Presentation no. 1

Sundhedsstyrelsen
Danish Health and Medicines Authority

EMA – EUnetHTA meeting

November 20, 2012

Copenhagen, Denmark

Sundhedsstyrelsen
Danish Health and Medicines Authority

Welcome to Danish Health and Medicines Authority (DHMA)

Else Smith

Director General and Chief Medical Officer

Sundhedsstyrelsen
Danish Health and Medicines Authority

Introduction to the EMA-EUnetHTA Meeting

Finn Børlum Kristensen

Agenda – November 20, 2012

Coffee – light refreshment	10.00 – 10.30
Welcome to Danish Health and Medicines Authority (DHMA): *Director General and Chief Medical Officer Else Smith* **Introduction to the EMA-EUnetHTA meeting:** *Finn Børlum Kristensen*	10.30 –10.50
EPAR improvement project – reporting of first experiences, additional proposals from EUnetHTA in light of the reviews of recent EPARS (HAS, EMA)	10:50 – 11:30
Databases for post-licensing studies (HAS) **Update on the new EU PhV Legislation and opportunities for bridging to HTA (EMA)** **The FP7 IMI Protect Project (DHMA)**	11:30 – 12:30
Lunch break	12.30 - 13.30
Rapid model for REA, pilot and future developments; i.e. possibilities to streamline the timelines of rapid pilots with EMA assessments **(CVZ)**	13:30 – 14:15
Early scientific advice; EMA-HTA scientific advice, and multi-HTA scientific advice (NICE, HAS, EMA)	14:15 – 15:15
Coffee	15.15 – 15.45
EUnetHTA Methodological guidelines for REA (HAS)	15.45 – 16.30
Significant benefit for orphan medicinal products: concept and experience (EMA)	16:30 – 17:00
Conclusion of EMA-EUnetHTA meeting and next steps: *Hans-Georg Eichler, Finn Børlum Kristensen*	17.00 - 17.30
END	

eunethta

European network for HTA

Joint Actions 2010-15 between European Commission and EU Member States

A total of 38 government appointed organisations from 26 EU Member States, Norway and Croatia and a large number of regional agencies and non-for-profit organisations that produce or contribute to HTA

eunethta

Directive 2011/24 EU on cross-border healthcare

Article 15 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…. That network shall be based on the principle of good governance including transparency, objectivity, independence of expertise, fairness of procedure and appropriate stakeholder consultations

eunethta

The time-line of reaching a sustainable and permanent HTA network in Europe

Health Programme

2005 Call for project proposals

2009 Call for Joint Action

2011 Call for Joint Action

2014+ European network for HTA

Legal basis: Cross Border Healthcare Directive

Financial support: 1) EU Budget 2) Member States

eunethta

2006-08 EUnetHTA Project

2009 EUnetHTA Collaboration

2010 -12 EUnetHTA JA

2012 -15 EUnetHTA JA 2

Legislation

2008 - 11 Draft Cross Border Healthcare Directive Article on HTA network

2011 CBHC Directive now decided

2011 - 13 CBHC Directive Expert Group for HTA network implementation

DG R&I

2011 FP7-Health 2012-Innovation-1 New methodologies for HTA

ethta

Conclusions and next steps

- To be developed during the day
- ……
- ……

Agenda – November 20, 2012

Coffee – light refreshment	10.00 – 10.30
Welcome to Danish Health and Medicines Authority (DHMA): *Director General and Chief Medical Officer Else Smith* **Introduction to the EMA-EUnetHTA meeting:** *Finn Børlum Kristensen*	10.30 –10.50
EPAR improvement project – reporting of first experiences, additional proposals from EUnetHTA in light of the reviews of recent EPARS (HAS, EMA)	10:50 – 11:30
Databases for post-licensing studies (HAS) **Update on the new EU PhV Legislation and opportunities for bridging to HTA (EMA)** **The FP7 IMI Protect Project (DHMA)**	11:30 – 12:30
Lunch break	12.30 - 13.30
Rapid model for REA, pilot and future developments; i.e. possibilities to streamline the timelines of rapid pilots with EMA assessments **(CVZ)**	13:30 – 14:15
Early scientific advice; EMA-HTA scientific advice, and multi-HTA scientific advice (NICE, HAS, EMA)	14:15 – 15:15
Coffee	15.15 – 15.45
EUnetHTA Methodological guidelines for REA (HAS)	15.45 – 16.30
Significant benefit for orphan medicinal products: concept and experience (EMA)	16:30 – 17:00
Conclusion of EMA-EUnetHTA meeting and next steps: *Hans-Georg Eichler, Finn Børlum Kristensen*	17.00 - 17.30
END	

eunethta

Presentation no. 2

eunethta

EPAR improvement project

EMA – EUnetHTA Meeting
20 November 2012
Copenhagen

EPAR improvement project
EMA – EUnetHTA collaboration

Background

- The **High Level Pharmaceutical Forum** recommended the EMA to consider how the EPAR can further contribute to relative effectiveness assessments

- Three EMA - EUnetHTA meetings in 2010 and 2011: discussions on adaptation of assessment report template in line with comments from MEDEV/EUnetHTA

- **Aug. – Nov. 2011: 10 EPARs "new template" evaluated by 10 HTA organizations with the same questionnaire used by the EMA to assess EPARs (parallel EMA – HTA review)**

- **22 Feb. 2012 in Paris (HAS):** presentation of the **outcome** of the parallel EPAR review by EMA and EUnetHTA

- **5th EMA - EUnetHTA meeting (Copenhagen): 20 Nov. 2012**

eunethta

EPAR improvement project
Observations: Format and Content

- High compliance regarding
  - Jointly developed summary table of main efficacy data
  - Presentation of patient flow

