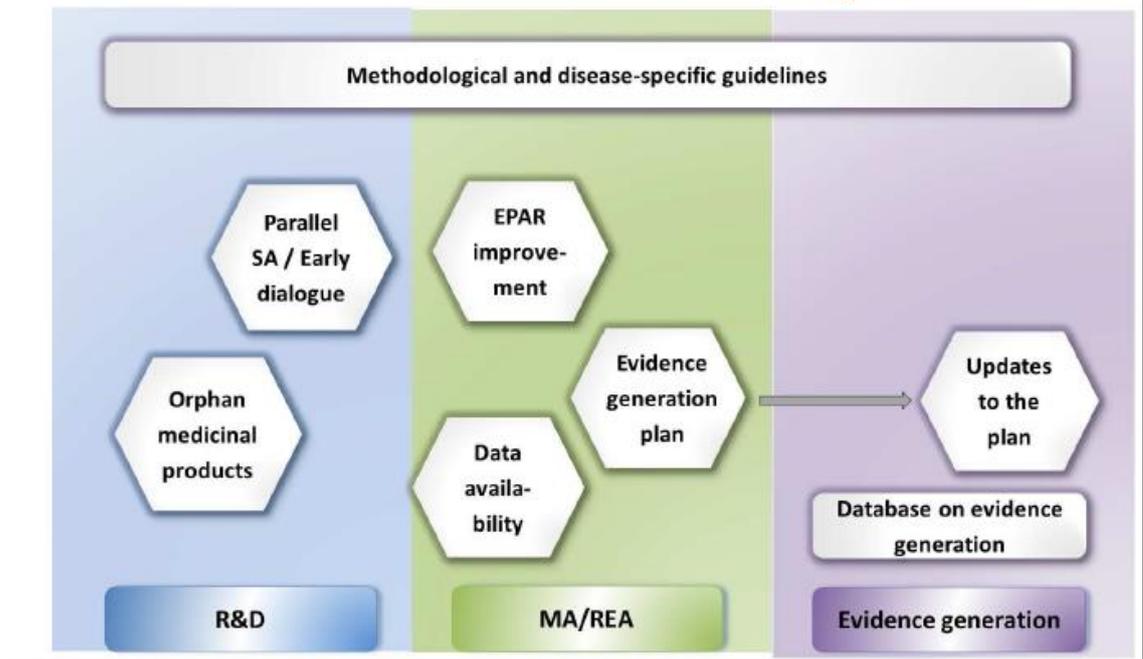


Fig.6: Relation of the various topics of the EMA-EUnetHTA collaboration to the different phases of the life cycle of a medicinal product (R&D: Research & Development; MA marketing authorisation) Source: [27]

## 5. Areas of collaboration of the EMA and EUnetHTA

### 5.1 Parallel Scientific Advice: Overarching principle of exchange between industry, Regulatory Authorities and HTA bodies

With respect to Scientific Advice a variety of modes of interaction between industry, regulators and HTA-bodies have evolved over the years both at national and European level (see Table 1). There are all kinds of Scientific Advice procedures (pilots, regular services) at the national level (industry-HTA, industry-regulatory, industry-HTA-regulatory). Multi-HTA procedures (with the EMA as observer or active participant) are performed/planned under the umbrella of European collaborations like the Tapestry Networks, EUnetHTA and SEED, and there is the EMA/multi-HTA pilot for parallel Scientific Advice running since 2010. Since most of the HTA-bodies that have been actively engaged in the EMA/multi-HTA pilots also have lead positions in EUnetHTA and SEED it would be somewhat artificial to discuss only the EUnetHTA/EMA perspective of (parallel) scientific advice. Rather it is the intention to provide the widest possible perspective of the current activities in the field.

Advisory Party/Parties	National Level	European / Transnational Level	Remarks
<i>Separate Advice by single Regulatory Authorities and single HTA bodies</i>	National Authorities	Regulatory: EMA HTA: No Pan-European HTA Authority	
<i>Regulatory-HTA Parallel Advice</i>	e.g. MHRA-NICE, G-BA/BfArm, AIFA, TLV-MPA,		
<i>Multi-HTA Advice</i>		<ul style="list-style-type: none"> <li>• <b>EUnetHTA JA2/WP7</b> (Lead HAS) (2012-2015): 6 pilots finished by April 2014 [28]</li> <li>• <b>SEED Consortium</b> (Lead HAS) 10 pilots (7 on drugs, 3 on medical devices)</li> </ul>	<u>EMA:</u> <ul style="list-style-type: none"> <li>• Observer status at EUnetHTA</li> <li>• participant in 3 SEED procedures</li> </ul>
<i>Regulatory-multi-HTA Advice</i>		<b>EMA/ multi HTA</b> <ul style="list-style-type: none"> <li>• Status June 2014: 23 procedures completed so far [29], including 3 multi-stakeholder pilots originating from the Tapestry Network [30]</li> <li>• Some procedures with patient representatives and Health Care professionals</li> </ul>	

Table 1: Various forms of Scientific Advice given by Regulatory Authorities and HTA-bodies.

Sources: in addition to the references listed in the table [31] [32] [33]

### 5.1.1 Scientific Advice by Regulatory Authorities

Scientific Advice procedures are well established at the national and the European level. A survey on the impact of Scientific Advice by EMEA on successful marketing authorisations during the period from January 2004 until December 2007 showed that when companies complied with the advice obtained by EMEA there was a high probability of obtaining marketing authorisation [34]. The important role that Scientific Advice plays in modern drug development is also impressively reflected by the ever-increasing number of procedures performed every year at the EMA. Starting with 63 procedures in 2001 the number has increased nearly six fold to 363 in 2013 [35].

### 5.1.2 Scientific Advice by national HTA Bodies

The importance of an early dialogue between industry and HTA bodies for the design of a clinical development program that supports the generation of the appropriate data for REA was emphasized in the recommendations of the High Level Pharmaceutical Forum [18]. Scientific Advice Procedures at the national level have already a certain past, e.g. NICE starting in 2008 [36] and some of the national HTA-bodies have already begun to run pilots or to even implement a regular process of parallel scientific advice together with regulatory authorities. NICE and MHRA started a parallel advice process in April 2010 [31] [36]. The Swedish regulatory agency MPA and the national HTA-body TLV offer parallel scientific advice on a regular basis since 2011 [32].

### 5.1.3 Parallel Scientific Advice by the EMA plus several HTA-bodies

In 2010 the EMA has started a pilot on Parallel Scientific Advice together with HTA-bodies and in June 2014 23 procedures have been completed [29]. In May 2014 the EMA released a “Best Practice guidance for Pilot EMA HTA Parallel Scientific Advice procedures” for public consultation [37]. The guidance document was prepared together with representatives from NICE, AIFA, G-Ba, TLV as the HTA-bodies that had most frequently participated in the parallel procedures so far.

Some of the corner stones of the draft guidance are summarized below:

- All medicinal products are eligible irrespective of their eligibility for the central procedure.
- It is the applicant’s choice which HTA-bodies should participate. Usually the number of HTA-bodies participating should not exceed 5.
- The invited HTA-bodies are not obliged to participate.
- A common briefing document is used.
- Advice is not legally binding.
- The process is confidential
- Administrative work done by the EMA

The whole procedure can be divided into 3 phases, the timetable of the actual advice procedure corresponding to the schedule of the 70 days procedure for Scientific Advice by the EMA in order to accommodate the usual EMA advisory process (see Fig.7):

- Pre-notification Phase:
  - Early informal contacts with HTA-bodies, pre-notification of the EMA,
  - Letter of Intent sent to the EMA according to submission timetable for the EMA 70 days procedure (with / without pre-submission meeting)

- Pre-validation Phase:
  - Sending out briefing documents (template provided in the draft guidance)
  - Option: Telephone conference with applicant, the EMA and HTA-bodies
  - Ends with sending of final briefing package by applicant (validation by the EMA)
- Meeting Phase:
  - Structured according to the EMA 70 days procedure
  - Pre-face-to-face teleconference: identification of major divergences of the EMA and HTA-bodies on proposed development plan
  - Face-to-face meeting: 4 hours, inclusion of patient representatives is encouraged
  - Applicant sends minutes to the EMA and HTA-bodies
- Advice Format:
  - EMA: Advice Letter containing CHMP advice
  - HTA-bodies: format differs with respect to HTA-body, i.e. direct response during meeting, annotation of applicant's minutes or written response

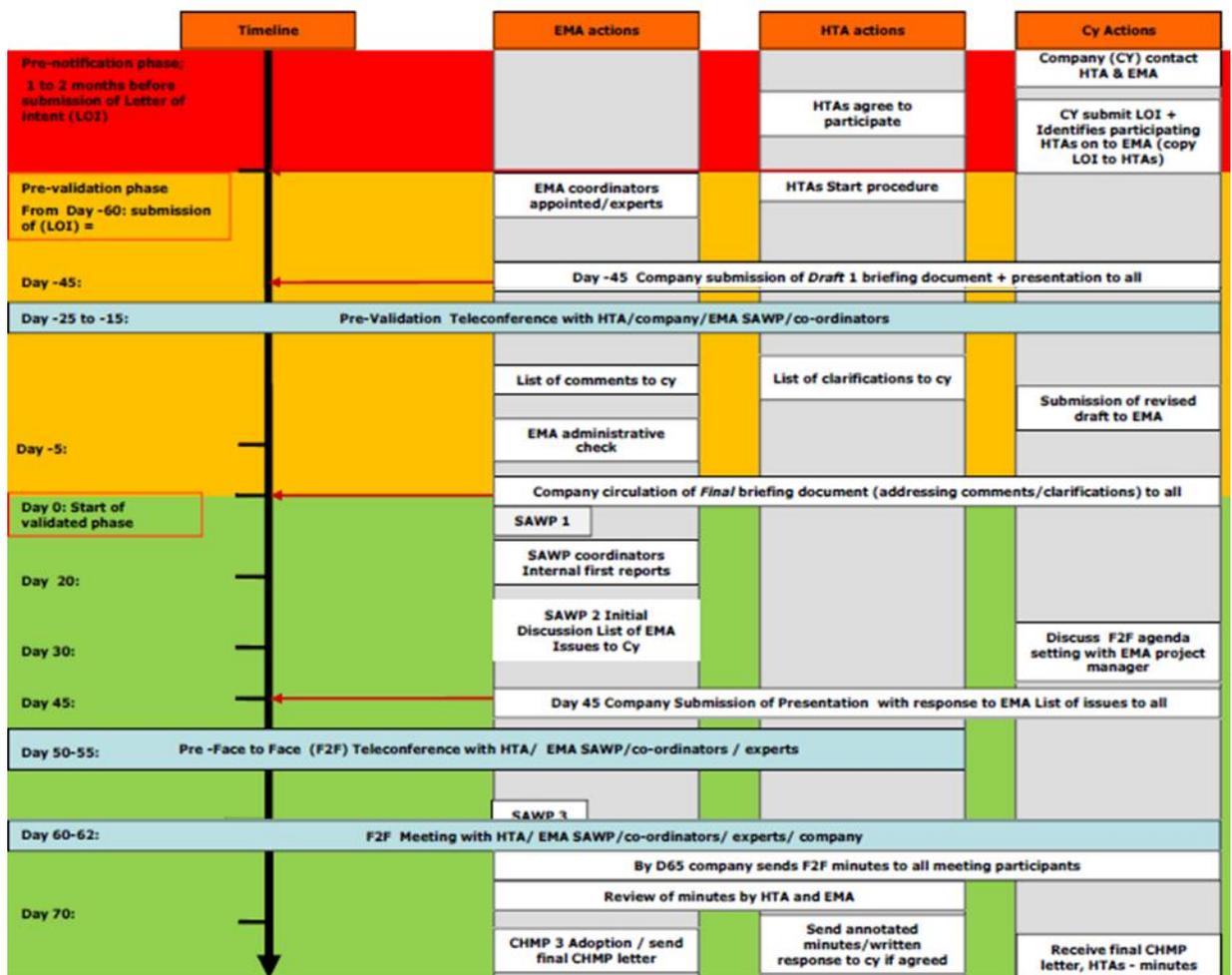


Fig.7: Timetable for Parallel Scientific Advice EMA/multi HTA-bodies, Source: [37]

#### 5.1.4 EUnetHTA: Early Dialogue

The project on Scientific Advice / Early Dialogues started in EUnetHTA with 2 pilot dialogues in 2012 with the participation of the following EUnetHTA partners: IQWIG, GBA, KCE, INAMI, HVB, CVZ, AIFA, NICE [33] . The draft procedure tested in these pilots was amended (see Table 2) according to the feedback of the participants and is now the basis for the pilots carried out in EUnetHTA JA2, within WP7 with HAS as lead (ibid.)

DAYS (calendar days )	ACTION
D-60: Start of procedure	<ul style="list-style-type: none"> <li>Submission by the company of the early dialogue request validated by HAS to all participating HTA bodies</li> </ul>
D-45	<ul style="list-style-type: none"> <li>A teleconference or e-meeting with HTA bodies is organized by HAS to identify possible missing information related to the application file and to the proposed development plan (list of main issues that should be addressed by the company either in writing or at the next face-to face meeting).</li> <li>The company is informed of the outcome of the teleconference/e-meeting and additional data or clarifications requested if needed</li> </ul>
D-30	The company provides additional information or clarification as needed
D -7:	Short written answers to company's questions are sent by each HTA participant to the coordinator
D -3:	Individual HTA positions are released to participating HTA organisations in the format of a compiled document
D 0: Early Dialogue Meeting	<ul style="list-style-type: none"> <li>Preliminary discussion among HTA organizations (without the company)</li> <li>Face-to-Face meeting with the company and HTA organizations</li> <li>Conclusions among HTA organizations (without the company)</li> </ul>
D +7	The draft detailed minutes of the meeting relating general and individual HTA bodies positions for each question is provided by the company
D +20: End of procedure	The detailed minutes are reviewed and corrected in writing by HAS and participating HTA organisations. In case of remaining uncertainties, a teleconference or e-meeting with HTA bodies may organized by coordinator

Table 2: Procedural Steps and Timelines of Early Dialogue Process (Source: [38])

Some corner stones of the procedure [33]

- Hosted by HAS
- It is non-binding and confidential
- One indication per dialogue
- Face to face meeting: one –two days at HAS (one product/day)
- Advice format: Minutes including individual responses from HTA-bodies to questions from sponsor (industry)

Originally 3 early dialogues on drugs were planned in JA2 with deadline of summer 2013. Experience from these pilots should then be the basis to establish a final procedure for early dialogue in 2014. By April 2014 6 early dialogues on medicinal products had been finished with the EMA having the position of an observer [28].

#### 5.1.5 SEED (Shaping European Early Dialogues) Consortium: Early Dialogue [39]

Under the lead of HAS 14 national and regional HTA-bodies, that are also partners in EUnetHTA JA2 form this consortium. The work plan includes the performing of 10 early dialogues (7 on pharmaceuticals including ATMPs). The EMA will participate in 3 of the early dialogues on pharmaceuticals. The timeframe for a joint HTA/EMA advice within SEED is similar to the early dialogue process of EUnetHTA (see above) but with start of the procedure at day -90 [39].

#### 5.1.6 Impact on Drug Development

The offering of Parallel Scientific Advice was very well received by industry which is reflected by the positive feedback and the steadily increasing applications for these procedures. Below is a collection of feedback responses from various stakeholders. By interpreting these statements it should be kept in mind that the process of parallel regulatory/HTA advice exists in Europe since about 2010 at national and European level. Some procedures are still in pilot phase, others have just managed the turning point from pilot to a more established process.

##### Feedback from representatives from Regulatory Authorities and HTA-bodies:

The recurring theme in the feedback from this group is the great appreciation of getting to know the other party's way of thinking.

