EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Brücke zwischen Zulassung und Health Technology Assessment (HTA) Bewertung

DGRA Annual Congress, 20 June 2013, Bonn

Presented by: Michael Berntgen
Head of Rheumatology, Respiratory, Gastroenterology and Immunology
Safety & Efficacy of Medicines

An agency of the European Union

Topics to be addressed

1/ Status update on the dialogue between the Agency and EUnetHTA

➔ Topics for the exchange and achievements so far

2/ Experience from parallel EMA/HTA Scientific Advice

➔ Overview of completed procedures to-date

➔ Views on evidence generation in relation to required decision making

Development of the dialogue on European level…

2010 → **2013**

eunethta

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16 February 2010
EMA/98431/2010
j.no.7-204-05-4/1
Press office

Press release

European Medicines Agency and EUnetHTA Joint Action start collaboration on European Public Assessment Report (EPAR) contribution to relative effectiveness assessments

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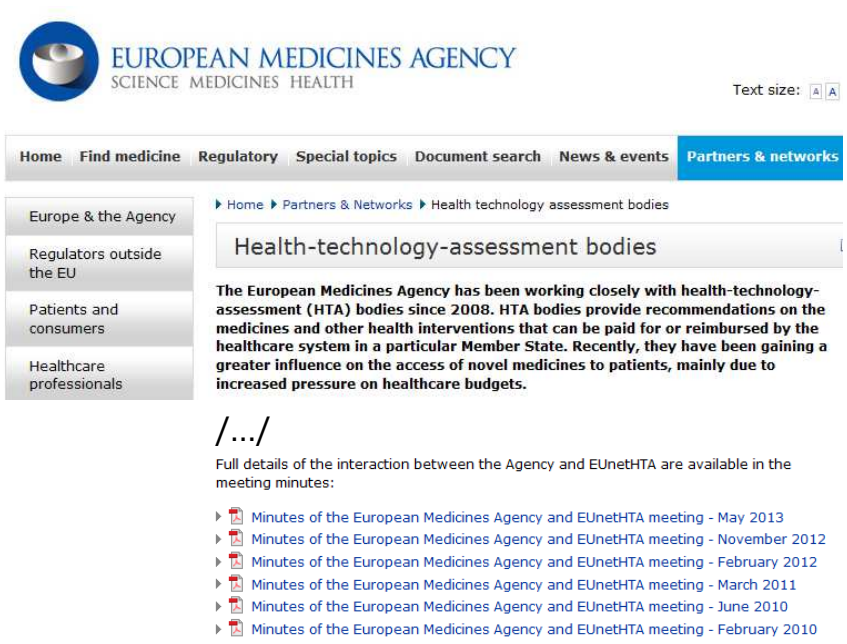
7 June 2013
EMA/303100/2013
Press Office