- There is space for improvement in the critical discussion of the **key elements of the clinical study design**.
  - Patient population, Comparators, Duration of the study, Endpoints and/or composite endpoint use

- **Shortcomings of efficacy data** would benefit from more discussion

- **Additional analysis** requested by the CHMP should be better identified and explained

eunethta

EPAR improvement project
HTA proposal

- **Increased granularity in the structure of the report template by introducing subheading to address main aspect of the clinical efficacy discussion**
  - Key elements of the study design, i.e. patient population, sub-groups and specific populations, choice of comparator, duration of the study, endpoints
  - Shortcomings/uncertainties of the efficacy data, i.e. additional analyses/data requested by the CHMP, consultation of opinion of external experts (SAG, ad-hoc expert group, PDCO)
- **Data from publications to be clearly referenced and listed**
- **SmPC to be improved**

eunethta

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Presentation no. 3

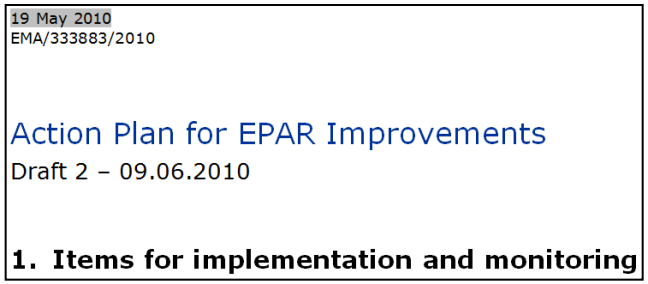
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Update on EPAR et al.

EMA-EUnetHTA meeting, 20 November 2012, Copenhagen

Presented by: Michael Berntgen
Head of Rheumatology, Respiratory, Gastroenterology and Immunology

EPAR Improvement Project


19 May 2010
EMA/333883/2010

Action Plan for EPAR Improvements
Draft 2 – 09.06.2010

1. Items for implementation and monitoring

- February 2010 – Kick-off
- June 2010 – Agreement on Action Plan
- March 2011 – Information about implementation regarding templates
- February 2012 – Presentation of parallel review

<u>Agreed items for implementation and monitoring</u>

- Update of the assessment report template
- Development of generic tables for specific areas
- Development of a template for extensions of indications
- Potential improvements of internal QC review procedures
- Monitoring of adherence to templates

The latest news regarding EPARs

1. Implementation of new Pharmacovigilance Legislation
2. Pilot for an Executive Summary
3. Guidance regarding data in geriatric patients
3. Further strengthening of internal review
4. Continuous reflection on the best approach for templates

Minutes from the February 2012 meeting:

Suggestions for improvements were proposed and discussed, mainly increasing the granularity in the structure of the report template to address main aspects of the clinical efficacy discussion and make the information more visible, elaborating more on shortcomings/uncertainties and reasons for requesting additional analysis from the company. However, no formal agreement was reached on these proposals during the meeting. It was agreed that EUnetHTA would make a consolidated proposal for further improvements of the EPAR, highlighting their expectations and a new face-to face meeting to solve the remaining issues could be envisaged. Also the review will be presented to the CHMP together with any additional suggestions for improvement.

Executive Summary

Executive Summary

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterised by intestinal pain or discomfort together with alteration of bowel habit, abdominal distension, bloating, constipation or diarrhoea[1]. Symptoms usually wax and wane for many years, often resulting in reduced quality of life and work productivity. The pathophysiology of IBS is incompletely understood.

Despite affecting 5 to 20% of the Western population, no medicines are authorised in the European Union (EU) specifically for the treatment of IBS. Patients and prescribers are limited to general symptomatic treatments such as laxatives, antidiarrhoeals and antispasmodics, which are recommended in current guidelines but on the basis of weak evidence. Alternatively, they may use unapproved treatments such as antidepressants and non-absorbable antibiotics when lifestyle modifications such as reducing stress, altering diet or psychological interventions prove ineffective.

In September 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the authorisation of Constella (linaclotide) to offer a new option for adults with moderate to severe IBS with constipation (IBS-C), a common subtype of the disease. The recommended dose is one capsule (290 micrograms) once daily, to be taken at least 30 minutes before a meal. Linaclotide, a synthetic 14-amino-acid peptide, is a new oral compound that works by increasing intestinal fluid secretion and accelerated transit. It stimulates guanylate-cyclase-subtype-C (GC-C) receptors on the luminal surface of the intestinal epithelium, leading to increased intra- and extracellular levels of cyclic guanosine monophosphate (cGMP). The increase in intracellular cGMP in turn activates the cystic fibrosis transmembrane conductance regulator (CFTR), leading to secretion of chloride and bicarbonate into the intestinal lumen.

In the two main clinical studies provided to support its authorisation[2], linaclotide showed superiority over placebo, with statistically significant improvements in abdominal pain and discomfort as well as considerable or complete relief from symptoms after 12 weeks. Both studies employed randomised, double-blind, parallel-group designs in a total of approximately 1600 patients who met criteria that correspond to a moderate to severe IBS population. Around 38% of the patients treated with linaclotide showed a 'relief response', defined as considerable or complete relief of symptoms for six out of 12 treatment weeks as measured on a seven-point Likert scale. This compared with around 18% of the patients treated with placebo. In addition, around 54% of the patients treated with linaclotide showed an at least 30% improvement in their abdominal pain or discomfort score for six out of 12 treatment weeks, compared with around 40% of those receiving placebo.