- "MHRA and NICE, whilst still giving independent advice, do so in the knowledge of each other's requirements" [40]
- "listening to each other's views, improves understanding, and allows contemporaneous evolution of your development to satisfy all parties before development plans and HTA/EMA decisions have been finalized" [35]

##### Feedback from pharmaceutical industry:

In general feedback is positive especially stressing the advantage of anticipating potential concerns from HTA-Bodies (and/or Regulatory Authorities). There is general agreement that Scientific Advice should be kept as flexible as possible and that it should be accessible at all levels of complexity i.e. pure national single advice, national parallel advice, multi-HTA advice and EMA/multi HTA advice. As Pan-European HTA advice would require major legislative measures this option is not regarded as to be available in the near future.

Some examples of feedback on the value of Parallel Scientific Advice from industry:

“Opportunities

- Early information of HTA stakeholders about development plan (and potential scientific boundaries within a global strategy)
- Consolidated view on comparators, endpoints, patient populations etc. from the HTA perspective
- Anticipation of HTA authorities’ concerns“ [41]

“Benefits

- One collaborative discussion
- ..
- Commonality of issues discussed (Comparators, end-points, PROs, Follow-up etc)
- Simultaneous feedback
- Value in Regulators and HTAs hearing from each other
- Understanding of similarities & differences of stakeholder requirements“ [42]

Concerning the rules of procedure and the outcome of parallel advice representatives from industry see still significant room for improvement. Suggestions for improvement of the process reflect the pilot character especially of the EMA/multi HTA parallel Scientific Advice Procedure:

Procedural: [42]

As the time table for parallel Scientific Advice by the EMA and HTA-bodies/EUnetHTA is an adoption of the EMA schedule some representatives from industry feel that the process is too time consuming as compared with advice by HTA-bodies only.

- It is bemoaned that there is no real discussion about the topics for advice especially as far as HTA-bodies are concerned.
- There is no common format of feedback from HTA-bodies.

With respect to outcome: [42]

- It is well appreciated by industry that in the current situation legal constraints at the national level leave only a small room for consensus building for HTA-bodies.
- Nevertheless the efforts of EUnetHTA to establish European standards for HTA are seen as an important step forward to build a reliable scientific and transparent base for HTA. In addition in its multiannual work program [12] the newly formed HTA Network (HTAN) has set priorities to reflect on conditions that facilitate the national use of joint HTA production and also develop a vision for increased collaboration between HTA-bodies and regulatory authorities with the goal
  - to achieve more synergy and de-fragmentation
  - to make business more predictable
  - to reduce administrative hurdles.

Concerning the actual and anticipated effects on drug development Parallel Scientific Advice is probably the single most important and most effective measure for interaction between Regulators and HTA-Bodies and industry. According to the feedback from all stakeholders this is true for all levels of interaction, from national level up to parallel Scientific Advice by the EMA and HTA-bodies/EUnetHTA [43] [32] [35] [42]. Of course it can be anticipated that the EMA/EUnetHTA collaboration will have a very decisive impact on the evolution of the future overall process due to the important role both organisations play in the European and international context.

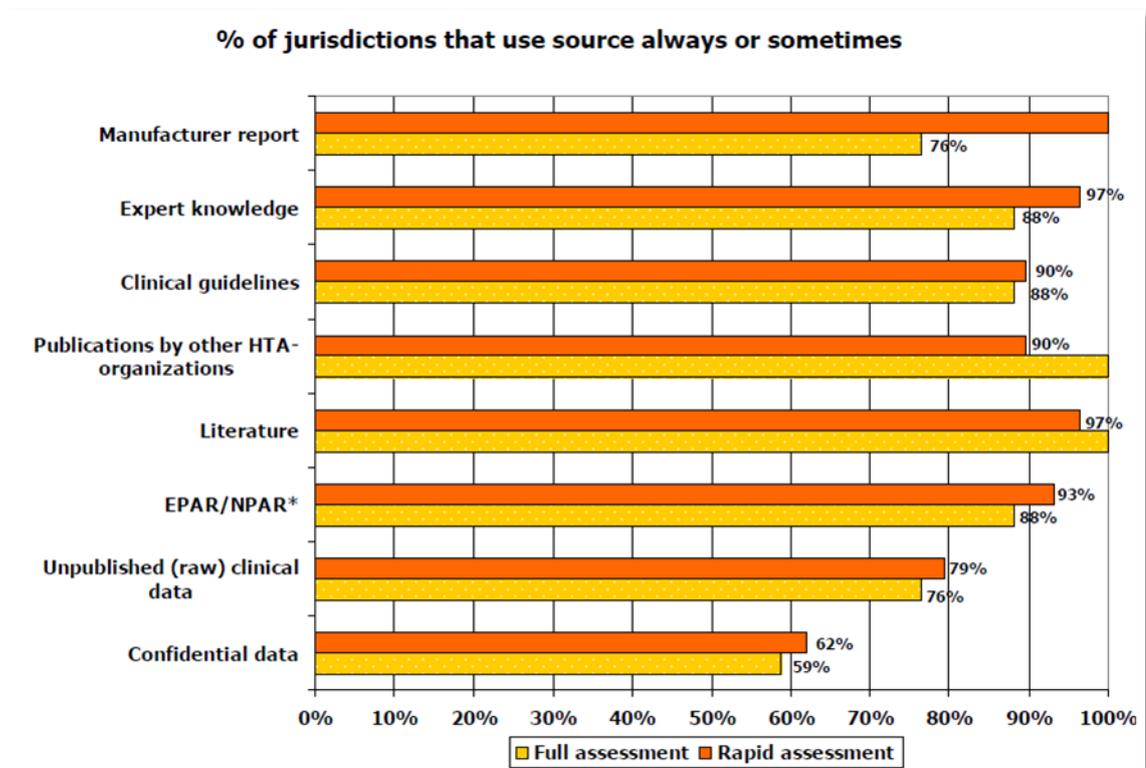
Within the collaborative network of the EMA and EUnetHTA Parallel Scientific Advice is the hub for sharing information, identification of issues and quest for commonalities. Parallel Scientific Advice is the forum where the various views and expectations from the different stakeholders are expressed. Here the opportunities for alignment or compromise come to light and the areas where guidance is needed become obvious. In this respect Parallel Scientific Advice can give impetus to the modification of existing or the development of novel guidelines. When novel concepts like post-authorisation efficacy studies and adaptive licensing which is discussed later in chapter 5.5 will become more broadly used Parallel Scientific Advice will probably become an integral part of every development path, not being limited to the prelicensing phase but covering the entire life cycle of a medicinal product.

The impact of Parallel Scientific Advice given in 2014 will become apparent probably only be end of this decade. For companies today the immediate value of Parallel Scientific Advice is to learn about the trade-offs and risks that are connected with diverging positions of regulators and HTA-assessors.

## 5.2 Best use of available data

### 5.2.1 Background survey on use of data sources for REA

As shown by the survey on REA practices in various jurisdictions the scientific assessment in the respective countries relies on a package of data sources that is highly comparable [2] (see Fig.8). In this background analysis a distinction is made between Full Assessment (Full REA) and Rapid Assessment (rapid REA). According to the nomenclature of EUnetHTA (single) Rapid REAs are defined as “...assessments of a new pharmaceutical at the time of introduction to the market in comparison with one or more alternative interventions” [2]. Full REAs are “assessments (non-rapid) of (all) available technolog(y)(ies) for a particular step in a treatment pathway or a specific condition and are often conducted several years after introduction to the market.” [2].As most of the pilot projects of JA2 are rapid REAs (10 for drugs, 4 for medical devices) [19] the following considerations also concentrate on the best use of available data for the rapid assessment.



\* EPAR= European Public Assessment Report; NPAR=National Public Assessment Report. These also include the summary of product characteristics (SPC).

Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

Number of jurisdictions for full assessment: 30; As CH, CZ, EE, FI, HU, LU, MA, NL, PT, SC, SI, SK and USA do not perform a full assessment the average is based on n=17.

Fig.8: Data Sources for REA, Source: [2]

### 5.2.2 Early REA: timing with respect to Marketing Authorisation

In many jurisdictions the pricing decision and consequently rapid REA have to be performed within a defined timeframe (see Fig.9) after submission of an application for reimbursement by a marketing authorisation holder.

**Figure 8. Jurisdictions in which the assessment to support reimbursement decisions of pharmaceuticals is subject to a specific timeframe (%)**

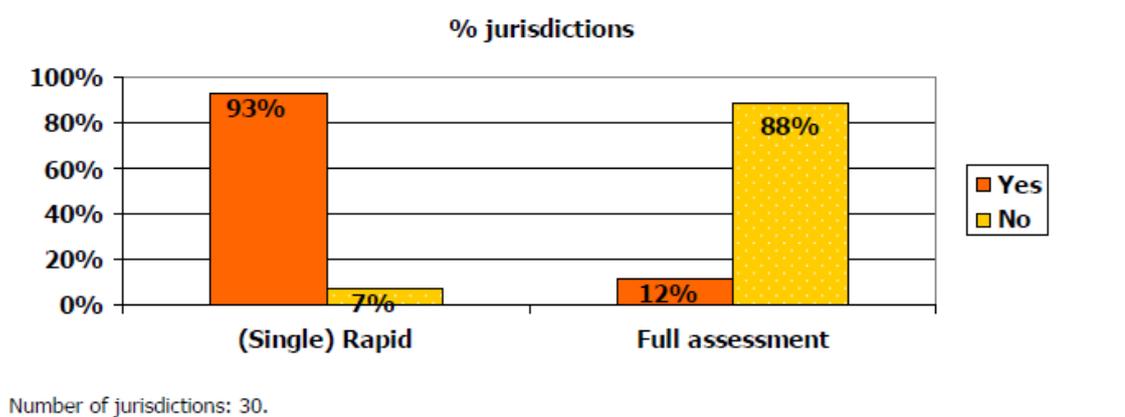


Fig.9: Survey on timing of REA (rapid and full) with respect to the submission of an reimbursement application by a marketing authorisation holder. Source: [2]

Most of the European Member States have implemented the time frame specified in the so-called Transparency Directive 89/105/EEC, where the time limit for a decision on pricing/reimbursement is 90 or 180 days from the day of application [44]<sup>4</sup>. As the application for reimbursement/pricing and the granting of the marketing authorisation are closely linked in terms of time it is evident that the data and documents relating to marketing authorisation are also substantial for rapid REA (see also Fig.9)<sup>5</sup>.

For the rapid REA pilots to be performed within EUnetHTA JA2 the time frame is even more ambitious as the start of the REA process is before getting marketing approval (see Fig.10). The so-called scoping phase where the scope of the assessment is defined according to the PICO methodology (Patients/population with disease of interest; Intervention: drug under assessment; Comparisons serving as reference; Outcomes: i.e. endpoints for assessment of effectiveness and safety) falls into the EMA assessment period prior to the CHMP decision and the whole rapid REA procedure shall be finished shortly after publication of the EPAR. Although it is clearly stated by EUnetHTA that this is an ideal world scenario the ambitious timelines underscore the importance of a well-coordinated interaction between drug company, the EMA and HTA bodies. Data and Documents have to be complete, of high quality, tailored to the need of their addressees and available on time. It is also clear that with regard to data content the submission documents for the EMA and EUnetHTA should be identical. Ideally and in avoidance of double work REA should profit from the assessment that is part of the regulatory process. This spirit was the driving force behind the effort to adopt style and contents of the EPAR to the needs of rapid REA as described in the following chapter.

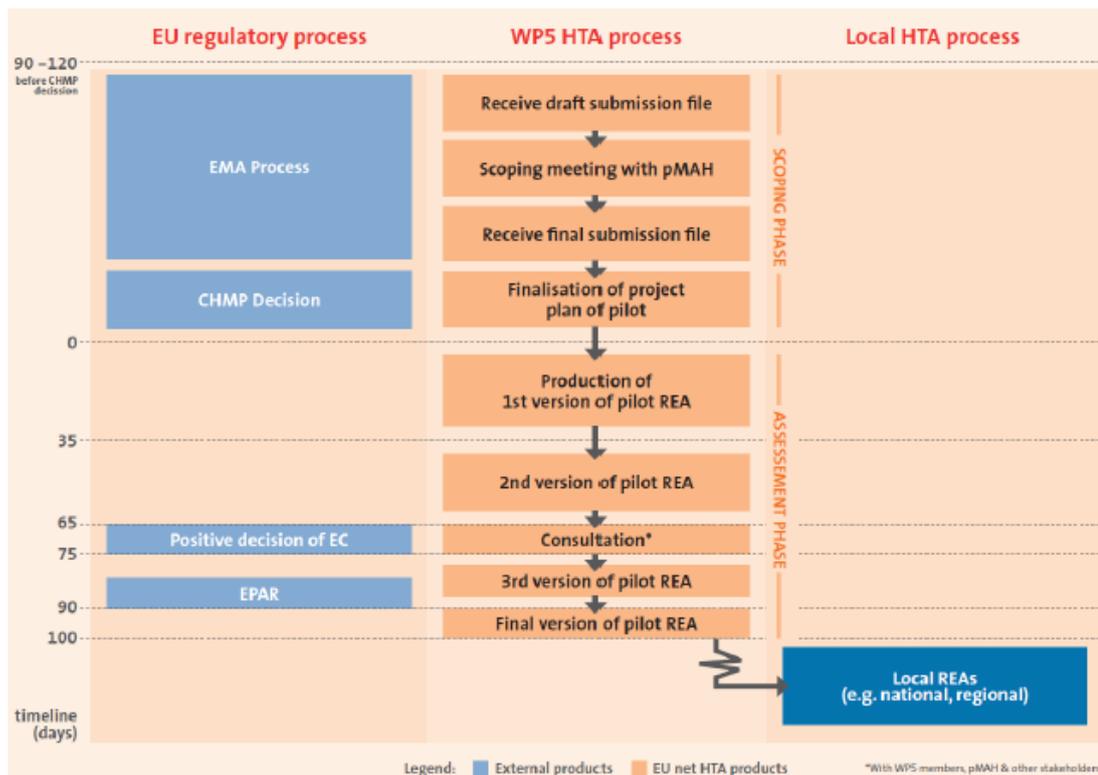
<sup>4</sup> A proposal for a new Directive of the European Parliament and of the Council relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems has aimed to formally incorporate HTA in the time frame for pricing/reimbursement decision, but the original proposal by the Commission was not accepted by the European Parliament

[Sources online available:(accessed 16.06.2014)

<http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2013-0015&language=EN#>

[http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/com2013168final2\\_en\\_.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/com2013168final2_en_.pdf)

<sup>5</sup> As at the time of marketing authorisation/launch the available data almost exclusively come from RCTs it is a matter of discussion to what extent these data reflect so-called real world evidence. So in consequence early REA is often dealing with efficacy data rather than efficiency data which in some cases leads to efforts to extrapolate efficiency from efficacy. At this early stage of HTA the terms efficacy and effectiveness are sometimes used interchangeably [2].



Abbreviations: CHMP - Committee for medicinal products for human use; EC – European Commission; EMA – European Medicines Agency; EPAR- European Public Assessment Report; EUnetHTA – European network of Health Technology Assessment; HTA – Health technology assessment; pMAH- prospective marketing authorisation holder; REA – Relative effectiveness assessment; WP5 – work package 5

**Figure 1. Schematic overview of the organisation of the process of the pilots –general overview**  
*It should be noted that these graphs represent the ideal picture; however, divergence is very possible for specific pilots*

Fig.10: Temporal sequence of the REA process and its temporal relation to the regulatory assessment Source [21]

### 5.2.3 EPAR Improvement Project [45] [46] [47]

According to the recommendations of WP5 the EPAR<sup>6</sup> is alongside the REA submission file the primary source of information for the assessment [22]. As the EPAR is published for centrally authorised medicinal products which constitute the majority of all novel medicines the quality of the EPAR makes a decisive contribution to the quality, efficiency and outcome of most REAs. The project started in 2010 and recently a summary report on the achievements obtained to date has been jointly published by the EMA and EUnetHTA [45].