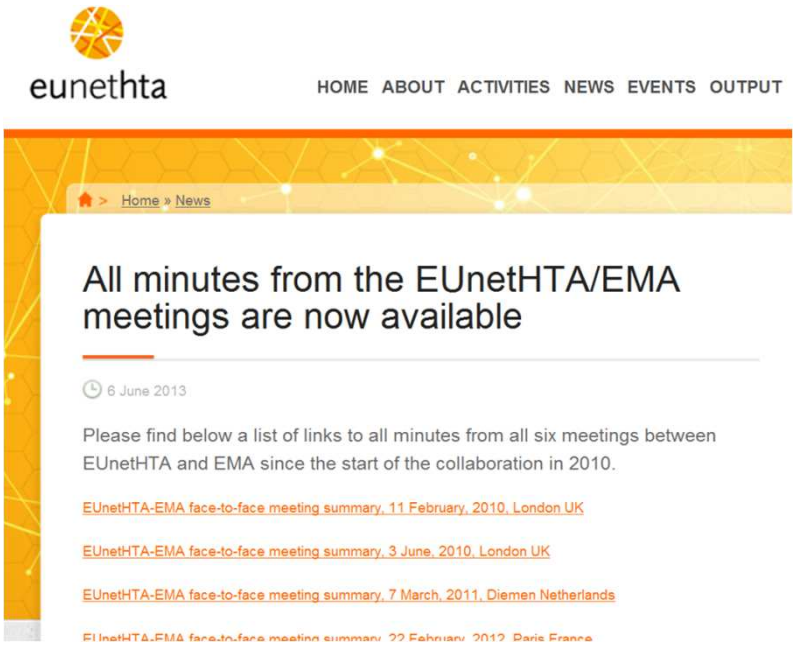
Press release

European Medicines Agency and EUnetHTA review progress of their cooperation

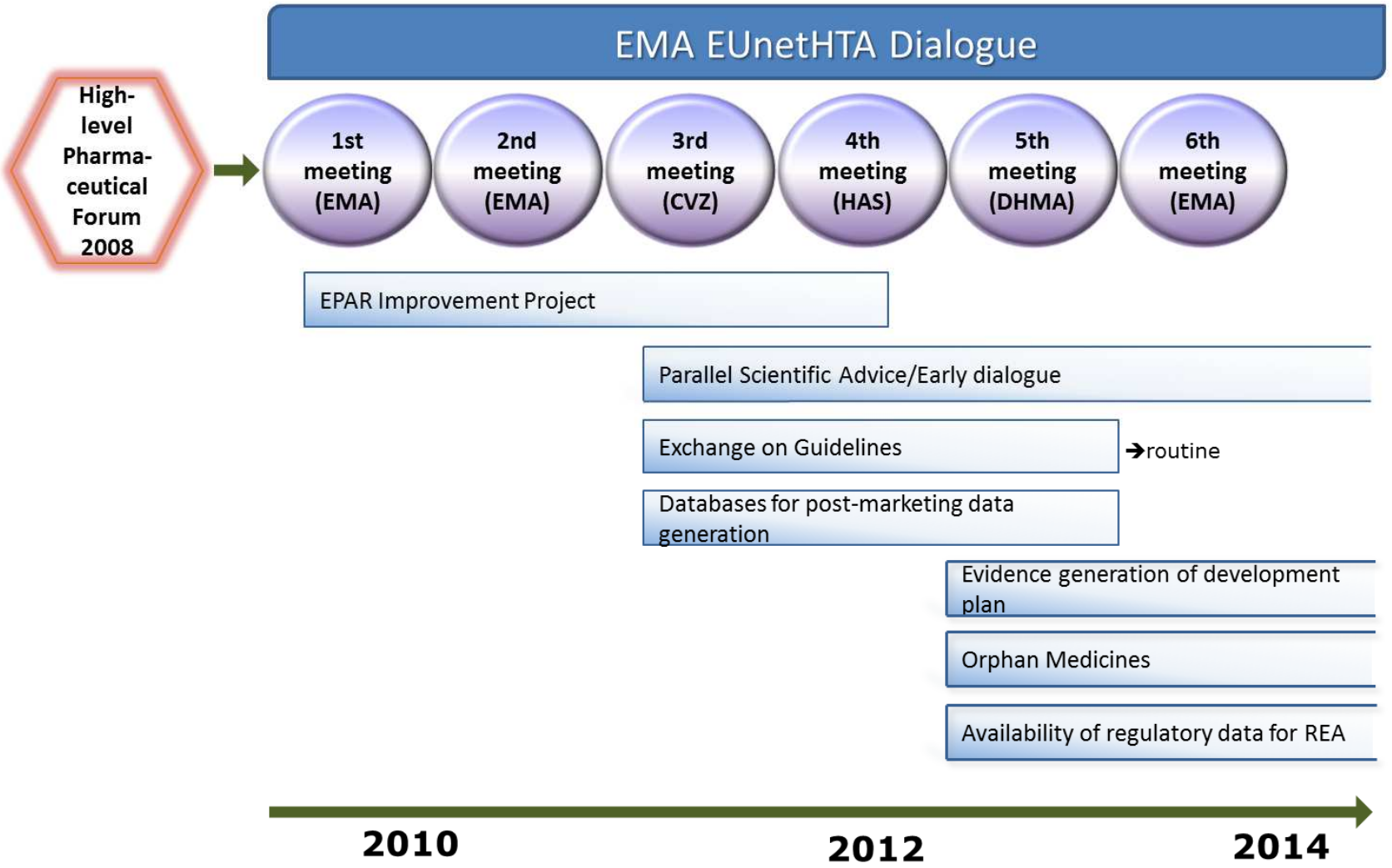
Focus on facilitation of development plans through advice procedures