The Committee judged these results to be clinically relevant, because the primary endpoints met a 14% to 20% margin of superiority over placebo, and because the results were consistent across the main trials. Nonetheless, it noted that around half of the patients in the main studies did not sufficiently respond to linaclotide, leading to the recommendation that prescribers should assess patients regularly and reconsider treatment if there is no improvement in symptoms after four weeks.

Although linaclotide is intended for long-term continuous use, only study MCP-103-302 evaluated the effects of the medicine for six months; this is the duration of treatment required by the Agency's guidelines for chronic IBS treatments. For both endpoints, the effect over placebo in this study after 26 weeks was statistically significant: 37% and 54% of the patients treated with linaclotide showed response to IBS degree of relief and to abdominal pain or discomfort, respectively, compared with 17% and 36% of those receiving placebo. These results were supported by additional justification from the applicant concerning the medicine's mode of action, the patient population studied and the consistency of its effects across sub-populations and a variety of endpoints.

No rebound effect was seen in study LIN-MD-31, which included a randomised withdrawal period of four weeks after three months of treatment. Although there are no data after longer treatment periods, the Agency accepted that these three-month withdrawal data could be extrapolated to later time points because the medicine showed sustained efficacy and in the absence of a biologically plausible reason for why withdrawal effects would differ after longer treatment duration.

Because diarrhoea was the most common adverse event seen, the Agency warns that patients with severe or prolonged diarrhoea should be monitored closely and that linaclotide should be used with caution in patients prone to a water or electrolyte-balance disturbances. Diarrhoea was reported in 160 (20%) of the linaclotide-treated patients but only 24 (3%) of those receiving placebo, with this being moderate or severe in 91 and 6 patients, respectively. In linaclotide patients, diarrhoea lasted more than 28 days in half of those affected, but less than a week in a third. Rarely, potentially more serious consequences of diarrhoea were seen, such as serum bicarbonate and potassium level changes, dehydration, dizziness, and syncope.

Only 5% of the study participants were above 65 years of age. The Committee noted that diarrhoea appeared to be more common in the elderly, leading to its recommendation that prescribers should afford special attention to older patients and assess the medicine's benefits and risks carefully before and during treatment in this age group. To further elucidate the safety profile of the medicine in this population, the Agency has requested a post-authorisation safety study that specifically includes elderly patients. Regarding children and adolescents, the absence of data led the Agency to restrict its recommended use of linaclotide to adults, especially since GC-C receptor is overexpressed in young children. Specific studies will need to be conducted before a conclusion on safe and effective use in the paediatric population can be made.

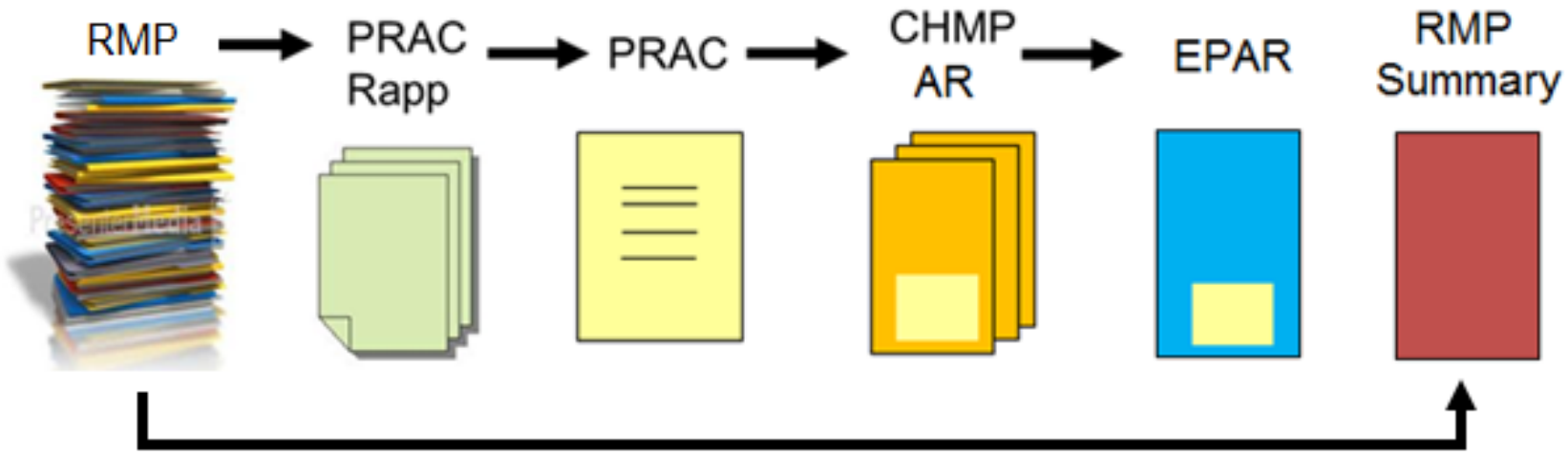
Linaclotide is expected to offer a useful treatment option for patients with moderate or severe IBS with constipation, once organic diseases have been ruled out and a diagnosis of IBS-C has been established. The Committee's conclusion that the medicine's benefits outweigh its risks is based on the medicine's robust superiority over placebo, clear clinical relevance, and acceptable safety profile. The Committee awaits the final results of the long-term safety study, and the data from the post-authorisation safety study, concentrating in particular on complications of diarrhoea in patients with associated risk factors as well as the medicine's risks in older patients, and will make further recommendations on its use in line with these and any other information that becomes available after the medicine is in use.