The project on EPAR improvement was originally based on the political mandate of the High Pharmaceutical Forum for the EMA to consider how the contribution of the EPAR to REA could be improved. Starting with the first meeting between representatives from the EMA and EUnetHTA in February 2010 the EPAR template was adapted in an iterative way:

1. Adaptation of the template according to comments from MEDEV/EUnetHTA (results of three joint meetings between 2010 and 2011): Major revisions were the creation of new

<sup>6</sup> The EPAR is not a single document but it consists in its core of the public friendly EPAR summary, authorisation details, product information including the Summary of Product Characteristics (SmPC) and most importantly the assessment history including the assessment report of the initial marketing authorisation with omission of commercially relevant details as well as the assessment reports concerning subsequent variations. The EPAR Improvement project started out with the focus on the improvement of the assessment report document.

subsections for increasing the granularity of the presentation and discussion of clinical studies and the joint development of a table for a structured summary of the main efficacy data [45].

2. Use of the modified templates
3. Development of a questionnaire (based on the action items) for monitoring the results: scope was the format of the EPAR, the scientific content, the relation to information contained in the SmPC
4. Parallel review performed by two HTA organisations and the EMA by using the same evaluation tools and comparison of results: 10 EPARs selected (Pumarix, Esbriet, Teysuno, Xeplion, Xiapex, Gilenya, Halaven, Jevtana, Pravafenix, Trobalt)
5. Presentation of the results in the joint meeting February 22, 2012: Despite high level of compliance with the adaptations there was still room for improvement with regard to e.g. critical discussion of clinical study design, a more detailed appraisal of shortcomings of efficacy data, a proposal to incorporate the requests for additional analysis and data by CHMP.
6. As an outcome of the meeting between the EMA and EUnetHTA in November 2012 [45] [48] a high level of compliance with the agreed objectives was acknowledged again and further action items for improvement of the EPAR were proposed by EUnetHTA:
  - a. Further improvement of the granularity of report template (e.g. tables, executive summary)
  - b. Still more detailed discussion of clinical data and shortcomings (opinions from Scientific Advisory Group, PDCO and other expert groups)
  - c. Impact of novel pharmacovigilance legislation on contents of EPAR, availability of the Risk Management Plan<sup>7</sup>

#### 5.2.4 Effects Tables.

Effects Tables (ET) are a tool developed within the framework of the EMA’s Benefit-Risk-Methodology Project [49]. The aim of this project that started in 2009 was to evaluate tools and methodologies that would help to improve the consistency and the transparency of risk-benefit assessment [50]. Effects Tables were established as a tool “to summarise the key benefits and risks, and supplement the benefit-risk section of the CHMP assessment report by presenting a compact and consistent display of the salient data and uncertainties that are drivers of the decision” [51].

Data and Information contained in the Effects Tables are displayed according to the following scheme:

<b>Table 2: The four-fold frame for separating the elements of the benefit–risk assessment.</b>	
<b>Four-fold benefit–risk frame</b>	
Favourable effects	Uncertainty of favourable effects
Unfavourable effects	Uncertainty of unfavourable effects

Table 3: Systematics of display of data and information in Effects Tables [50].

<sup>7</sup>Since the adoption of the new pharmacovigilance legislation a section referring to pharmacovigilance aspects like pharmacovigilance plan and risk management plan is an integral part of the published assessment report.

**Table 1.** Effects Table for **vandetanib** / Based on the EPAR EMEA/H/C/002315 published on 02/03/2012

	Effect	Short Description	Unit	Plac ebo	Vandetanib	Uncertainties/ Strength of evidence	References
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46 95% CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
	PFS (median)	Weibull model	Mo	19.3	30.5	Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?	Single-arm study in RET negative patients post-approval.
	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13	45	No clear effect on PRO/QoL (missing data)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; Life-threatening	%	2.0	10.8	Duration of follow up in the pivotal study is short vs. the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4)
	QTc related events Grade 3-4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4	Risk of developing further major cardiac SAEs including Torsades de pointe?	Restrict to symptomatic and aggressive disease (see SmPC 4.1).
	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4	49.8		Explore lower dose (see See Table 20. Summary of the RMP)

Abbreviations: PFS, progression-free survival; ORR objective response rate; Mo, months; OS, overall survival; RET, "rearranged during transfection" gene, see text.

Table 4: Hypothetical Example of an Effects Table for an authorized medicinal product, Caprelsa (Vandetanib) that is licensed for the treatment of medullary thyroid cancer [52]. Data and information used for the Effects Table were based on the EPAR [51].

The Effects Table Project is still in its pilot phase. For ten new active medicinal products Effects Tables will be prepared by both Rapporteur and Co-Rapporteur at day 80 of the assessment and updated until day 210. The tables will be integrated into the benefit-risk section of the assessment report. The CHMP will perform an interim evaluation in the middle of 2014 [51]. It is not yet clear if and when Effects Tables will be part of the Public Assessment Report of the EPAR<sup>8</sup>

### 5.2.5 Transparency Project

Underreporting of clinical trial data has long been bemoaned in the medical community [53]. In a recent series of publications in Lancet entitled "Research: increasing value reducing waste" the problem of inaccessible research has received renewed attention [54]. The authors of this article cite an estimate that only about half of health-related studies are ever reported (ibid.). By pushing forward a novel policy on publication and access to clinical trial data the EMA is making considerable efforts in closing this information gap [55]. After two rounds of extensive consultation the EMA management board finally agreed on the policy. After final amendments adoption is scheduled for mid-July with the policy becoming effective from October 1 2014 [56].

<sup>8</sup> According to Thomas Salmonson it is yet undecided whether Effects Tables will appear in the EPAR (personal communication on the occasion of his presentation at the annual congress of DGRA, Bonn May 2014.)

Despite much criticism from industry, the high level management of the EMA expects a positive impact on drug development and public health: “We predict that it will help to increase the efficiency of drug development, improve cost-effectiveness, improve comparative-effectiveness analysis, and reduce duplication of effort among trial sponsors.” [57]

#### 5.2.6 Impact / Relevance for Drug Development

As pointed out in the section above on rapid REA the same data that are the basis for marketing authorisation are the major source of information for rapid REA. Efforts like the EPAR improvement project and the project on Effects Tables are important milestones of presentation of data and their evaluation in a way that facilitates exchange of information between the regulatory and the HTA field. This transparency will help in creating understanding and trust in the judgment of the EMA and help to avoid doubling of assessment efforts on the HTA side. Currently the assessment documents become only available to HTA-assessors either in the moment when they are published by the EMA or if they are transmitted in the forehand by the drug company. Maybe in the future the EMA and EUnetHTA will find a way that allows official sharing of documents early in the evaluation process.

How the transparency project concerning clinical trial data will impact the drug development process is not clear in the moment. Expectations are high on the side of the initiators. Besides providing the optimal data base for making decisions on best medical therapy another important aim is to avoid doubling of clinical studies, which could certainly lead to cost reductions.

### 5.3 Evidence Generation until marketing authorisation

The distinction between collaborative efforts relating to the pre-licensing period and those more important for the post-licensing period is mainly based on the primary focus of the work programs of the various initiatives described below. But in the context of an efficacy-efficiency continuum and considering the adaptive licensing concept which will be discussed in chapter 5.5. this classification should be regarded “cum grano salis”.

#### 5.3.1 Need for Guidance: Lessons from Parallel Scientific Advice

As a first analysis of 11 Parallel Scientific Advice procedures by the EMA and several HTA-bodies has shown most of the questions relate to the design of clinical studies which per se is not much astonishing as the data from such studies is the common substratum for assessment by both regulatory authorities and HTA-bodies. But what figure 11 below highlights is the necessity for alignment between regulators and HTA-assessors whenever possible.

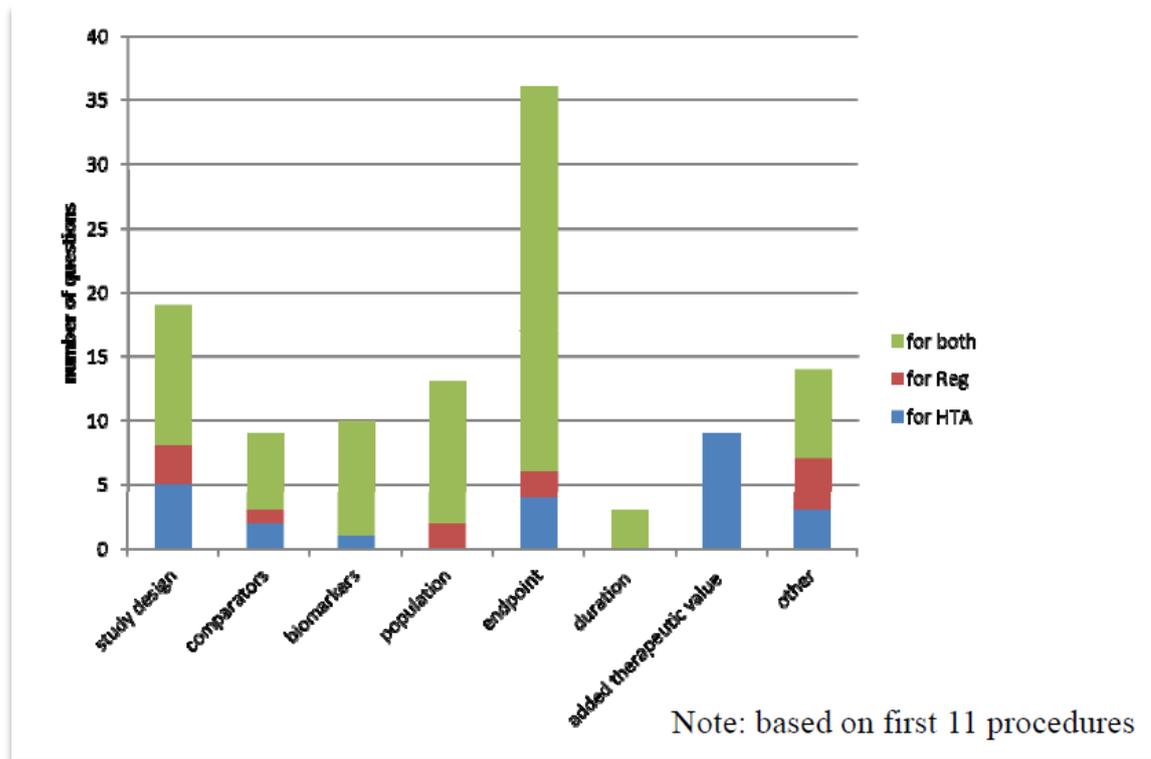


Fig.11: Thematic clusters of questions submitted for Parallel Scientific Advice by the EMA and HTA-bodies, Source: [58]

### 5.3.2 Mutual consultation between the EMA and EUnetHTA with respect to guideline development

Early in their interaction the EMA and EUnetHTA made regular exchange of information and mutual consultation with respect to guidelines an integral part of their collaboration. Whereas the EUnetHTA collection of guidelines related to clinical studies seems to be more static [20], the EMA continuously produces novel clinical guidelines. A selection of those recently drafted is given in the table below.

04/08/2014	<u>Concept paper on good genomics biomarker practices</u>
31/07/2014	<u>Draft guideline on clinical evaluation of medicinal products used in weight control</u>
01/07/2014	<u>Draft guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency</u>
17/06/2014	<u>Draft reflection paper on the use of patient reported outcome (PRO) measures in oncology studies</u>
03/03/2014	<u>Draft reflection paper on the wording of the indication for medicinal products for the treatment of type-2 diabetes</u>
03/02/2014	<u>Draft guideline on the investigation of subgroups in confirmatory clinical trials</u>

Table 5: Examples of draft Clinical Guidelines released for consultation by the EMA [59]

### 5.3.3 IMI GetReal

Within the Innovative Medicines Initiative (IMI) which is a joint undertaking of the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) the program GetReal is focused on novel approaches to incorporate real life data into drug development. IMI GetReal (Kick-off Meeting January 2014) is a multi-stakeholder program bringing together pharmaceutical companies, research organisations, the EMA and HTA bodies (CVZ, NICE, EUnetHTA) [60].

GetReal is structured into 4 work packages:

WP1	<p><b>“Create the decision-making framework for Pharma R&amp;D for the systematic identification and assessment of different development strategies,</b> considering:</p> <ul style="list-style-type: none"> <li>• the incremental value of information from the study programme in the estimation of relative effectiveness at launch and after launch</li> <li>• the technical and practical challenges of different designs</li> <li>• <b>the interaction with regulatory, HTA and other review processes.”</b> [61]</li> </ul>
WP2	<p><b>“Examine clinically meaningful patient subgroups based on actual care pathways.</b></p> <ul style="list-style-type: none"> <li>• Use of drugs within defined treatment strategies.</li> <li>• Most relevant <b>outcome</b> measures /<b>endpoints</b>.</li> <li>• <b>Patient and healthcare organisation factors</b> that may drive variability of patient outcome in actual clinical practice for any given treatment strategy.</li> <li>• <b>Most appropriate comparator/s</b> (drug and non-drug treatment strategies) for key subgroups.”[ibid.]</li> </ul>
WP3	<p><b>“Develop a better understanding of how study designs used mainly for post launch RE (relative effectiveness [insert by the author]) can be applied successfully to investigational (unlicensed) medicines.</b></p> <ul style="list-style-type: none"> <li>• Assess designs <u>against current regulatory guidance/opinion</u> and operational challenges: <ul style="list-style-type: none"> <li>– Degree to which <u>design meets HTA agencies’ technical guidance</u></li> <li>– Any <u>conflict with regulatory guidance</u></li> <li>– Ethical/legal issues concerning study of investigational medicines</li> <li>– Operational impacts of different designs”[ibid.]</li> </ul> </li> </ul>
WP4	<p><b>“Examine how RE (relative effectiveness [insert by the author]) be estimated from phase II and III RCT efficacy studies alone</b></p> <ul style="list-style-type: none"> <li>• How should RCTs, additional relative effectiveness studies and observational data best be integrated to <u>address specific decision making needs of regulatory and HTA bodies at launch?</u></li> <li>• <u>How can relative effectiveness in one country be modeled from raw data on relative effectiveness in another?</u>”[ibid.]</li> </ul>

The work programs of GetReal have been presented in such detail to demonstrate the complementarity of this initiative to the EUnetHTA effort. Whereas EUnetHTA is the forum for HTA-bodies and has its focus on standardization of the scientific and technological base of HTA, GetReal is more industry oriented and concentrates its efforts on novel approaches of (real world) evidence generation especially in the pre-licensing phase that meets both regulatory and HTA demands.

#### 5.3.4 GreenPark Collaborative (GBC)

The GreenPark Collaborative is another recently formed multi-stakeholder forum (industry, representatives from the EMA and FDA, EUnetHTA and national HTA bodies) that focuses on the regulatory/HTA interface [62]. It started out with an international pilot in 2011 the goal being

“To determine the feasibility of developing recommendations for the design of clinical studies in specific therapeutic areas that address the information needs of payers and HTA bodies

- Informed by existing regulatory guidance and current best practices in research methods
- To develop a draft guidance for Alzheimer’s disease drugs in order to develop and evaluate this process” [ibid.]

The outcome of the international pilot was all in all positive, but it was also recognized that the international scope presents challenges and that for further activities a more regional approach should be chosen. This finally led to the formation of GreenPark Collaborative USA which had its inaugural meeting in March 2013. GreenPark Collaborative USA carries on in the spirit of the pilot by defining its program

- “..to support dialogue and consensus on methodological standards for clinical research”
- “Develop condition-specific “effectiveness guidance documents” [ibid.]

With the focus now being the US the evidence guidance documents created will have their regulatory focus also in the US and it is to be awaited how well these guidance documents will fit into the European regulatory/HTA environment [63] [64].