Publications on 7 June 2013





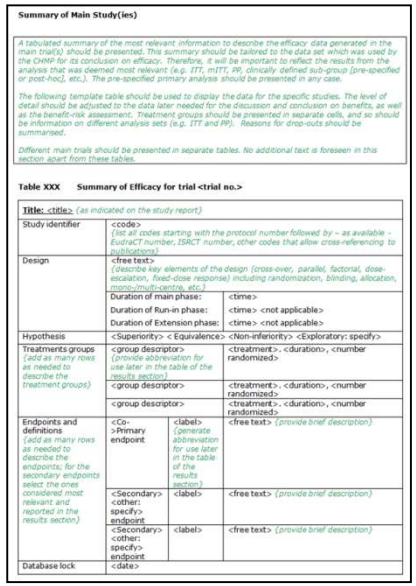
Joint press release and publication of all minutes from joint meetings available on websites of both EMA and EUnetHTA


EMA EUnetHTA Dialogue
High-level Pharma-ceutical Forum 2008
1st meeting (EMA)
2nd meeting (EMA)
3rd meeting (CVZ)
4th meeting (HAS)
5th meeting (DHMA)
6th meeting (EMA)
EPAR Improvement Project
Parallel Scientific Advice/Early dialogue
Exchange on Guidelines
➔routine
Databases for post-marketing data generation
Evidence generation of development plan
Orphan Medicines
Availability of regulatory data for REA
2010
2012
2014

"EPAR improvement" project

Summary of changes in the templates and guidance:

Area	Updated Section (s)	Brief description of changes introduced
General	List of Abbreviations	• A comprehensive list of all abbreviations used throughout the assessment report has been included
	List of References	• Consider generation of a reference list
Quality	Section relative to the Active Substance	• Addition of the structural formula for chemical substances and of structural characteristics for biologicals
Non-clinical / Clinical	Discussion on (non)clinical aspects	• Guidance is given in order to ensure that all information in the SPC is explicitly assessed and supported by the scientific assessment
Clinical	Discussion on clinical efficacy and clinical safety	• Additional guidance is given on how to discuss critical aspects of the design like endpoints and comparators • More explicit reasoning of the CHMP's view on the data and the analysis (including additional analysis) in the context of the final conclusions is encouraged, as well as discussion of the shortcomings of the data
	Summary table on main efficacy studies	• Inclusion of a standardised tabular overview of the main efficacy data from the pivotal studies



Summary of Main Study(ies)

A tabulated summary of the most relevant information to describe the efficacy data generated in the main trial(s) should be presented. This summary should be tailored to the data set which was used by the CHMP for its conclusion on efficacy. Therefore, it will be important to reflect the results from the analysis that was deemed most relevant (e.g. ITT, mITT, PP, clinically defined sub-group [pre-specified or post-hoc], etc.). The pre-specified primary analysis should be presented in any case.

The following template table should be used to display the data for the specific studies. The level of detail should be adjusted to the data later needed for the discussion and conclusion on benefits, as well as the benefit-risk assessment. Treatment groups should be presented in separate cells, and so should be information on different analysis sets (e.g. ITT and PP). Reasons for drop-outs should be summarised.

Different main trials should be presented in separate tables. No additional text is foreseen in this section apart from these tables.