[1] Currently the Rome III criteria are widely accepted as the gold standard for the diagnosis and classification of IBS.
[2] LIN-MD-31 and MCP-103-302.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7418 8416
E-mail info@ema.europa.eu Website www.ema.europa.eu
An agency of the European Union

PRAC Advice and CHMP Assessment Report

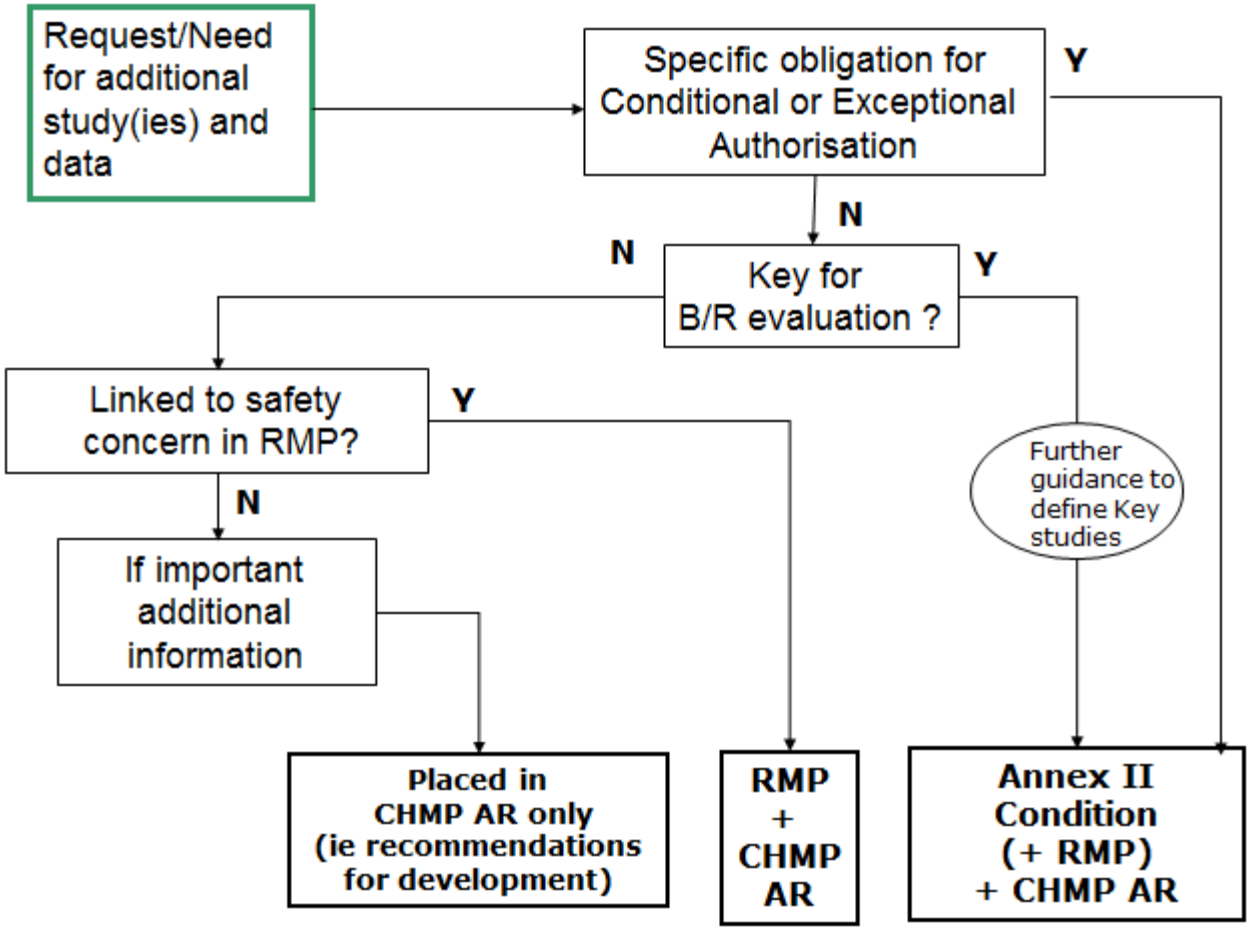
RMP Information flow in a procedure



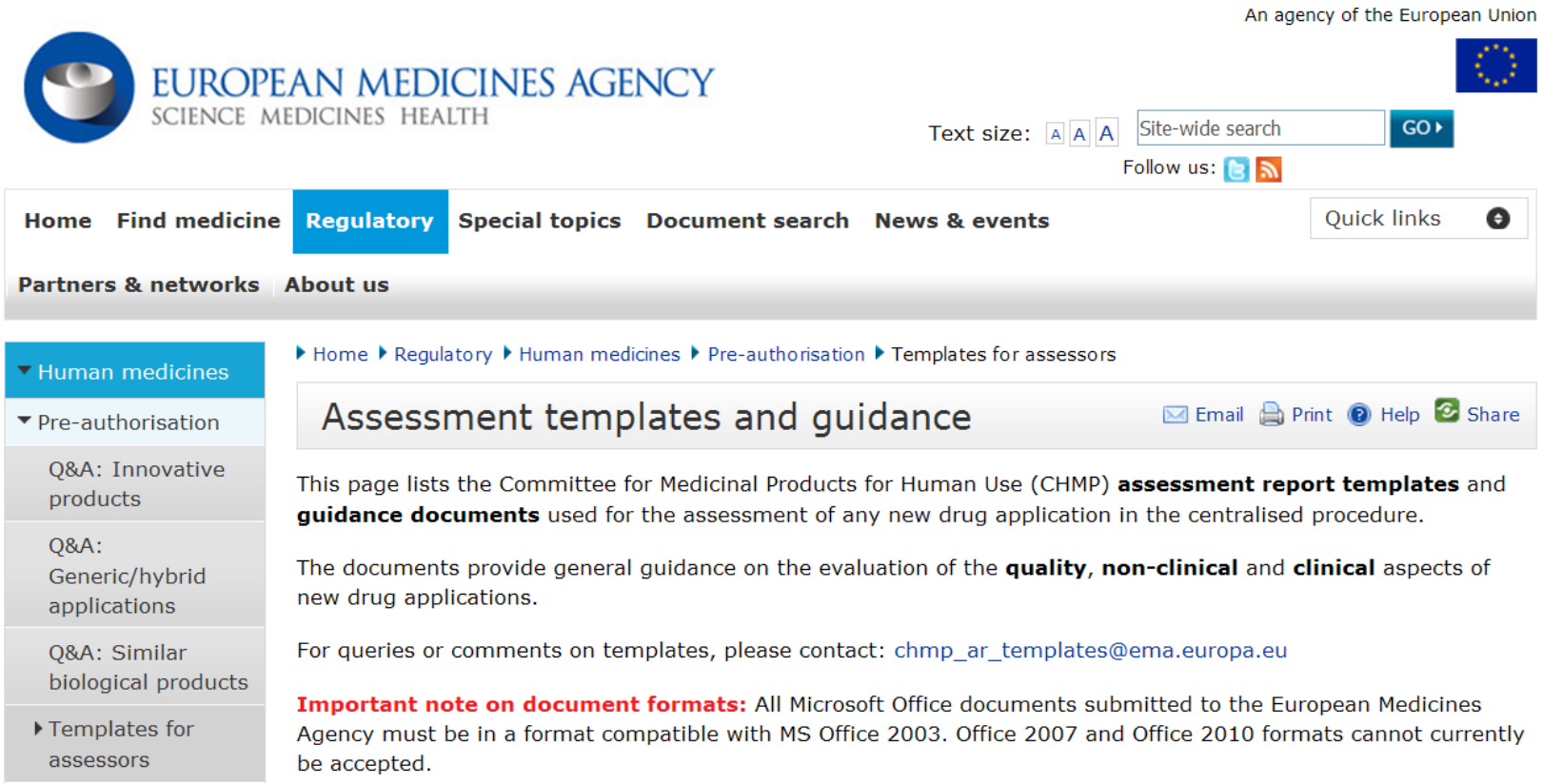
Quality of Opinion Exercise

- Initiative in collaboration with the European Commission
- Post-authorisation Measures are being brought into their appropriate legal framework
- Initiated also in anticipation of the PRAC and the implementation of the PhV legislation
- There will be more monitoring and tracking of fulfilment of those PAMs
- RMP will be an important element -> revised RMP template under development

Post-authorisation Measures



Templates on the EMA website



Transparency regarding ongoing assessments

Initial Marketing authorisation (since March 2012)

International non-proprietary name (salt, ester, derivative, etc.) / Common Name	Therapeutic area[1]
Afatinib (dimaleate)	Antineoplastic medicines
Aflibercept	Antineoplastic medicines
Alemtuzumab	Immunosuppressants
Alogliptin	Medicines used in diabetes
Alogliptin / metformin	Medicines used in diabetes

Extensions of indications (since October 2012)

07/11/2012

European Medicines Agency increases transparency of ongoing applications for human medicines

The European Medicines Agency has started publishing information on ongoing applications for extensions of indication of human medicines today in the minutes of the Pharmacovigilance Risk Assessment Committee (PRAC).

Presentation no. 4

eunethta

EVIDENT Database

JA 1 WP 7 New Technologies, Strand A: Facilitating evidence generation on new health technologies

Irena Guzina (HAS, France)

Summary

- Short summary of the results of JA1 WP7 Strand A – Facilitating evidence generation on new health technologies

- Presentation of the EVIDENT database

eunethta

Background