#### 5.3.5 Relevance for drug development

Drug development is mostly done at the international level with mid- and late stage studies being often multinational. The challenge for drug companies then is to incorporate as many regulatory and HTA requirements as possible into this study plan. As Regulatory Authorities and HTA-bodies often have quite different needs with respect to evidence generation drug development has become very challenging:

- What is the value of non-inferiority trials, e.g. in diseases with well-established treatment algorithm like diabetes, coronary heart disease etc.?
- How much of the real world setting (e.g. pragmatic clinical trials) can be incorporated into clinical study design already in the pre-licensing period? What are possible trade-offs with respect to quality of data or size, duration and costs of such studies?
- Choice of comparator(s), e.g. off-label-use in case of standard of care is a recurrent theme in trial design.
- Inclusion of patient perspective (Patient Reported Outcomes)
- As the use of biomarkers for patient selection is predicted to become more and more a key factor for successful development [65] (see also chapter 6.1.) regulatory processes like the EMA’s process for qualification of methodologies and surrogate markers will continue to gain importance. Collaboration between the EMA and EUnetHTA in this field can significantly contribute to the development of a sustainable drug development paradigm.

All initiatives where Regulators and HTA experts collaborate in developing guidance for evidence generation are therefore highly welcomed by industry. As shown above the EMA and EUnetHTA are heavily involved in such activities. Especially the recently launched IMI GetReal, where both organisations participate, has in its focus the exploration of new ways of pre-

licensing drug development and the deliverables of this program will certainly be awaited with excitement.

## 5.4 Generation of evidence after marketing authorisation

In the traditional way of thinking drug development ended with marketing authorisation and efforts that followed after launch of the product were mostly seen as part of the marketing strategy. This conception is fading and gives way to the notion that drug development is an effort that lasts throughout the life-cycle of a medicinal product. This new view has emerged as a reaction to commercial failures of novel products and to the change in the regulatory field brought about by the novel pharmacovigilance legislation and pilot concepts like adaptive licensing. Payers are more and more unwilling to reimburse treatments where the so-called real world evidence is lacking or minimal and Regulators nowadays regard the benefit risk ratio as an evolving and changing indicator of the medical value of a drug. Marketing Authorisation is no longer the end of development but rather the starting point to develop the medical value in the regulatory sense and the socio-medical and economic value in the HTA-sense. The lifecycle concept of drug development can be seen as steady advance on the efficacy/effectiveness scale (see also Fig.1 on page 9).

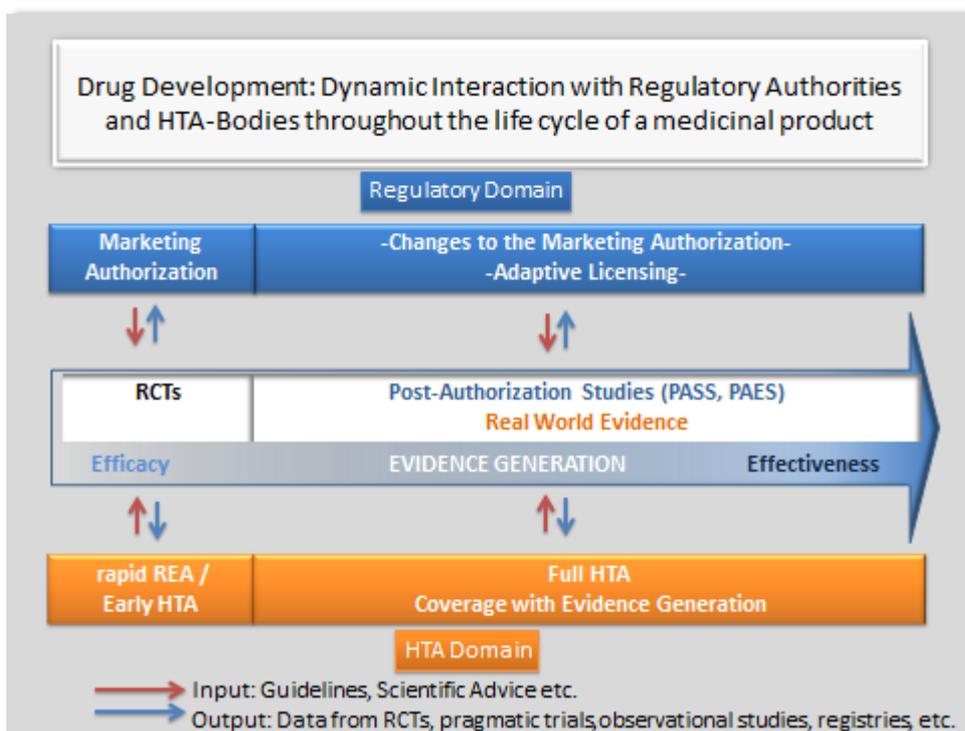


Fig.12: Drug Development: Interaction with Regulatory Authorities and HTA-bodies along the efficacy/effectiveness axis (evidence continuum)

In this process interactions with regulators are no longer limited to the phase before and around marketing authorisation but accompany the medicinal product throughout its life cycle. At the same time interactions with HTA bodies start well before regulatory approval and are an integral part of the life cycle after launch. By the implementation of the adaptive licensing concept (chapter 5.5) and the novel pharmacovigilance legislation Regulatory Authorities have shifted their view towards real world evidence generation and it is just natural that Regulatory Authorities and HTA-bodies are heading for close collaboration in this area.

#### 5.4.1 Pharmacovigilance / Post Authorisation Efficacy Studies (PAES)

In 2010 a new pharmacovigilance legislation was adopted, namely Directive 2010/84/EU and Regulation (EU) 1235/2010. The new legislation put forward the idea that at the moment of marketing authorisation only a limited data set is available for the benefit-risk assessment and that it will take continuous monitoring and in justified cases additional data will be needed to verify that the benefit of a medicinal product still outweighs its risks. In this context the legislation provides the possibility for regulatory authorities not only to mandate post-authorisation safety studies but also post-authorisation efficacy studies. Although the possibility for post-authorisation efficacy studies already existed in the context of conditional licensing, medicinal products for use in pediatric populations or advanced therapy medicinal products (ATMPs) [66] the scope is now extended to all medicinal products.

The spirit of this new pharmacovigilance legislation is oriented towards real world evidence. Below are some examples taken from the legislative texts and accompanying documents:

- “The Commission should therefore be empowered to impose on the marketing authorisation holder the obligation to conduct **post-authorisation studies on safety and on efficacy**. ...Such studies may be aimed at collecting data to enable the assessment of safety or efficacy of medicinal products for human use **in everyday medical practice**.” (emphasis by the author) Recital 16 of Regulation (EU) 1235/2010
- „**5.7. Studies in everyday medical practice**  
**Studies of everyday medical practice** are expected to be requested mainly in those circumstances where there is clear evidence that **the benefits of the medicinal product** under discussion as shown by randomized controlled clinical trials might be **significantly affected by the real-life conditions of use**. This could be the case, for example, where there is a non-negligible impact of behavioral and compliance aspects on health outcomes. Another scenario might be a situation where, despite a high degree of **internal validity** of the results from pivotal clinical trials, the **external validity of the data presents clear uncertainties that warrant further evaluation in the post-approval setting**, e.g. impact of co-morbidities and polypharmacy on the effect of a specific intervention in a geriatric context.” (emphasis by the author) [66]

In 2013 the European Commission initiated a public consultation on a Delegated Act on Post-Authorisation Efficacy Studies [66]. The Commission received 33 contributions, among which were also contributions from national HTA bodies like NICE, HAS, IQWiG and from EUnetHTA [67]. Overall the feedback was very positive and both the individual HTA-bodies as well as EUnetHTA stressed the need for consultations between the EMA and EUnetHTA in order to mandate studies that would be optimal use both for regulatory and REA-aspects (ibid.). In the EMA/EUnetHTA meeting in March 2013 a special collaboration between the EMA and EUnetHTA on PASS/PAES was envisaged and also the concept of “late stage scientific advice” was put forward [68]

In October 2013 the EMA held a workshop with invited experts “on methods for efficacy studies in the everyday practice”, a project directly pertinent to PAES [69].

Finally in 2014 the European Commission adopted the Commission Delegated Regulation (EU) 357/2014 concerning PAES. According to this regulation [70] post authorisation efficacy studies may be required in situations

- where surrogate endpoints have been used to establish efficacy
- when a medicinal product is regularly used in combination with other drugs
- when different sub-populations have not been adequately represented
- when the proof for long-term efficacy is missing

- “In exceptional situations, studies in everyday medical practice could be requested where there is clear evidence that the benefits of a medicinal product demonstrated in randomised controlled clinical trials is significantly affected by the real-life conditions of use or where the specific scientific concern is best studied by having access to data collected in everyday medical practice...”(ibid.)
- when there is a significant change in the standard of care.

#### 5.4.2 ENCePP

An additional element of combining efforts in generating post-authorisation evidence is the beginning collaboration between ENCePP and EUnetHTA. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) is a network of over 170 research centers, existing networks and providers of healthcare data, which is coordinated by the European Medicines Agency. Its goal is to strengthen post-authorisation monitoring of medicines by facilitating the conduct of multicenter, independent studies focusing on safety and on the balance of benefits and risks, using available European research expertise.” [71] ENCePP was established in 2006 by the EMA, is coordinated by the EMA and is an important tool in the European pharmacovigilance system. ENCePP and EUnetHTA have formed a working group that has the obligation to explore ways of collaboration in developing guidance for the performance of post authorisation safety and/or efficacy studies. [72]

The ENCePP work plan for 2013-2014 includes several deliverables with respect to post-authorisation studies and collaboration with EUnetHTA [73] [74] [75] [76]

- Discussion with EUnetHTA concerning of linkage of the ENCePP database containing pharmacoepidemiology and pharmacovigilance data about drugs with EUnetHTA database EVIDENT containing clinical data of health technologies (drugs, devices etc.)
- Collaborate with the EMA and EUnetHTA in guidance concerning post authorisation efficacy and/or safety studies
- Concept paper on the conduct of post authorisation studies that meet the requirements of both the EMA and HTA bodies

At the end of this effort ENCePP could constitute an important bridge to overcome the repeatedly invoked efficacy-efficiency gap [77], being a hub for the exchange of data and know how concerning pharmacovigilance and post-authorisation studies.

#### 5.4.3 Relevance for drug development

The drug development paradigm is changing with the old distinction between prelicensing clinical development to serve the demands of Regulatory Authorities and postlicensing “marketing studies” to help establish a drug in the market being more and more replaced by the concept of continuous evidence generation and it depends on the perspective whether the new pharmacovigilance legislation is seen as a result or a key driver of this process. Net effect is the growing perception that drug development is not a finite process but embedded in an evidence continuum and that the medical value of a drug is not static but can change with the accumulation of evidence.

The new pharmacovigilance concept with post-licensing evidence generation by post-authorization safety and/or efficacy studies has a conceptual counterpart in the HTA-world

best known as coverage with evidence development<sup>9</sup> or more generally as managed entry [78].

The EMA and EUnetHTA have already started the exchange of views on design of post-authorisation efficacy studies and as experience in this area will accumulate on both sides possibilities for alignment and collaboration in developing guidance for industry will emerge.

## 5.5 Adaptive Licensing

The most consistent way to adopt the regulatory practice to ideas like the life cycle concept of drug development, the efficacy-effectiveness continuum and the concept of a changing benefit/risk ratio as discussed in the previous chapter is the EMA's project on adaptive licensing that has recently culminated in the announcement of the two first pilots in June 2014 [79].

Much of the conceptual framework of adaptive licensing was generated in the New Drug Development Paradigms (NEWDIGS) collaboration, that started in 2010 as initiative of the Massachusetts Institute of Technology (MIT) and was hosted by the MIT Center for Biomedical Innovation [80]. The collaboration involved representatives from regulatory agencies including the EMA, FDA and Health Canada as well as representatives from US and European pharmaceutical industry, payers, HTA-bodies and academic researchers.

The focus of the NEWDIGS adaptive licensing project was on modeling of various adaptive licensing scenarios (case-based, economic modeling, retrospective simulations etc.) in order to put forward a viable proposition of future projects in this field [80] [81] [82]. The NEWDIGS collaboration finally resulted in the publication coauthored by representatives from all groups of stakeholder of a proposal for future adaptive licensing approaches in 2013 [83].

The cornerstones of the propositions made in this concept paper are the following: (keywords from the publication are set in parenthesis)

- Drug licensing is no longer “a binary decision”. Instead with respect to the “acknowledged uncertainty” that is linked to the limited data set available at the time of initial marketing authorisation licensing should become a process of “stepwise learning” with “iterative phases of data gathering and evaluation.” Adaptive licensing is intended to replace “the single magic moment between non-approval and approval” by a process of “progressive management and reduction of uncertainty.”
- Adaptive licensing is not a completely new regulatory approach as regulatory measures like conditional marketing authorisation (EU), accelerated approval (US) and post-authorisation studies are already instruments for a staggered licensing process. But instead of reserving these approaches for selected medicinal products adaptive licensing is intended to become a tailor-made licensing path for all new drugs.
- Adaptive licensing is therefore defined as “a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made” (ibid., emphasis by the author)

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<sup>9</sup>Definition taken from [78]: “The main aim ... is to generate additional evidence to address uncertainty highlighted during the drug review process...”.

Adaptive licensing is a regulatory project that certainly will require an unprecedented level of collaboration and flexibility among all stakeholders:

- “Under the paradigm of AL, all stakeholders will need to accept that initial approval is not just early but also conditional.”
- “The pre- and post-initial authorization collection of clinical data might be navigated by astute planning of the development and licensing pathways and will require a new level of cooperation among industry, regulators, and payers”.
- “For most drugs, treatment access also involves a subsequent decision on coverage (reimbursement) of an authorized drug by third-party payers such as Medicare in the United States or national health services in the European Union, followed by a prescriber’s decision to select a drug for treatment and a patient’s agreement to treatment. Gatekeepers to treatment access therefore include not only regulators but also payers, physician prescribers, and other health-care providers. To be successful, AL would require some alignment between the regulatory, payer, and prescriber decisions. Under the current system, the lack of alignment has led to payers unwilling to cover new treatments when they consider the evidence basis to be insufficient to justify the cost.”

The authors then present examples for various scenarios where the level of initial uncertainty is reduced by follow-up measures which in turn leads to the adaptation of the initial license (see Table 6).

**Table 2** Examples of potential “design features” of AL pathways

Aim	Initial license based on	Subsequent license based on	Comment
Reduce uncertainty around end point	(Not fully validated) surrogate end point	Clinical end point	Not a new concept; it is the basis for AA/CMA but may be used more frequently; there are challenges to enrolling postmarket RCTs
Broaden treatment-eligible population	Studies in enriched population with highest need based on benefit–risk	Studies in broader population	Currently common for oncology drugs but sees limited use in other therapeutic areas
Reduce statistical uncertainty	Superiority studies: greater than conventional significance level Noninferiority studies: wider than normal CI	Conventional significance level ( $P < 0.05$ ) Stringent CI	For example, for a follow-on drug with safety advantage, drugs for rare conditions, long follow-up; may be challenging to do studies after the initial license for ethical reasons
Enable new–new combination development	Study showing improved efficacy (or risk profile) of combination vs. SOC	Full regulatory work-up to demonstrate the contribution of individual components	Allows initially for smaller (two-arm) trials, enabling shorter time to initial licensing
Reduce uncertainty around study design	Single-arm study; observational study; registry	RCT	Not a new concept; it has been the basis for AA/CMA for some cancer, orphan drugs
Ensure “real-world” effectiveness	Explanatory trial	Pragmatic RCT or observational study	Applicable to situations where real-life performance is in doubt
Address rare AEs	Trial powered for efficacy	Trial powered for defined AE (and, perhaps, in more confounded, real-world population)	Where there is a concern over a defined rare or difficult-to-detect AE; example: FDA diabetes drug guideline; “delinking” of the efficacy and safety populations; see text

Different drug classes will probably require different regulatory pathways; elements from each of these pathways could also be combined for the AL of a single drug.

AA, accelerated approval; AE, adverse event; AL, adaptive licensing; CI, confidence interval; CMA, conditional marketing authorization; FDA, US Food and Drug Administration; RCT, randomized controlled trial; SOC, standard of care.