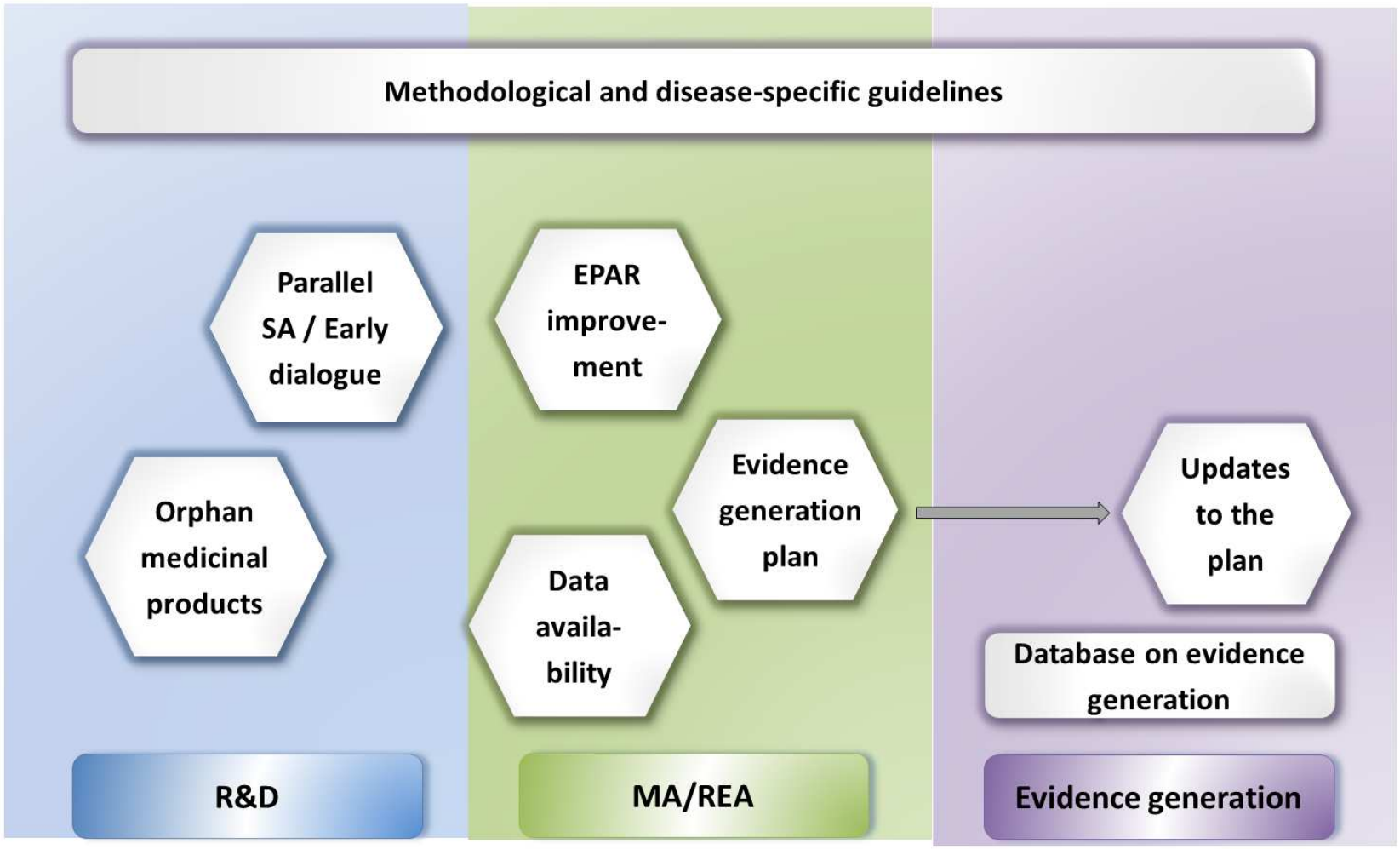
Table XXX Summary of Efficacy for trial <trial no.>

Title: <title> *(as indicated on the study report)*			
Study identifier	<code> *(list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications)*		
Design	<free text> *(describe key elements of the design [cross-over, parallel, factorial, dose-escalation, fixed-dose response] including randomization, blinding, allocation, mono-/multi-centre, etc.)*		
	Duration of main phase:		<time>
	Duration of Run-in phase:		<time> <not applicable>
	Duration of Extension phase:		<time> <not applicable>
Hypothesis	<Superiority> < Equivalence>		<Non-inferiority> <Exploratory: specify>
Treatments groups *(add as many rows as needed to describe the treatment groups)*	<group descriptor> *(provide abbreviation for use later in the table of the results section)*		<treatment>, <duration>, <number randomized>
	<group descriptor>		<treatment>, <duration>, <number randomized>
	<group descriptor>		<treatment>, <duration>, <number randomized>
Endpoints and definitions *(add as many rows as needed to describe the endpoints; for the secondary endpoints select the ones considered most relevant and reported in the results section)*	<Co->Primary endpoint	<label> *(generate abbreviation for use later in the table of the results section)*	<free text> *(provide brief description)*
	<Secondary> <other: specify> endpoint	<label>	<free text> *(provide brief description)*
	<Secondary> <other: specify> endpoint	<label>	<free text> *(provide brief description)*
Database lock	<date>		

Highlights from the review of the impact of changes

- Overall high compliance rates with revised templates for EPAR format and scientific content
- Achievement is introduction of tabular overview of main efficacy data
- Space for further improvement in the critical discussion of the key elements of the clinical study design
- Substantiation of the SmPC appropriate for most sections
- Special attention needed for discussion of the shortcomings of efficacy data as well as additional analysis requested during the regulatory review

Elements of EMA/EUnetHTA dialogue



Status parallel EMA/HTA Scientific Advice (06/13)

Number: 18 parallel EMA/HTA scientific advice procedures completed; several others in preparation