- Assessment of new health technologies often highlights important gaps in evidence
  →Recommendations for additional evidence generation

- But from recommendations to actual new data…
  →Challenges to address:
    - Data requirements not clearly specified, coordinated, harmonized
    - Multiple and heterogeneous studies, inconsistent results
  →Waste of time and money

- Need for collaboration
  →Reduce redundancy
  →Best use limited resources
  →Gather consistent endpoints across studies

eunethta

WP7A - Objectives

- criteria to select new technologies for further evidence generation

- minimum dataset to allow early information sharing on requested or planned policy relevant clinical studies (NETSCC)

- database (EVIDENT) that contains useful information and functionalities to enable operational collaboration on additional evidence generation

eunethta

WP7A - Results

✓All deliverables finalized:

- Minimum dataset delivered to HAS in June 2011 and integrated into EVIDENT database
- Selection criteria published on EUnetHTA's website in August 2012 http://www.eunethta.eu/en/Public/Work_Packages/EUnetHTA-Joint-Action-2010-12/EUnetHTA-JA-Public-Consultations/Public-consultation-WP7/Criteria-to-select-and-prioritize-health-technologies-for-additional-evidence-generation/
- EVIDENT database launched in November 2012

eunethta

EVIDENT database

https://evident.has-sante.fr/has/login.xhtml

Evidence database on new technologies (EVIDENT)

- goals:
  - promote generation of further evidence (critical mass of consistent data)
  - facilitate European collaboration in conducting requested additional data collection

- scope:
  - studies requested by European HTA bodies after HTA,
  - studies in initial stage of development
  - all health technologies (drugs, devices, procedures)

- content: information on
  - additional studies or any kind of additional data collection (ADC) (PICO structure, protocols, results)
  - related health technology (assessment status, evidence gaps, research questions, required additional studies, coverage decision status)