**Table 6:** Examples for the application of the adaptive licensing scenario to reduce uncertainty present at the time of the licensing decision , Source [83]

### 5.5.1 Impact on drug development:

To be a success adaptive licensing needs various changes in attitudes among stakeholders and also changes in general health care systems:

- A process of interaction and communication between stakeholders in public health including patients that will deal with various levels of uncertainty during the evolution of the license

- Greater adherence to use in the eligible patient populations and the importance of the labelling conditions
- Extensive use and building of tools for surveillance and evidence generation (with all the anticipated issues concerning privacy in the context of EU legislation)
- Incentives for drug companies ( issue of patent expiry in the context of a prolonged development phase and staggered reimbursement schedules)

In this process of adaptive licensing HTA-bodies are important gatekeepers to access of these novel medicinal products and their participation in the process will be seminal for this project to be become a success. Although EUnetHTA is not the direct partner in the pilot projects and it is left to the discretion of the national HTA-bodies to participate in the pilots, these HTA-bodies as being members of EUnetHTA will probably help to disseminate the idea of adaptive licensing and EUnetHTA is consulted by the EMA in this field and EUnetHTA can significantly contribute to the project via deliverables from its several work packages (e.g. guidelines, unified methodology) [84].

## 5.6 Orphan Medicinal Products

When discussing the licensing and reimbursement situation for so called orphan medicinal products it is important to mention some newer developments in this field, that may have a major influence on future regulatory and HTA practice and in consequence on drug development. Currently roughly one third of all designations relate to medicinal products for the treatment of cancers (see Fig.14).

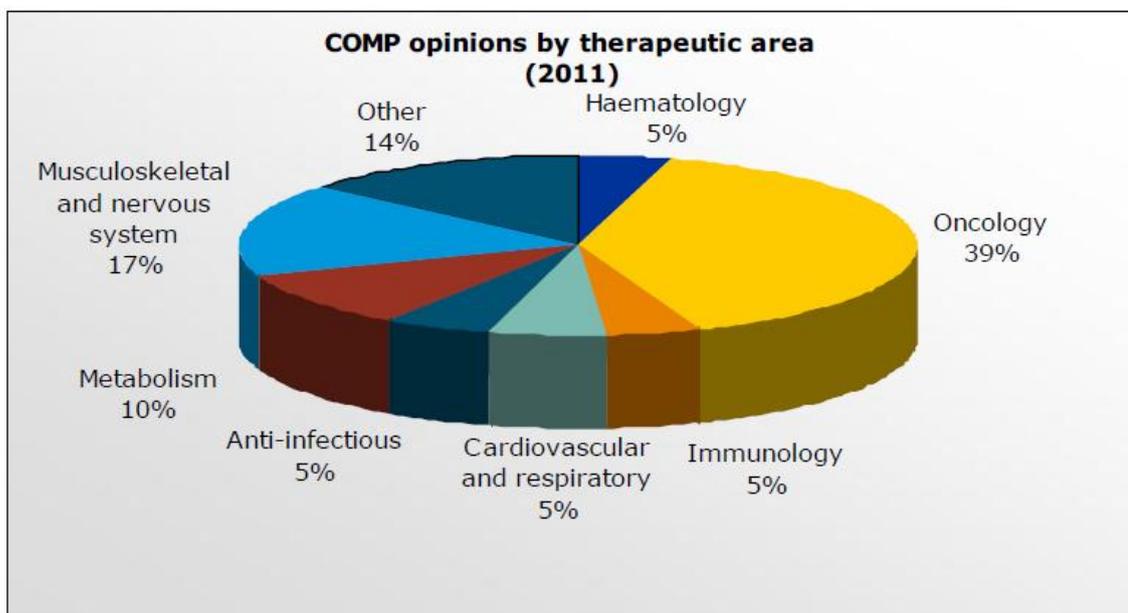


Fig.13: Oncology drugs constitute a large proportion of orphan medicinal products [85]

Classically the orphan designation originates from the rarity of the underlying disease as classified by conventional methods. With the advent of pharmacogenomics and the availability of respective biomarkers a process of “orphanisation” in oncology by biomarker guided patient stratification was initiated and it is predicted that this will be the future development path for most of the new anticancer therapies [65] (For a more detailed discussion see also Chapter

6.1.). A major challenge arising for all stakeholders (drug companies, regulators and HTA-bodies) from this development is to find ways to facilitate development and reimbursement of companion (in vitro) diagnostics [86] and to support the timely access of patients to these novel cancer therapies which means a highly concerted interaction of regulatory and HTA institutions.

In 2011 the European Commission published the Ernst & Young Study on the Clinical Added Value on Orphan Drugs (CAVOD) [87].

The objectives of this study were

- to map the regulatory and HTA landscape in Europe with regards to orphan medicinal products
- to identify the best way for data generation and collection for REA
- to describe a way of collaboration between the EMA and HTA-bodies

The result was the proposition of a development path than can be regarded as a special case of adaptive licensing: (see Fig.15 below).

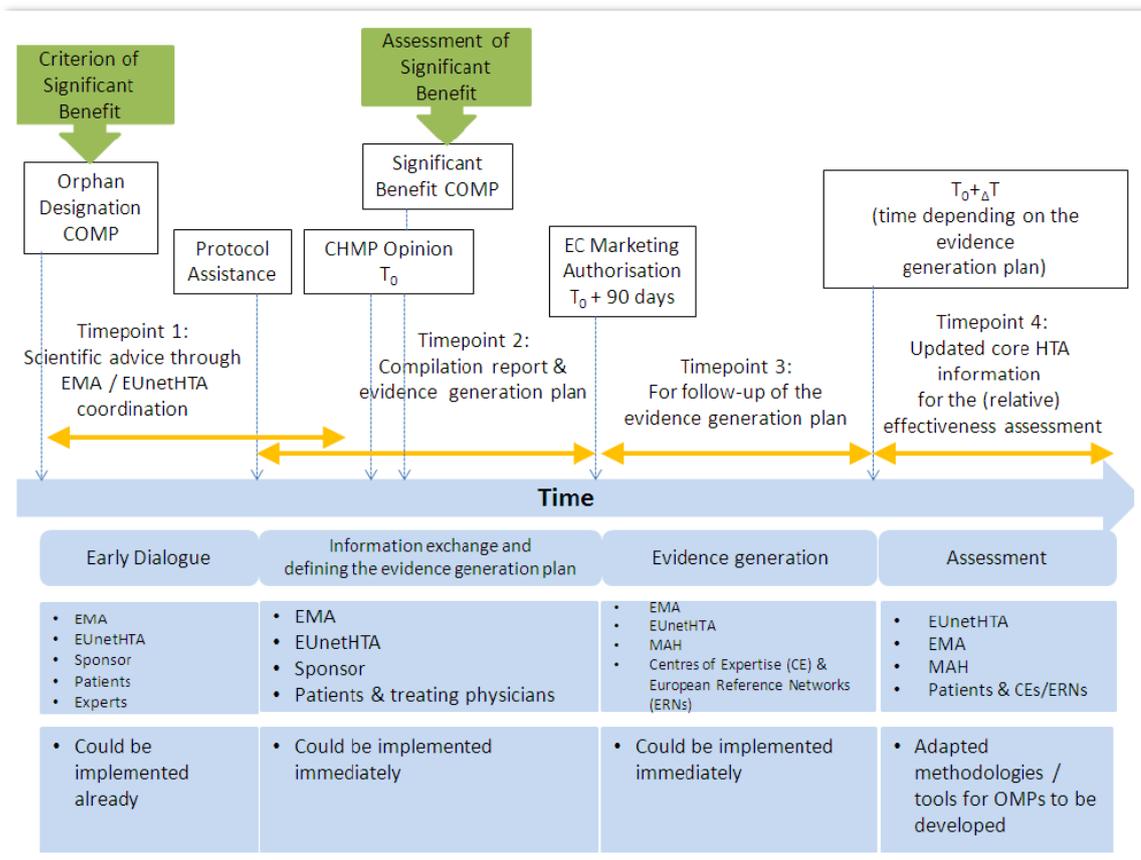


Fig.14: The Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow.

Source: [88]

This procedure has subsequently endorsed by the EUROPEAN UNION COMMITTEE OF EXPERTS ON RARE DISEASES (EUCERD) in September 2012 [88] and is now waiting for implementation. The EMA and EUnetHTA playing an instrumental role in this process [87] have made orphan medicinal products one of their topics for collaboration [26]

## 6. The overall impact of the EMA / EUnetHTA collaboration on drug development

As shown in this thesis the EMA/EUnetHTA collaboration is part of a complex landscape of national, European and international networks of multi-stakeholder platforms that involve Regulatory Agencies and HTA-bodies like NEWDIGS, Greenpark Collaboration or the Tapestry Networks. Therefore the role of the EMA/EUnetHTA collaboration should not be seen in isolation but as part of a paradigm change in drug development that has international dimensions.

EUnetHTA is a voluntary network with the aim to consolidate the scientific and technological base of HTA with a current focus on rapid REA. The success of EUnetHTA's current Joint Action 2 Work Program depends on the willingness of national HTA-bodies to adopt the tools and workflows developed by EUnetHTA. With the formation of the Health Technology Assessment Network in 2013 a European forum was created with the clear mission to develop a strategy for HTA policy which will include the future role of the EUnetHTA collaboration. The Joint Action 2 Program ends in 2015 but there are already thoughts to initiate a Joint Action 3 within the frame of HORIZON 2020 [89] which is the successor of the IMI Project and has an explicit focus on collaboration between Regulators and HTA-bodies/Payers (see Fig.16, below).

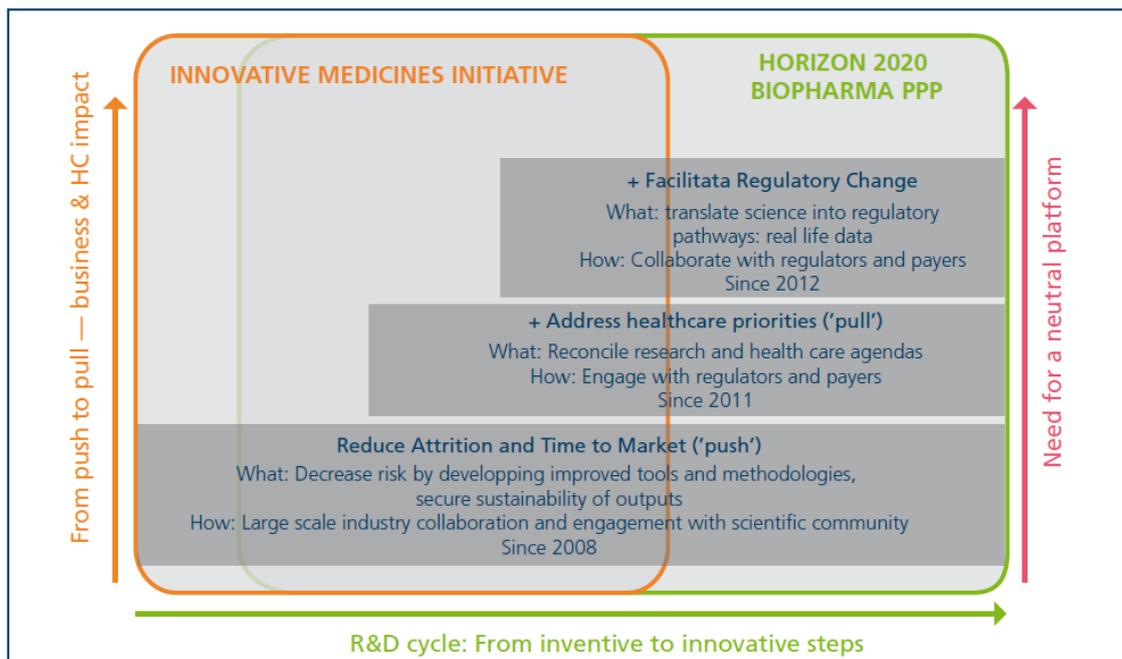


Fig.15: The scope of Horizon 2020 and its relation to the current IMI. Source [90]

Currently the impact of the EMA/EUnetHTA collaboration is based on two major activities,

- the best possible alignment concerning the use of data supporting the evidence for efficacy and efficiency (EPAR project, Effects Tables, SmPC)
- parallel scientific advice

The EPAR project has certainly an immediate impact on regulatory and even more on HTA practice. It has often been bemoaned by industry that the same set of data leads to very different assessments by regulators and HTA-assessors. The new EPAR format has been adapted to the needs of HTA-bodies by making the scientific base of the assessment more transparent and thereby the decision clearly comprehensible. This will help reducing double

work during the REA process and thereby reduce time lines. It will have no impact on the national requirements for REA and reimbursement but the process of EPAR improvement has certainly contributed to foster understanding the operational rules of the EMA and to build trust in the scientific assessment process by CHMP.

Parallel Scientific Advice by the EMA and EUnetHTA members on the other hand will have a long reaching impact on drug development. The dialogue between industry, the EMA and HTA-bodies will first of all help to understand the other party's views and needs and as a consequence will facilitate the identification of action items like the current call for disease specific guidelines or more streamlined procedures of feedback by HTA-bodies [ 42]. Probably there will be no single kind of Scientific Advice in the future, rather depending on the special circumstances there will be Regulatory or HTA Advice at the national or European level as well as Parallel Advice in all different kinds (national, European, single-/multi HTA ).

Initiatives like adaptive licensing, the new rules for post authorisation efficacy studies, the IMI GetReal project etc. are all still in the beginning. Future will show their impact on the way how the EMA and HTA bodies collaborate and how this will affect drug development. All these new concepts have yet to be tried but they all have already fulfilled an important part of their purposes: They have detailed the shortcomings of the current drug development model concerning a close collaboration of industry, regulatory authorities and HTA-bodies/payers and in addition they have proved not only on paper that alternatives are not only possible but can also become driving forces for more sustainable concepts of drug development and health care provision.

## 6.1 The impact of the collaboration of Regulatory Authorities and HTA-bodies/ Payer Organisations on the classical drug development paradigm and on the organisational rules of pharmaceutical companies.

Today most of the pharmaceutical companies act internationally, their clinical development programs are international and they have to fulfill regulatory and reimbursement requirements imposed by the various national and supranational authorities. Therefore it is nearly impossible to sort out the conceptual and organisational changes due to a single interaction with regulatory authorities and HTA-bodies (e.g. with the EMA or with EUnetHTA or both), in most cases the impact is rather the net sum of all interactions a company has.

The majority of companies is rather open towards the new concepts of collaboration between Regulatory Authorities and HTA-bodies/Payers. Reasons for the optimism with which these initiatives are welcomed could be

- **Rising overall costs of drug development due of commercial failures of recently licensed drugs**

High attrition rates in late stage development [91] and a high percentage of commercial failures (see Fig.17) are major drivers for the steady increase in overall costs of drug development [92]. Lack of differentiation seems to be a major cause for unsuccessful market penetration and it can be taken as one sign for a deficit in the ability to demonstrate the value, i.e. the effectiveness of the newly introduced therapies.