Companies: Big Pharma (including multiple use) as well as SMEs

Therapeutic areas: variety of indications including diabetes, breast cancer, heart failure, Alzheimer's, asthma, rheumatoid arthritis, osteoporosis, depression, NSCLC and melanoma, but also orphan diseases

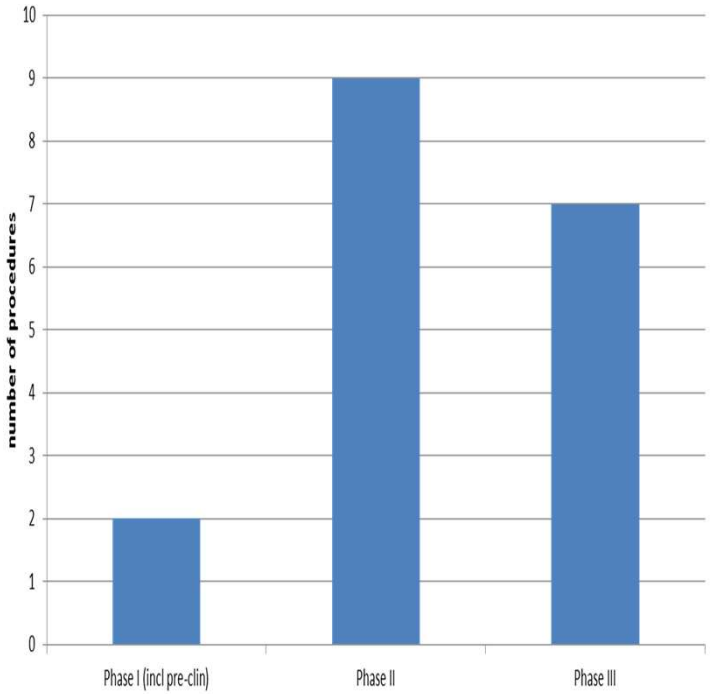
EU member states' HTA/payer organisations: Sweden, UK, France, Netherlands, Spain, Italy, Germany, Belgium, Austria

Outline of procedural steps for parallel EMA/HTA scientific advice

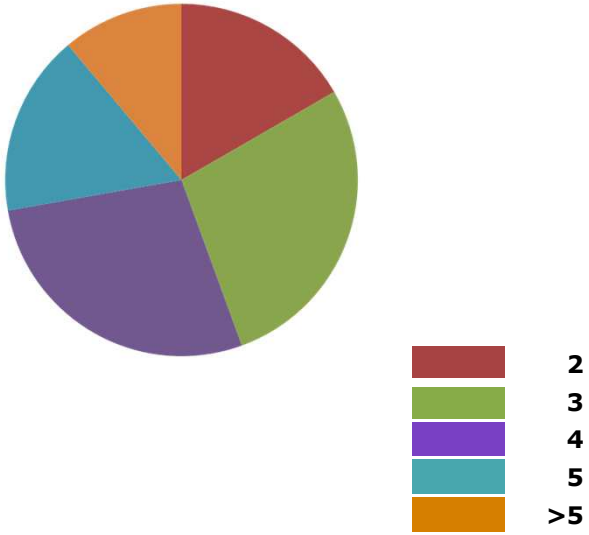
- Letter of intent: Company announces intent for parallel SA and preferred HTAs to be involved. Up to the company to contact HTAs directly or ask EMA to facilitate.
- Company submits draft: Questions to Regulators & HTAs
  Questions to Regulators only
  Questions to HTAs only
- Pre-submission TC: all
- Final Briefing Package
- Always 70-day procedure to incorporate a 4h face-to-face meeting
- Outcome:
  - SA letter
  - Minutes with HTA and Regulators responses provided by the company and commented/agreed upon by the participants

Current experience with parallel EMA/HTA scientific advice (n=18)