Using EVIDENT

1. Sharing early information on evidence gaps and ADC request and development in Europe

- express the need for Additional Data Collection (ADC)
- being informed on ongoing studies and avoid duplication of work
- launch a call for collaboration on ADC
- seek information on evidence gaps and ADC for ongoing assessments

2. Knowing assessment and reimbursement status of technologies in Europe thanks to the input from other agencies

In clear, EVIDENT is:

- A full registration form → data entry
- Mini query form → input from other agencies
- A search engine → consultation

eunethta

Plans for JA2

WP7: Methodology development and evidence generation: guidelines and pilots production

- **Specific objective:** to develop and test a methodological basis for Europen cooperation on HTA and to improve quality of initial and **additional** evidence generation for HTA:

→ **EVIDENT database**

- Promote active use of the database
- IT upgrading and maintenance

→ **Guidelines and pilots**

- Review / Survey on the possibilities and the conditions for performing harmonised Additional Data Collection (ADC) in different countries
- Pilot of a common core protocol for ADC (for a technology of common interest)
- Methodological guidelines on how to formulate the research question and how to decide on the appropriate trial design

eunethta

Please ask if any questions

&

Thank you for your attention

i.guzina@has-sante.fr
evident@has-sante.fr

eunethta

Annex: Selection criteria

Selection/prioritization criteria

Primary criteria: eligibility for ADC?

1. Did you identify any critical evidence gaps during HTA? (yes, no)
2. Is the research question explicitly defined? (yes, no)
3. Is ADC feasible (especially in terms of timeframe, type of study, population and costs)? (yes, no)
4. Is there a planned/ongoing similar study elsewhere?

a) Yes, but there is an additional value of performing this one too (yes, no).

b) No, thus this one is really necessary (yes).

5. Is there an added value of additional data for the subsequent HTA and decision making? (yes, no)

Secondary criteria: further selection and prioritization

1. Burden of target disease (mortality, morbidity prevalence, incidence, DALYs, QALYs)
2. Expected benefit of the technology (on the burden of disease/on the management of disease/economical benefit/organisational/social/ethical benefit)
3. Potential of the technology to cover unmet health care needs or to substantially improve the healthcare system compared to existing alternatives
4. Importance of ADC for confirming expected benefit and/or monitoring/optimizing the conditions of use.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Presentation no. 5

Update on the new EU Pharmacovigilance Legislation and opportunities for bridging to HTA

Ana Hidalgo-Simon
EMA-EUnetHTA
November 2012

Agenda

- Update on implementation of New Pharmacovigilance Legislation
- The ENCePP task force on HTA
- Questions for discussion

New PHV objectives

- Clear roles and responsibilities
- Engage patients and healthcare professionals
- Science based - integrate benefit and risk
- Risk based and proportionate
- Increased proactivity and planning
- Reduced duplication/redundancy
- Robust and rapid EU decision-making
- Increase transparency and provide better information on medicines

Promote and protect public health by reducing burden of ADRs and optimising the use of medicines

Pharmacovigilance legislative aims

Prioritised implementation agreed by EMA Management Board in December 2011

- **Criteria for prioritisation:**
  - Firstly, public health activities
  - Secondly, transparency and communication activities
  - Thirdly, simplification activities (primarily for pharmaceutical industry)
- **Activities grouped into four main topic areas:**
  - Collection of key information on medicines
  - Better analysis and understanding of data and information
  - Regulatory action to safeguard public health
  - Communication with stakeholders
- **Detailed slides at the back for reference**

GVP Modules – 1st wave: FINAL June 2012

I PhV Systems and their Quality Systems

II PhV System Master File

V Risk Management Systems

VI Individual Case Safety Reports

VII Periodic Safety Update Reports

VIII Post-Authorisation Safety Studies

IX Signals

GVP Modules – 2nd wave: ONGOING

III Audits PUBLIC CONSULTATION finished 21 SEP 2012

IV Inspections PUBLIC CONSULTATION CLOSED, being finalised

X Additional monitoring PUBLIC CONSULTATION CLOSED, being finalised

XI Public participation **DRAFTING ONGOING**

XII Continuous phv, benefit-risk evaluation, and decision-making for regulatory action **DRAFTING ONGOING**

XV Safety communication PUBLIC CONSULTATION CLOSED, being finalised

XVI Risk minimisation measures **DRAFTING ONGOING**

Continue in 2013

- New risk management process
- Periodic Safety Update Reports: list, centrally authorised product (CAP) assessment, joint CAP and nationally authorised product (NAP) single assessment
- Safety studies: oversight of protocols and results for CAPs and NAPs
- Adverse reaction reports: collection, training, data management
- Signal detection and management for CAPs/NAPs
- PRAC Committee: assessment and "decision-making"
- Publish adverse reaction data for CAPs
- Transparency: PRAC agendas and minutes
- Coordination of safety messages

New for 2013 - Subject to agreement by EMA MB/HMA

- Legal proposal from the European Commission on fees for pharmacovigilance
- Medication error workshop 28 Feb/ 1 March + best practice document
- Collaboration procedure for joint industry safety studies
- Additional monitoring: list published + introduction of new symbol / wording
- Public Hearings for Urgent Union Procedure
- Further increase in transparency: CHMP + CMDh agendas and minutes for PV
- Revised process for PV inspections
- 1st EMA and National Competent Authority system audits