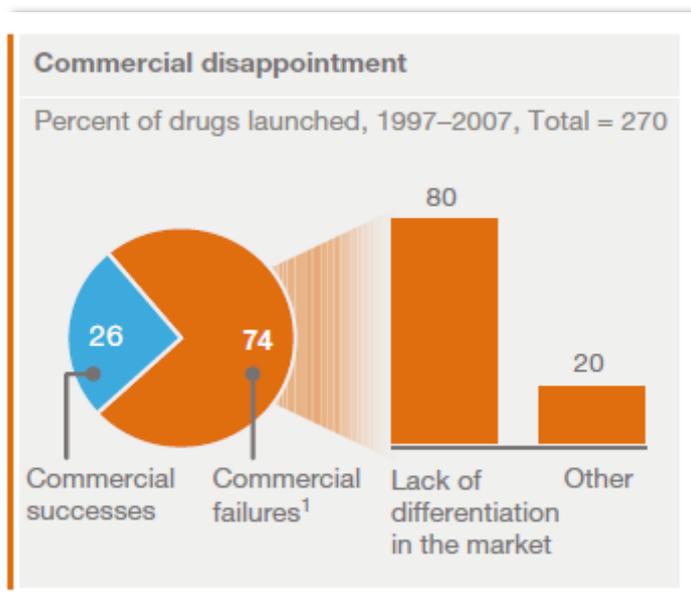


Fig.16: Percentage of commercial successes and failures of drug launched during 1997-2007.  
(Source [92])

- **The advent of Stratified Medicine**

Many of the currently available therapies are ineffective in a significant portion of the overall patient population irrespective of the therapeutic area (see Fig.18). This fact poses both great opportunities and challenges to drug development. Demonstrating clear efficacy/effectiveness in a subpopulation of patients that is not responsive to the available treatment is certainly a great success. On the other side identification of this subpopulation via an appropriate biomarker, the development of a so-called companion in-vitro diagnostic and clinical

development by dealing with relatively small patient populations (see Fig.19) can be methodically challenging and commercially very risky.

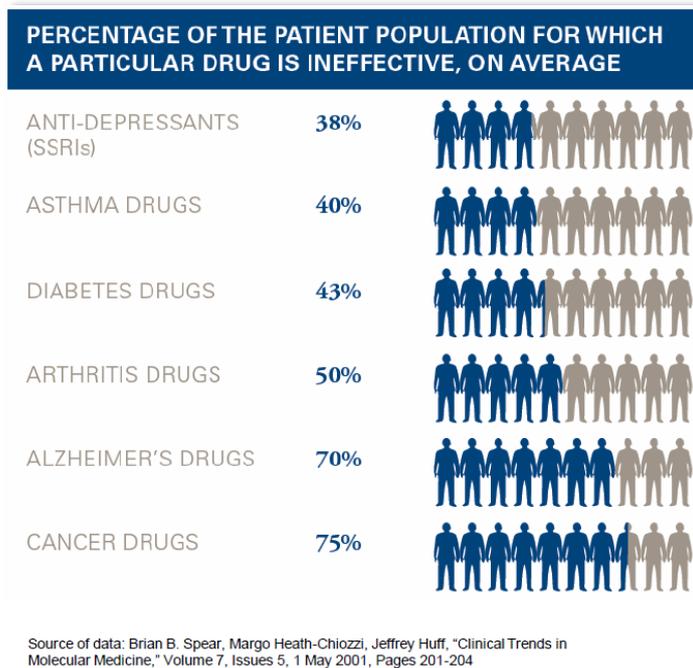


Fig.17: Lack of efficacy of current treatments broken down the therapeutic area [93]

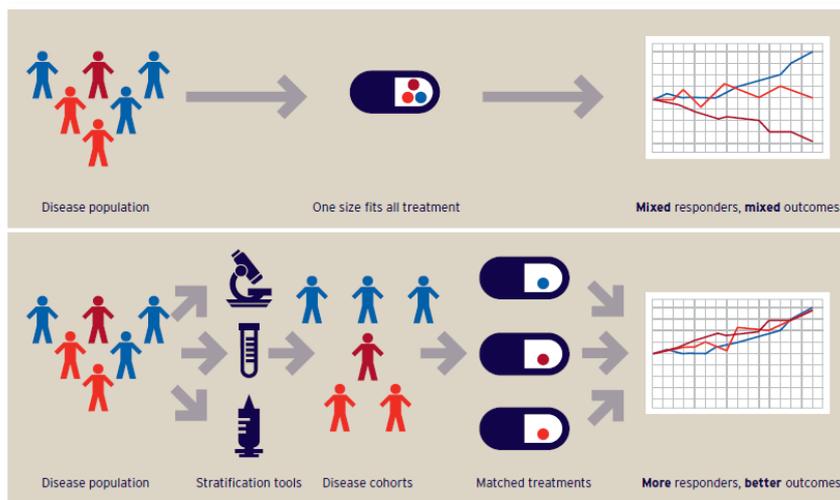


Fig.18: Schematic presentation of stratified medicine concept: Upper panel: no stratification, all patients receive same medication. Lower panel: Stratification of patient by biomarker test (in vitro companion diagnostic, IVD) and assignment of appropriated treatment according to stratification parameter. Source [94]

The advent of Stratified Medicine<sup>10</sup>, today primarily in oncological indications, has heralded a new era of drug development that is sometimes characterised as an orphanisation of diseases

<sup>10</sup> Definition: " 'Stratified medicine' is the grouping of patients based on risk of disease or response to therapy by using diagnostic tests or techniques"

[Source: Academy of Medical Sciences (2013) Realising the potential of stratified medicine. Available at: <http://www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf>, accessed 17-07-2014]

Stratified medicine helps to guide the right choice of care for these preselected groups of patients. It can be seen as a step towards personalised medicine.

[86]. There are forecasts that stratified medicine will be the model of choice for many new therapeutics [65] and therefore a close collaboration between Regulatory Authorities, HTA-bodies and industry will be essential for developing sustainable paths of drug development in this challenging environment.

- **Evidence gap**

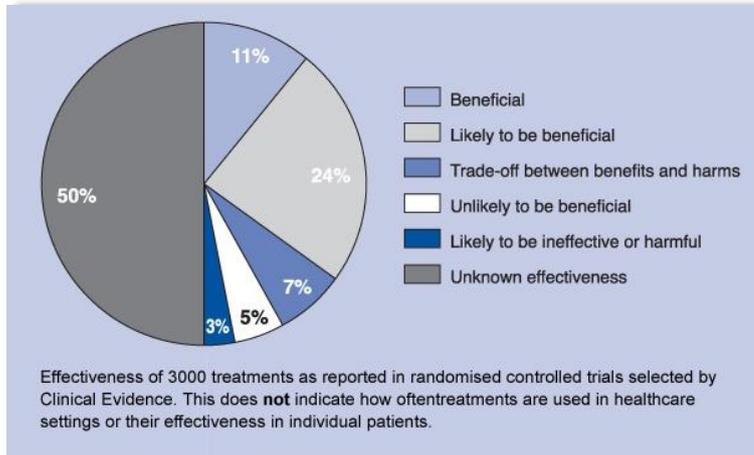


Fig.19: Clinical evidence based proof of effectiveness of 3000 treatments currently available.  
Source [95]

As dramatically illustrated in Fig.20 a large portion of treatments is applied today without an adequate proof of effectiveness shown in clinical trials. With the universal rise of health care expenditures and as payers, health care institutions and patient organisations are gaining more and more influence and power of decision-making in health care systems proof of “real world value” of a novel medicine is becoming key for inclusion of the respective treatment into the medical armamentarium and for gaining reimbursement.

## 6.2 The impact of US and European demands for evidence of comparative effectiveness<sup>11</sup>/relative effectiveness – a survey from pharmaceutical industry

As many of the collaborative projects between regulatory authorities and HTA-bodies including the EMA/EUnetHTA collaboration have been launched only recently feedback from industry with regard to their impact on drug development is rather limited and restricted to a small number of companies [42]. The interaction of companies with HTA-bodies per se has a longer history and here a survey from international pharmaceutical companies addressing the impact of these interactions on the drug development process was published recently [96]. Although this paper addresses the role of collaboration between Regulatory authorities and HTA-bodies only indirectly it highlights the areas where collaborative efforts between Regulators and HTA-bodies are needed.

The survey involved 19 experts of comparative effectiveness research/ relative effectiveness from 5 companies (Amgen, Eli Lilly, GlaxoSmithKline, Novartis, Sanofi-Aventis). It was based on semi-structured interviews that focused on changes of the classical drug development paradigm in the context of increasing importance of provision of “real world data”.

International context for a change of drug development paradigm:

- Rising R&D costs of successful new medicines due to high percentage of clinical and commercial failures (allowing the costs of those drugs that fail)
- Companies have traditionally focused their development program around registration
- Decision making power of payers is ever increasing and also in emerging countries interest in evidence of value to inform decisions about healthcare resource allocation is growing
- Disconnect between expectations of regulators/HTA bodies with respect to evidence needs

Issues concerning drug development:

1. At which point of development should pragmatic approaches, i.e. closer match of the clinical setting to the real world situation, incorporated in the development program
2. How much of this can be done pre-launch
3. Which of data post-launch would fit best the needs of the decision makers, e.g. observational studies, data from patient registries or electronic health records
4. Given the global nature of drug development, how will industry adapt to national or regional requirements for additional evidence generation?

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<sup>11</sup> Comparative Effectiveness is the US synonym for Relative Effectiveness

Outcome of the survey: (as a summary of the responses from the interviewees)

1. The classical drug development paradigm as depicted in Fig.21 below is no longer valid.

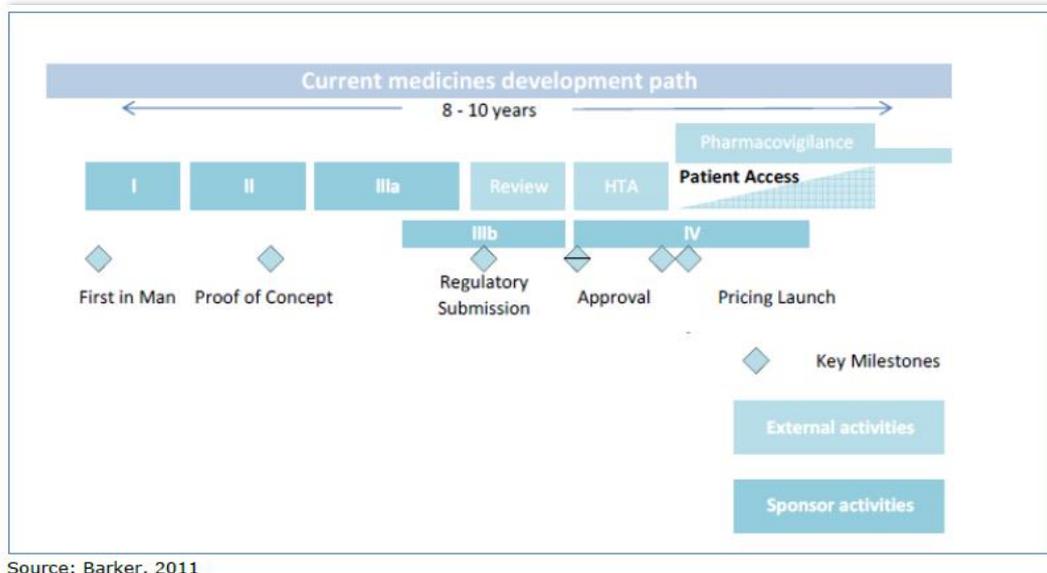


Fig.20: Traditional Drug Development Paradigm. (Source [96])

- a. Changes were seen more evolutionary and incremental rather than disruptive
- b. The process has become "more exploratory and confirmatory" rather than the "old learn and confirm concept" [96], e.g. Proof of Concept Studies are performed as early as possible, Phase IIIa and IIIb studies are often combined in a single study
- c. Scientific Advice by HTA-bodies is asked for earlier by companies
- d. Considerations about commercial success are made much earlier e.g. in phase II
- e. Patient views are incorporated into the development plan more consequentially and at a much earlier phase
- f. Comparative effectiveness / Relative effectiveness is affecting go/no-go decisions with respect to portfolio management
- g. The impact of Comparative effectiveness / Relative Effectiveness considerations varies with product type: In a market where several treatment alternatives are available and for "me-toos" it is much more important than in therapeutic areas where no established standard of care exists.
- h. Consultation with external stakeholders is key but varies with experience of company
  - Advisors
  - Advice by HTA-bodies and Regulatory Authorities (joint advice by the EMA and HTA-bodies mentioned)
  - Patients
- i. Development programs usually are global, but companies have 5 to 15 key markets, where they ascertain whether regional evidence has to be provided
- j. Internal barriers to change: lack of trained personal, lack of understanding and of sharing the same views concerning evidence requirements by members of the clinical development teams, champion needed
- k. External barriers:
  - no clear standards with regards to HTA-bodies in Europe
  - lack of harmonisation between regulators and HTA-bodies

Finally the expectations for future direction of the drug development paradigm sound like an industry vote for adaptive licensing:

“Many interviewees stated that they hoped that since much of the CER/RE data (or at least elements of it, such as relative efficacy data i.e. having a head to head comparative study) are now being collected in phases III and IIIb, drugs could receive conditional approvals earlier with a requirement for observational studies post-approval or those regulatory agencies would accept observational studies for approval. The net effect would be to try to balance the increased evidence requirements of CER/RE with innovative regulatory strategies so that drug development timelines would not inevitably be extended.” [96]

Factors that were regarded as the biggest drivers of these changes:

“...the expectation on the part of the interviewees was that there was going to be greater transparency from the payers regarding acceptable methods and comparators and ideally more effective communication between regulators and payers.” [96]

This feedback clearly advocates for EUnetHTA and the Health Technology Assessment Network and underscores the importance of the EMA/EUnetHTA collaboration.

## **7. Conclusion and Outlook**

The collaboration between the EMA and EUnetHTA takes place in an environment where interactions between Regulatory Authorities and HTA-bodies/Payer Organisations are becoming increasingly popular [97] as a promising approach to shape future drug development and health care systems. With Europe being the second largest pharmaceutical market [98] the EMA-EUnetHTA collaboration is of particular importance. The three year working joint working plan of the EMA and EUnetHTA will end in 2015 as will the Joint Action 2 Project. If and how EUnetHTA will be carried on will surely depend on the strategic orientations of the European HTA Network (HTAN). EUnetHTA itself is already planning a Joint Action 3 Project under the umbrella of HORIZON 2020 [28].

Pharmaceutical Industry has welcomed the collaboration and expectations for the future are high. Many of the projects are still pilots and it is much too early to make projections on how concepts such as post authorisation efficacy studies or adaptive licensing will shape the drug development process.

But , as underscored many times by representatives from the EMA, EUnetHTA and industry, already with entering into a dialogue the EMA and EUnetHTA have taken a decisive step towards a harmonization of regulatory and HTA requirements and hopes are high on all sides that all these exciting developments that link regulatory and HTA perspectives will finally help to develop a sustainable drug development model.

## 8. Summary<sup>12</sup>

Current drug development occurs in the field of tension between the requirements of regulatory authorities in the context of licensing and health technology assessment (HTA) bodies in the context of reimbursement and pricing. Whereas the regulatory field is highly harmonized in Europe, HTA assessment is still done at the national level and Europe-wide efforts for harmonization in the HTA-field are just emerging. A major step towards this goal was the foundation of EUnetHTA in 2006, a voluntary network of national HTA bodies with the aim to develop methodologies and tools for standardized evaluation and reporting that allow the transnational sharing of HTA information. An important aspect of HTA is relative effectiveness assessment (REA) which seeks to determine the value of a medicinal product in relation to an established standard of care under real world conditions. In the field of REA there is big overlap between the activities of HTA bodies and Regulatory Authorities, especially in the context of so-called rapid REA which relates to HTA at the time of marketing authorisation. Here both Regulatory Authorities and HTA bodies use the same set of clinical data for their analysis. Accordingly, the collaboration between the EMA and EUnetHTA started out in 2010 as a project for the adaptation of the contents of the European Public Assessment Report (EPAR) to the needs of HTA bodies for REA. In the meanwhile the scope of the collaboration has been extended to all aspects of drug development including the evolving area of post authorisation evidence generation e.g. in the context of post-authorisation efficacy studies. A particularly important aspect of the collaboration is the procedure of Parallel Scientific Advice by the EMA and HTA-bodies. It serves as a hub for information sharing between the EMA, EUnetHTA and industry and thereby helps uncover areas for potential alignment and areas of conflict of interest. The three year joint work program between the EMA and EUnetHTA will end in 2015, as will EUnetHTA's own work program "Joint Action 2". In 2013 a European HTA Network has been established by the European Commission. This network has the task to elaborate a strategy for collaboration of HTA-bodies and EUnetHTA currently has the role of a scientific advisory platform. The future of EUnetHTA will depend on the availability of funding, possibly under the umbrella of HORIZON 2020. The EMA-EUnetHTA collaboration is embedded in a network of interactions between regulatory authorities and HTA bodies at all levels, national, European and international. This makes it sometimes difficult to sort out the specific effects of the EMA-EUnetHTA collaboration on drug development. Some of the joint projects of EMA and EUnetHTA are in the planning phase, others are pilots or have just moved into field testing. Nevertheless the EMA-EUnetHTA collaboration has already fulfilled an important part of its purpose: It has helped to detail the shortcomings of the current drug development model concerning a close collaboration of industry, regulatory authorities and HTA-bodies/payers and in addition it is proving that alternatives are possible. The EMA-EUnetHTA collaboration occurs at a time where the old drug development paradigm is fading because it is no longer sustainable for the following reasons: Industry is faced with a significant number of dropouts in late stage development and commercial failures causing a constant rise in development costs. Medical practice is adopting the concept of stratified/personalised medicine which leads to clinical development strategies dealing with smaller patient populations and narrower indications which can be commercially very risky. Payers and patients are gaining more and more influence on everyday health care practice.