Status of development programme

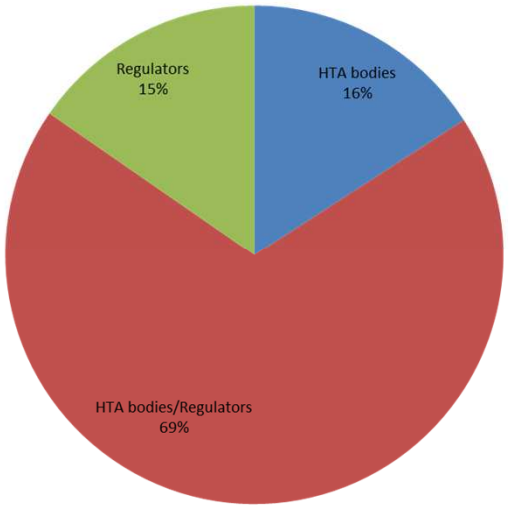


Number of HTA bodies involved

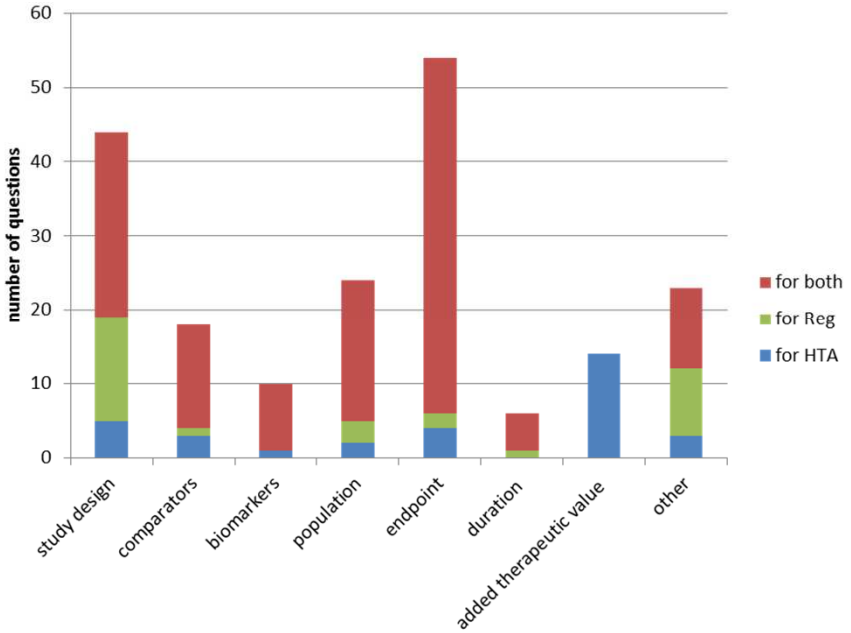


Topics subject to parallel EMA/HTA scientific advice (n=18)

Questions raised by the applicant



Topic areas



Different scope in terms of decision making

Regulatory approval	HTA	Coverage
Does the product do more good than harm for patients with defined indications in this jurisdiction?	HTA seeks to support decisions on whether an intervention offers useful, appropriate, and affordable benefits for patients in a particular healthcare system	Will the product offer useful, appropriate (and affordable) benefits for some or all eligible patients in this healthcare system?

Taken from: Henshall C et al.; Interactions between health technology assessment, coverage, and regulatory processes: Emerging issues, goals, and opportunities; International Journal of Technology Assessment in Health Care, 27:3 (2011), 253–260

Views on evidence generation: 1/ Comparator and treatment duration

- Impact of heterogeneity within patient population on appropriate active comparator to reflect available treatment options
- Choice of comparator for efficacy vs. significant benefit vs. relative effectiveness
- Comparator for new formulation of known active substance to address SOC as well as cost-effectiveness
- Duration of treatment to evaluate long-term safety vs. clinical benefit over SOC vs. cost-effectiveness

Views on evidence generation: 2/ Endpoints

- The value of OS data in terms of clinical relevance vs. association with HrQoL vs. the overall economic model compared to SOC
- Weight of evidence through general HrQoL scales (e.g. SF-36, EQ5D) vs. disease-specific scales vs. individual domains
- Validation of a PRO in terms of acceptability vs. relevance of domains vs. applicability to EU population

Views on evidence generation: 3/ Patient population

- Spectrum of patient population included in a study and impact on comparator and treatment duration to reflect current clinical practice
- Inclusion criteria to reflect patient population allowing sub-analysis depending on severity to reflect proposed indication vs. to support cost-effectiveness
- Strength of the data in a sub-population for labelling vs. cost-effectiveness analysis

Summary and Outlook

- Dialogue between European regulators and HTA bodies is progressing and multiple topics are subject to the exchange
- The current focus is on how regulators and HTA bodies can work together to facilitate drug development by cooperating in giving advice to pharmaceutical companies
- Experience with parallel EMA/HTA scientific advice is growing

This development is significant for patients to facilitate patients' timely access to an effective medicine and for sponsors to enable reducing the development costs