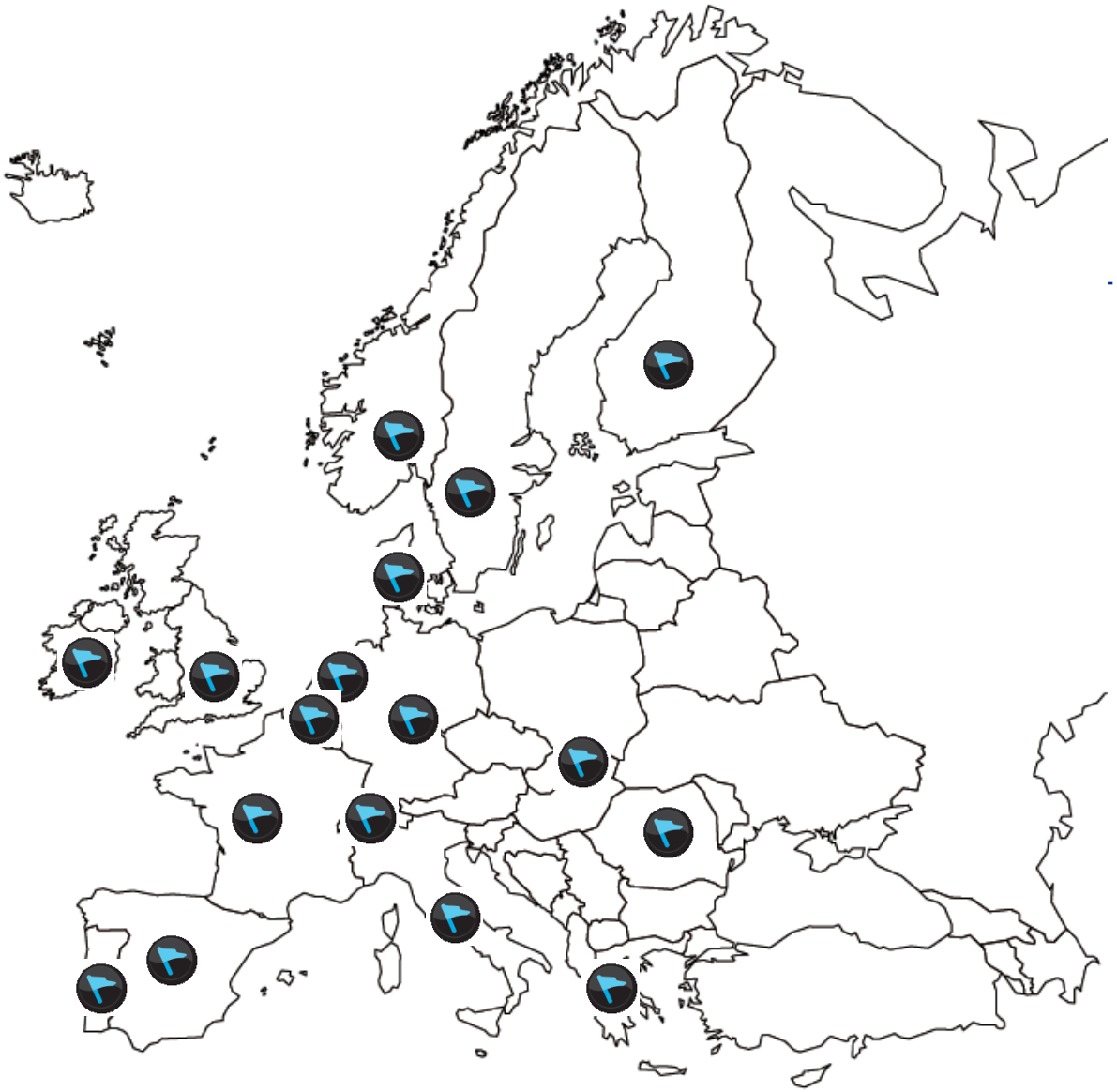
Beyond 2013

- Further IT development: EudraVigilance (EV) functionalities, PSUR repository
- EMA literature monitoring for adverse reactions and entry in EV
- Payments to rapporteurs
- PSUR single assessment for substances not included in CAPs
- Programme for monitoring effectiveness of risk minimisation
- Public hearings outside the scope of Urgent Union Procedures

Who are the E

- 114 Centres
- 17 Networks
- 26 Data-sources

from 17 different European countries



(Data as of 05 November 2012)

ENCePP Guiding Principles and key developments

- **Independence**

Roles and responsibilities of stakeholders

Freedom to publish results (–ve and +ve)

Code of Conduct

- **Standards**

Stimulate consideration of important methodological principles in design of studies