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<sup>12</sup> to be published at the Internet Site of DGRA

At the same time the new pharmacovigilance legislation with the possibility to mandate post authorisation efficacy studies and regulatory strategies like adaptive licensing as well as pricing and reimbursement procedures according to the concept of coverage with evidence generation promote the concept of drug development as a process of continuous evidence generation. There is general agreement among all stakeholders that these challenges can only be mastered by close interaction of Regulatory Authorities, HTA-bodies and industry.

In this context the EMA-EUnetHTA collaboration is welcomed by industry as an import step towards the alignment of regulatory and HTA needs and expectations are high that it will become one of the driving forces for the creation of more sustainable ways of drug development and health care provision.

As many of these collaborative projects have been launched only recently their impact on drug development is difficult to assess, but industry is ready to adopt the idea of drug development as a process that covers the whole life cycle of a medicinal product where continuous generation of evidence is becoming a prerequisite to support a positive benefit/risk ratio and to justify reimbursement and pricing in an ever changing health care environment.

## 9. List of References

- [1] H. L. P. F. W. G. o. R. Effectiveness, "Core principles on relative effectiveness," [Online]. Available: [http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea\\_principles\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf). [Accessed 24 6 2014].
- [2] EUnetHTA, "EUnetHTA JA WP5: Relative Effectiveness Assessment (REA) of Pharmaceuticals. Background review July 2011 (Version 5B)," EUnetHTA, 7 2011. [Online]. Available: <http://www.eunethta.eu/outputs/final-version-background-review-relative-effectiveness-assessment>. [Accessed 1 6 2014].
- [3] H. L. P. F. R. E. W. Group, "Data availability to conduct on relative effectiveness assessment," [Online]. Available: [http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea\\_data\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_data_en.pdf). [Accessed 24 6 2014].
- [4] [Online]. Available: <http://www.ispor.org/HTARoadMaps/Spain.asp>. [Accessed 23 5 2014].
- [5] F. B. Kristensen, M. Mäkelä, S. A. Neikter and N. Rehnquist, "European network for Health Technology Assessment EUnetHTA: Planning, development, and implementation fo a sustainable European network for Health Technology Assessment," *International Journal of Technology Assessment in Health Care*, vol. 25, no. Supplement 2, pp. 107-116, 2009.
- [6] M. S. Hriday and K. C. Chung, "Archie Cochrane and his vision for evidence-based medicine," *Plast Reconstr Surg.*, vol. 124, no. 3, pp. 982-988, 2009.
- [7] L. Sampietro-Colom, "Once upon a time...The rise and use of HTA throughout the world," *Michael Quarterly*, vol. 9, pp. 90-94, 2012.
- [8] WHO, "European Observatory on Health Systems and Policies. Health technology assessment. An Introduction to objectives, role of evidence and structure in Europe," 2005. [Online]. Available: [http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0018/90432/E87866.pdf](http://www.euro.who.int/__data/assets/pdf_file/0018/90432/E87866.pdf). [Accessed 30 5 2014].
- [9] F. B. Kristensen, "Development of European HTA: from Vision to EUnetHTA," *Michael Quarterly*, vol. 9, pp. 147-156, 2012.
- [10] "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," [Online]. Available: <http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1400955960760&uri=CELEX:32011L0024>. [Accessed 24 5 2014].
- [11] "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," *Official Journal of the European Union*, vol. L175, pp. 71-72, 27 6 2013.
- [12] E. Commission, "Multiannual Work Programme 2014-2015 adopted by the 1st HTA Network Meeting 16 October 2013," [Online]. Available: [http://ec.europa.eu/health/technology\\_assessment/docs/hta\\_network\\_wp2014\\_15\\_en.pdf](http://ec.europa.eu/health/technology_assessment/docs/hta_network_wp2014_15_en.pdf). [Accessed 8 7 2014].
- [13] "The timeline of reaching a sustainable and permanent HTA network in Europe," [Online]. Available: [http://www.who.int/medical\\_devices/Sat\\_am\\_HTA\\_3\\_CERBO.pdf](http://www.who.int/medical_devices/Sat_am_HTA_3_CERBO.pdf). [Accessed

- 24 5 2014].
- [14] "EUnetHTA Organisaton," EUnetHTA, [Online]. Available: <http://www.eunethta.eu/about-us/organisation>. [Accessed 8 6 2014].
- [15] "The Organisational and Governance Structure of the EUnetHTA Collaboration," EUnetHTA, [Online]. Available: <http://www.eunethta.eu/outputs/organisational-and-governance-structure-eunethta-collaboration>. [Accessed 8 6 2014].
- [16] EUnetHTA, "Common Questions EUnetHTA: What is the difference/relation between Associated Partners, Collaborating Partners, EUnetHTA Founding Partners, EUnetHTA Partners and EUnetHTA Associates ?," [Online]. Available: <http://www.eunethta.eu/faq/EUnetHTA#t327n619>. [Accessed 11 6 2014].
- [17] EUnetHTA, "EUnetHTA Final Technical Report 2010-2012," 5 2013. [Online]. Available: [http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/EUnetHTA%20JA%20Final%20TechnicalReport2010\\_2012FinalVersion20130531\\_0.pdf](http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/EUnetHTA%20JA%20Final%20TechnicalReport2010_2012FinalVersion20130531_0.pdf). [Accessed 11 6 2015].
- [18] "High Level Pharmaceutical Forum 2005-2008 Final Conclusions," [Online]. Available: [http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/pharmaforum\\_final\\_conclusions\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/pharmaforum_final_conclusions_en.pdf). [Accessed 23 5 2014].
- [19] EUnetHTA, "EUnetHTA Joint Action 2 on HTA 2012-2015 3-year work plan," 5 2013. [Online]. Available: <https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/EUnetHTA%20JA2%203-year%20Work%20Plan%20%282013%29.pdf>. [Accessed 11 6 2014].
- [20] EUnetHTA, "EUnetHTA JA1 Final Technical Report," 2013. [Online]. Available: <http://www.eunethta.eu/outputs/eunethta-ja1-final-technical-report>. [Accessed 12 6 2014].
- [21] EUnetHTA, "EUnetHTA WP5 Joint Action 2 Apply(ing) the HTA Core Model for Rapid Assessment for national/local adaptation and reporting," 5 2013. [Online]. Available: [http://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/2012123627%20-%20Procedure\\_manual\\_REA%20pilots\\_WP5\\_Strand%20A\\_V3\\_POVOOPEN.pdf](http://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/2012123627%20-%20Procedure_manual_REA%20pilots_WP5_Strand%20A_V3_POVOOPEN.pdf). [Accessed 16 6 2014].
- [22] EUnetHTA, "HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals," 1 3 2013. [Online]. Available: [https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals\\_final\\_20130311\\_reduced.pdf](https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf). [Accessed 16 6 2014].
- [23] "Minutes of the Workshop on High Level Pharmaceutical Forum Recommendations on EPARS' contribution to Relative Effectiveness Assessment. 11 February 2010 –chaired by Hans-Georg Eichler," [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Minutes/2013/06/WC500143997.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/06/WC500143997.pdf). [Accessed 23 5 2014].
- [24] M. Berntgen, "G-BA Conference "Drei Jahre Frühe Nutzenbewertung"-Contribution from the European Medicines Agency," AMNOG Fachtagung G-BA, 30 4 2014. [Online]. Available: [https://www.g-ba.de/downloads/17-98-3702/12-2014-04-30-AMNOG-Fachtagung-G-BA\\_Berntgen.pdf](https://www.g-ba.de/downloads/17-98-3702/12-2014-04-30-AMNOG-Fachtagung-G-BA_Berntgen.pdf). [Accessed 31 5 2014].
- [25] EMA, "Health-technology-assessment bodies," [Online]. Available: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000476.jsp&mid=WC0b01ac0580236a57](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000476.jsp&mid=WC0b01ac0580236a57). [Accessed 23 5 2014].

- [26] EMA, "EMA-EUnetHTA 3-year work plan," [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2013/11/WC500154588.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/11/WC500154588.pdf). [Accessed 23 5 2014].
- [27] M. Berntgen, "Brücke zwischen Zulassung und Health Technology Assessment (HTA) Bewertung," DGRA Annual Congress 2013, 20 6 2013. [Online]. Available: <http://dgra.de/media/pdf/fortbildung/kongresse/2013/kongr2013-berntgen.pdf>. [Accessed 31 5 2014].
- [28] EUnetHTA, "EUnetHTA Plenary Assembly April 10-11 2014 Madrid Spain," 2014. [Online]. Available: [https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Appendix%20A\\_General%20Presentation.pdf](https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Appendix%20A_General%20Presentation.pdf). [Accessed 20 6 2014].
- [29] EMA, "Scientific Advice and Protocol Assistance Adopted during the CHMP meeting 23-26 June 2014," 26 6 2014. [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2014/06/WC500169363.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/06/WC500169363.pdf). [Accessed 8 7 2014].
- [30] T. Networks, "Multi-stakeholder Drug Development Pilots," [Online]. Available: <http://www.tapestrynetworks.com/initiatives/healthcare/multi-stakeholder-drug-development-pilots.cfm>. [Accessed 7 7 2014].
- [31] I. Hudson, "Topra Presentation 2010: Obtaining scientific advice from the MHRA and NICE – a pilot parallel process," [Online]. Available: [http://www.topra.org/sites/default/files/5.\\_Ian\\_Hudson\\_Presentation.pdf](http://www.topra.org/sites/default/files/5._Ian_Hudson_Presentation.pdf). [Accessed 19 6 2014].
- [32] W. Cheng, "Parallel Scientific Advice-TLV's Perspective," DIA Euromeeting Vienna 26th March 2014, [Online]. Available: <http://www.epaccontrol.com/common/sitemedia/PrePost/PostPDFs/36696.pdf>. [Accessed 19 6 2014].
- [33] M. Pavlovic, "Topra Annual Symposium:Multi-HTA Early Dialogues," 10 2013. [Online]. Available: [https://www.toprasymposium.org/sites/default/files/media/4.2%20MiraPRESENTATION\\_TOPRA\\_Lisbon%202013%20MP.pdf](https://www.toprasymposium.org/sites/default/files/media/4.2%20MiraPRESENTATION_TOPRA_Lisbon%202013%20MP.pdf). [Accessed 30 5 2014].
- [34] J. Regnstroem, F. Koenig, B. Aronsson, T. Reimer, K. Svendsen, S. Tsigkos, B. Flamion, H. Eichler and S. Vamvakas, "Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the," *Eur.J.Clin.Pharmacol.*, vol. 66, no. 1, pp. 39-48, 2010.
- [35] T. Salmonson, "Parallel Scientific Advice by EMA with MAHs and HTAs," DGRA Annual Meeting 2014, 5 2014. [Online]. Available: <http://dgra.de/media/pdf/fortbildung/kongresse/2014/kongr2014-salmonson.pdf>. [Accessed 30 5 2014].
- [36] L. Osipenko, "Early Engagement between Manufacturers, HTA Accessors and Regulators: Learning from the past to guide the future," ISPOR Congress Dublin 11, 2013, [Online]. Available: <http://www.ispor.org/congresses/Dublin1113/presentations/SecondPlenary-Leeza-Osipenko-Slides.pdf>. [Accessed 19 6 2014].
- [37] EMA, "Draft best practice guidance for pilot European Medicines Agency health technology assessment parallel scientific advice procedures," 8 5 2014. [Online]. Available: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document\\_detail.jsp?webContentId=WC500166226&mid=WC0b01ac058009a3dc](http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500166226&mid=WC0b01ac058009a3dc). [Accessed 19 6

- 2014].
- [38] EUnetHTA, "Amended draft procedure for early dialogue pilots," 10 2012. [Online]. Available: <https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/WP5%20EARLY%20DIALOGUE%20PROCEDURE%20OCTOBER%202012.pdf>. [Accessed 30 5 2014].
- [39] SEED, "Procedure for SEED EMA multi-HTA early dialogues," 2014. [Online]. Available: <http://www.earlydialogues.eu/has/?p=271>. [Accessed 4 8 2014].
- [40] I. Hudson, "Collaboration between HTA and Regulators," 2010. [Online]. Available: [http://www.topra.org/sites/default/files/5.\\_Ian\\_Hudson\\_Presentation.pdf](http://www.topra.org/sites/default/files/5._Ian_Hudson_Presentation.pdf). [Accessed 7 7 2014].
- [41] B. Paschen, "Science- How can the scientific information needs of both HTAs and regulatory be accomodated in a common development track ?," 2013. [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2013/11/WC500155673.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500155673.pdf). [Accessed 7 7 2014].
- [42] C. Mayer-Nicolai, A. Griffin, J. Creba and J. Andersen, "Industry Perspective on Advice Models," EFPIA, 2013. [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2013/11/WC500155674.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500155674.pdf). [Accessed 7 7 2014].
- [43] T. Networks, "Pilots of mult-country, multi-stakeholder consultations in drug development: from proof of concept to tangible benefits," 6 6 2012. [Online]. Available: <http://www.tapestrynetworks.com/initiatives/healthcare/upload/Pilots-of-multi-stakeholder-consultations-in-drug-development-6-June-2012.pdf>. [Accessed 7 7 2014].
- [44] "Council Directive 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," *Official Journal of the European Communities*, vol. L40, pp. 8-11, 11 2 1989.
- [45] M. Berntgen, A. Gourvil, M. Pavlovic, W. Goettsch, H.-G. Eichler and F. B. Kristensen, "Improving the Contribution of Regulatory Assessment Reports to Health Technology Assessments- A Collaboration between European Medicines Agency and the European network of Health Technology Assessment," *Value in Health*, in Press 2014.
- [46] M. Pavlovic, "REA of Pharmaceuticals.Collaboration between EMA and EUnetHTA.Development of Consensus on HTA Methodologies," ISPOR: International Scientific and Practical Conference "International Experience in Health Technology Assessment and Prospects of its Implementation in Russia"(Moscow), 21 5 2012. [Online]. Available: [http://www.hta-rus.ru/files/pavlovic\\_1\\_eng\\_1341389991.pdf](http://www.hta-rus.ru/files/pavlovic_1_eng_1341389991.pdf). [Accessed 31 5 2014].
- [47] "Presentations 1-13 from the EMA-EUnetHTA Meeting November 2012," EMA-EUnetHTA Meeting Copenhagen 2012, 20 11 2012. [Online]. Available: <http://5026.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Presentations%201-13%20from%20the%20EMA-EUnetHTA%20meeting,%2020%20November%202012.pdf>. [Accessed 31 5 2014].
- [48] "EMA-EUnetHTA Meeting November 20, 2012 Copenhagen Summary report," [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Minutes/2014/02/WC500160507.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2014/02/WC500160507.pdf). [Accessed 23 6 2014].
- [49] EMA, "Benefit-risk methodology project, Work package 4 report: Benefit-risk tools and

- processes," 9 5 2012. [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2012/03/WC500123819.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf). [Accessed 23 6 2014].
- [50] N. Zafiroopoulos, L. Phillips, F. Pignatti and X. Luria, "Evaluating Benefit-Risk: An Agency Perspective," *Regulatory Rapporteur*, vol. 9, no. 6, pp. 5-8, 2012.
- [51] EMA, "Benefit-risk methodology project: Update on workpackage 5: Effects Table Pilot (Phase I)," 6 2 2014. [Online]. Available: [www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2014/02/WC500162036.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/02/WC500162036.pdf). [Accessed 23 6 2014].
- [52] EMA, "Caprelsa," [Online]. Available: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002315/human\\_med\\_001529.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002315/human_med_001529.jsp&mid=WC0b01ac058001d124). [Accessed 23 6 2014].
- [53] I. Chalmers, "Underreporting research is scientific misconduct," *JAMA*, vol. 263, no. 10, pp. 1405-1408, 1990.
- [54] A.-W. Chan, A. Vickers, T. Jefferson, K. Dickersin, P. C. Gøtzsche, H. M. Krumholz, D. Gherzi and H. B. van der Worp, "Increasing value and reducing waste: addressing inaccessible," *Lancet*, vol. 383, pp. 257-266, 2014.
- [55] EMA, "Publication and access to clinical trial data DRAFT," 24 6 2013. [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2013/06/WC500144730.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf). [Accessed 23 6 2014].
- [56] EMA, "European Medicines Agency agrees policy on publication of clinical-trial data with more user-friendly amendments. EMA Management Board to formally adopt policy in coming weeks," 12 6 2014. [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2014/06/WC500168342.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/06/WC500168342.pdf). [Accessed 23 6 2014].
- [57] H.-G. Eichler, F. Petavy, F. Pignatti and G. Rasi, "Access to Patient-Level Trial Data-A Boon to Drug Developers," *The New England Journal of Medicine*, vol. 369, no. 17, pp. 1577-1579, 2013.
- [58] J. Moseley, "HTA-EMA Scientific Advice," *Topra*, 2012. [Online]. Available: <http://www.topra.org/sites/default/files/assets/pdf/mosley.pdf>. [Accessed 7 7 2014].
- [59] EMA, "Public Consultations," 7 2014. [Online]. Available: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/document\\_library/landing/landing\\_page.jsp&mid=WC0b01ac05801b7e46](http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/landing/landing_page.jsp&mid=WC0b01ac05801b7e46). [Accessed 17 7 2014].
- [60] I. GetReal, "GetReal," [Online]. Available: <http://www.imi-getreal.eu/>. [Accessed 9 7 2014].
- [61] M. Chambers and M. Egger, "GetReal: Clinical effectiveness in drug development," 4 6 2013. [Online]. Available: <http://www.ceb-institute.org/bbs/wp-content/uploads/2013/06/1.2.2-Egger-Basel.pdf>. [Accessed 9 7 2014].
- [62] S. R. Tunis, "An Overview of the Green Park Collaborative - USA," *CMTP*, 2013. [Online]. Available: [http://www.cmtptnet.org/docs/resources/Tunis\\_Overview\\_of\\_GPC-USA.pdf](http://www.cmtptnet.org/docs/resources/Tunis_Overview_of_GPC-USA.pdf). [Accessed 9 7 2014].
- [63] *CMTP*, "CMTP Resource Center Effectiveness Guidance Documents Resources," [Online]. Available: <http://www.cmtptnet.org/resource-center/category/effectiveness-guidance-documents/>. [Accessed 9 7 2014].

- [64] CMTPT, "Green Park Collaborative," [Online]. Available: <http://www.cmtptnet.org/featured-projects/green-park-collaborative/>. [Accessed 9 7 2014].
- [65] McKinsey, "Personalized Medicine The Path Forward," 3 2013. [Online]. Available: [http://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CCMQFjAA&url=http%3A%2F%2Fwww.mckinsey.com%2F~%2Fmedia%2Fmckinsey%2Fdotcom%2Fclient\\_service%2FPharma%2520and%2520Medical%2520Products%2FPMP%2520NEW%2FPDFs%2FMckinsey%2520on%2520Personalize](http://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CCMQFjAA&url=http%3A%2F%2Fwww.mckinsey.com%2F~%2Fmedia%2Fmckinsey%2Fdotcom%2Fclient_service%2FPharma%2520and%2520Medical%2520Products%2FPMP%2520NEW%2FPDFs%2FMckinsey%2520on%2520Personalize). [Accessed 10 7 2014].
- [66] E. C. H. a. C. D. General, "Delegated act on post-authorisation efficacy studies. (ARTICLE 10B OF REGULATION (EC) NO 726/2004 AND ARTICLE 22B OF DIRECTIVE 2001/83/EC) Deadline for Public Consultation: 18 February 2013," 2013. [Online]. Available: [http://ec.europa.eu/health/files/pharmacovigilance/2012\\_11\\_28\\_pc\\_paes.pdf](http://ec.europa.eu/health/files/pharmacovigilance/2012_11_28_pc_paes.pdf). [Accessed 30 6 2014].
- [67] E. C. D. H. a. Consumers, "Responses to the public consultation on the delegated act on post-authorisation efficacy studies," 2013. [Online]. Available: [http://ec.europa.eu/health/human-use/pharmacovigilance/developments/2013\\_pc\\_paes\\_en.htm](http://ec.europa.eu/health/human-use/pharmacovigilance/developments/2013_pc_paes_en.htm). [Accessed 30 6 2014].
- [68] E. UNETHA, "Final minutes of EMA/EUnETHA meeting 14 March 2013," 2013. [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Minutes/2013/06/WC500144002.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/06/WC500144002.pdf). [Accessed 30 6 2014].
- [69] EMA, "Highlights from the "Workshop on methods for efficacy studies in everyday practice," 12 2013. [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Minutes/2013/11/WC500155692.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/11/WC500155692.pdf). [Accessed 30 6 2014].
- [70] E. Commission, "Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in whi," 2014. [Online]. Available: [http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L\\_.2014.107.01.0001.01.ENG](http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.107.01.0001.01.ENG). [Accessed 30 6 2014].
- [71] EMA, "European Network of Centres for Pharmacoepidemiology and Pharmacovigilance," [Online]. Available: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000229.jsp&mid=WC0b01ac05801df747](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000229.jsp&mid=WC0b01ac05801df747). [Accessed 30 6 2014].
- [72] ENCePP, "Mandate of ENCePP Working Group on Health Technology Assessment (HTA)," 2013. [Online]. Available: <http://www.encepp.eu/structure/documents/ENCEPPWGHTAMandate.pdf>. [Accessed 30 6 2014].
- [73] EMA, "ENCEPP Work Plan 2013 - 2014," 2012. [Online]. Available: <http://www.encepp.eu/publications/documents/ENCEPPWorkPlan2013-2014Rev2.pdf>. [Accessed 30 6 2014].
- [74] EMA, "Health Technology Assessment (HTA) & integration in Pharmacoepidemiology," 2012. [Online]. Available: [http://www.encepp.eu/publications/documents/4.4\\_HTA.pdf](http://www.encepp.eu/publications/documents/4.4_HTA.pdf). [Accessed 30 6 2014].
- [75] EUnETHA, "Synergies between ENCePP and Health Technology Assessment," [Online]. [Accessed 30 6 2014].

- [76] ENCePP, "ENCEPP Working Groups: Report from the Chair. Working Group: Health Technology Assessment," 2 2014. [Online]. Available: [http://www.encepp.eu/publications/documents/ReportfromWGHTAChairtoSG\\_Feb2014.pdf](http://www.encepp.eu/publications/documents/ReportfromWGHTAChairtoSG_Feb2014.pdf). [Accessed 30 6 2014].
- [77] H.-G. Eichler, "Addressing the Efficacy-Effectiveness Gap," EMA, 2010. [Online]. Available: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2011/01/WC500100970.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/01/WC500100970.pdf). [Accessed 30 6 2014].
- [78] L. S. o. E. a. P. Science, "Managed entry agreements for pharmaceuticals: The European experience," 4 2013. [Online]. Available: [http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea\\_report\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf). [Accessed 21 7 2014].
- [79] EMA, "European Medicines Agency selects first two medicines to be included in its adaptive licensing pilot project," 6 6 2014. [Online]. Available: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2014/06/news\\_detail\\_002119.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002119.jsp&mid=WC0b01ac058004d5c1). [Accessed 2 7 2014].
- [80] scripregulatoryaffairs.com, "Adaptive licensing: creating a safe haven for discussions," 2013. [Online]. [Accessed 2 7 2014].
- [81] G. Hirsch, "NEWDIGS: New Drug Development ParaDIGMS," 2012. [Online]. Available: <http://casmi.org.uk/wp-content/uploads/2012/11/GHirsch-Adaptive-Licensing-UK-Workshop-2April2012.pdf>. [Accessed 2 7 2014].
- [82] L. G. Baird, M. R. Trusheim, H.-G. Eichler, E. Berndt and G. Hirsch, "Comparison of Stakeholder Metrics for Traditional and Adaptive Development and Licensing Approaches to Drug Development," *Therapeutic Innovation & Regulatory Science*, vol. 47, no. 4, pp. 474-483, 2013.
- [83] H.-G. Eichler, K. Oye, L. Baird, E. Abadie, J. Brown, C. Drum, J. Ferguson and S. Garner, "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval," *Clinical Pharmacology & Therapeutics*, vol. 3, pp. 426-437, 2013.
- [84] E. EUnetHTA, "EMA / EUnetHTA meeting- Summary Report 10 December 2013,," 2013. [Online]. Available: [ww.eunetha.eu/sites/5026.fedimbo.belgium.be/files/EMA-EUnetHTA\\_meeting\\_Cologne\\_December\\_2013\\_meeting\\_summary\\_FINAL.pdf](http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/EMA-EUnetHTA_meeting_Cologne_December_2013_meeting_summary_FINAL.pdf). [Accessed 2 7 2014].
- [85] Y. Le Cam, "Rare Cancers Consensus Meeting and Conference: Improving the Methodology of Clinical Research on Rare Cancers," EORORDIS, 10 2 2012. [Online]. Available: <http://www.rarecancerseurope.org/content/download/16593/289710/file/benefit-clinical-added-value-orphan-drugs-le-cam.pdf>. [Accessed 10 7 2014].
- [86] J. Müller-Berghaus, "Individualized Medicine: Regulatory Challenges," 10 9 2013. [Online]. Available: [http://www.gesundheitsforschung-bmbf.de/\\_media/Vortrag\\_Innovationsmarktplatz\\_Mueller-Berghaus.pdf](http://www.gesundheitsforschung-bmbf.de/_media/Vortrag_Innovationsmarktplatz_Mueller-Berghaus.pdf). [Accessed 10 7 2014].
- [87] E. Commission, "The Ernst and Young study on the Clinical Added Value of Orphan Drugs (CAVOD) has been made public (November 2011)," 1 12 2011. [Online]. Available: <http://ec.europa.eu/eahc/news/news96.html>. [Accessed 10 7 2014].
- [88] EUCERD, "RECOMMENDATION OF THE EUROPEAN UNION COMMITTEE OF EXPERTS ON RARE DISEASES TO THE EUROPEAN COMMISSION AND THE MEMBER STATES ON IMPROVING INFORMED DECISIONS BASED ON THE CLINICAL ADDED VALUE OF ORPHAN

- MEDICINAL PRODUCTS (CAVOMP) INFORMATION FLOW," 2012. [Online]. Available: [http://www.eucerd.eu/?post\\_type=document&p=1446](http://www.eucerd.eu/?post_type=document&p=1446). [Accessed 30 6 2014].
- [89] EUnetHTA, "Preparation for the Plenary Assembly meeting, Madrid, 10-11 April 2014, Guiding Document," 2014. [Online]. Available: [https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/3%20Preparing%20for%20the%20PA%20meeting%20Madrid%20Apr%2010-11\\_Guiding%20Document.pdf](https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/3%20Preparing%20for%20the%20PA%20meeting%20Madrid%20Apr%2010-11_Guiding%20Document.pdf). [Accessed 14 7 2014].
- [90] EFPIA, "The right prevention and the right treatment for the right patient at the right time: Outline Strategic Research Agenda for a biomedical research public private partnership under Horizon 2020," 8 7 2013. [Online]. Available: [http://www.efpia.eu/uploads/Modules/MCMedias/1373296554546/IMI2%20Strategic\\_Research\\_Agenda\\_v%208%20July%202013.pdf](http://www.efpia.eu/uploads/Modules/MCMedias/1373296554546/IMI2%20Strategic_Research_Agenda_v%208%20July%202013.pdf). [Accessed 17 7 2014].
- [91] J. Arrowsmith and P. Miller, "Phase II and Phase III attrition rates," *Nature Reviews Drug Discovery*, vol. 12, p. 569, 2013.
- [92] McKinsey, "Value-driven drug development: Unlocking the value of your pipeline," 2011. [Online]. Available: [http://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CCAQFjAA&url=http%3A%2F%2Fwww.mckinsey.com%2F%2Fmedia%2Fmckinsey%2Fdotcom%2Fclient\\_service%2Fpharma%2520and%2520medical%2520products%2Fpmp%2520new%2Fpdfs%2F780416\\_value\\_driven\\_drug\\_develo](http://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CCAQFjAA&url=http%3A%2F%2Fwww.mckinsey.com%2F%2Fmedia%2Fmckinsey%2Fdotcom%2Fclient_service%2Fpharma%2520and%2520medical%2520products%2Fpmp%2520new%2Fpdfs%2F780416_value_driven_drug_develo). [Accessed 14 7 2014].
- [93] K. Redekop, S. Hass , A. Grogg and T. Bramley, "The Promise of Personalized Medicine: "Getting it Right the First Time", " ISPOR, [Online]. Available: [http://www.ispor.org/meetings/neworleans0513/releasedpresentations/Symposium-Xcenda-ALL\\_SPEAKERS.pdf](http://www.ispor.org/meetings/neworleans0513/releasedpresentations/Symposium-Xcenda-ALL_SPEAKERS.pdf).
- [94] U. T. & Investment, "UK Stratified Medicine," 4 2013. [Online]. Available: [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/301775/UK\\_Stratified\\_Medicine.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/301775/UK_Stratified_Medicine.pdf). [Accessed 14 7 2014].
- [95] ClinicalEvidence, "What conclusions has Clinical Evidence drawn about what works, what doesn't based on randomised controlled trial evidence?," *British Medical Journal*, [Online]. Available: <http://clinicalevidence.bmj.com/x/set/static/cms/efficacy-categorisations.html>. [Accessed 14 7 2014].
- [96] J. Mestre-Ferrandiz, P. Deverka, M. Pistollato and E. Rosenberg, "The Current Drug Development Paradigm: Responding to US and European Demands for Evidence of Comparative Effectiveness and Relative Effectiveness," *CMTP*, 4 2014. [Online]. Available: [http://www.cmtpn.net/docs/resources/Current\\_Drug\\_Development\\_Paradigm\\_Mestre-Ferrandiz\\_2014.pdf](http://www.cmtpn.net/docs/resources/Current_Drug_Development_Paradigm_Mestre-Ferrandiz_2014.pdf). [Accessed 16 7 2014].
- [97] K. Fronsdal, "Interaction initiatives between regulatory, health technology assessment and coverage bodies and industry," *International Journal of Technology Assessment in Health Care*, vol. 28, no. 4, p. 374–381.
- [98] EFPIA, "The Pharmaceutical Industry in Figures," 2014. [Online]. Available: <http://www.efpia.eu/uploads/Modules/Mediaroom/figures-2014-final.pdf>. [Accessed 23 7 2014].

## **10. Eidesstattliche Erklärung / Affirmation in lieu of an oath**

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

Dr. Georg Tschank

Essenheim, am 08.08.2014