Checklist & Guide of Methodological Standards

- **Transparency**

Registration of studies

Publication of protocols and results

Resources Database & E-Register of Studies

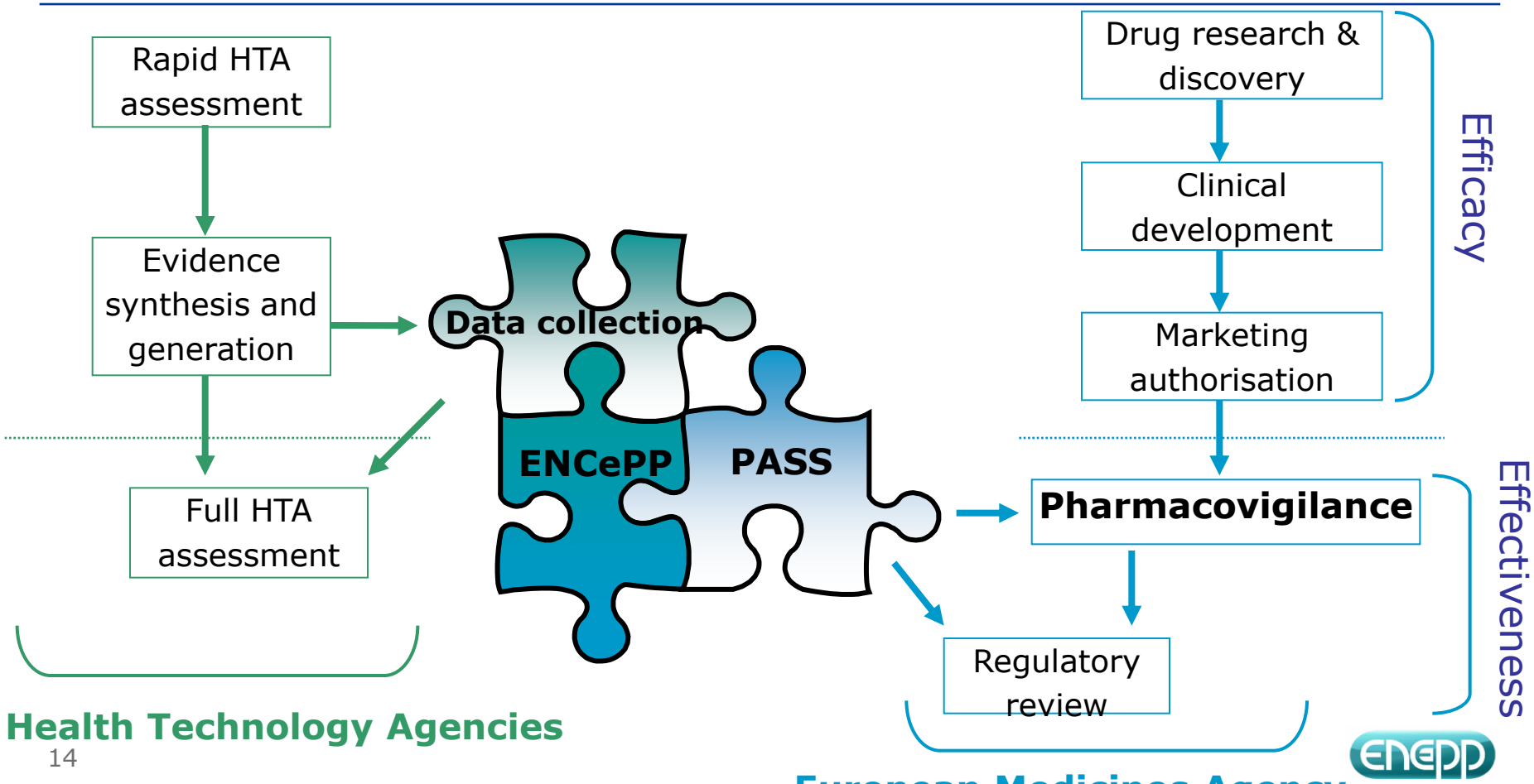
ENCePP Database of Resources

- Fully searchable, it allows the identification of:
    - Research Centres
    - Research Networks
    - Data sources

(http://www.encepp.eu/encepp/resourcesDatabase.jsp)

- Linked to ENCePP e-register of studies

A potential bridge from medicines regulation to HTA



ENCePP Task Force (TF) on Health Technology Assessment

- It is an ENCePP working sub-group
- Driven by network interest
- Face to face initial meeting: 11 October 2012
- 1 member and 1 alternate per participating organization
- Chair: Marlene Sinclair (University of Ulster, The Institute of Nursing and Health Research)
- Liaison with HTA bodies: François Meyer
- EMA support: Luis Prieto (Pharmacovigilance & Risk Management)
- First TC to take place before Christmas 2012

ENCePP Task Force (TF) on Health Technology Assessment - mandate

The following TF Mandate has been approved:

- The work of the Task Force will lead and inform, where applicable, future activities of ENCePP in terms of health technology assessment.
- The Task Force shall lead on the **development of methodological guidance for studies of health technologies taking account of existing guidance,** including the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, and data integration.
- Provision of a forum to discuss HTA research-related activities between ENCePP and other including HTA organisations.
- Respond to specific queries on HTA from ENCePP Steering Group.

Questions for discussion

- Would it be beneficial for public health to involved HTA bodies at every stage over the product life-cycle, i.e. is involvement of HTA in the post authorisation phase as important as in the pre-authorisation phase?

- Is there a need for further methodological work to ensure we can collect observational data in the post authorisation phase that is it relevant to both regulation and HTA?

- How can we make the most from already available data for mutual benefit?

- Are there other types of data that we can explore?

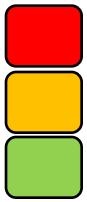
- Is it appropriate, and can we develop a mechanism to consult HTA bodies on the endpoints of post-authorisation studies, both safety and efficacy?

Thank you

Back up slides for reference

Prioritised implementation agreed by EMA Management Board in December 2011

- **Criteria for prioritisation:**
  - Firstly, public health activities
  - Secondly, transparency and communication activities
  - Thirdly, simplification activities (primarily for pharmaceutical industry)
- **Activities grouped into four main topic areas:**
  - Collection of key information on medicines
  - Better analysis and understanding of data and information
  - Regulatory action to safeguard public health
  - Communication with stakeholders
- **Traffic light:**



Not started

On-going implementation

Implemented

Implementation of the pharmacovigilance legislation by the EMA in 2012:

Collection of key information on medicines (1/2)

1. Risk Management Plans:		
Establishment and operation of new procedure for requesting and assessing RMP		• Started July 2012 • Templates for industry (Oct) • Format compulsory (Jan 2013)
2. Periodic Safety Update Reports:		
Operation of new procedures related to PSURs for CAPs		• Started July 2012
Development and publication of harmonised birthdates to support PSUR submission		• First list published in Oct 2012 (monthly update)

Implementation of the pharmacovigilance legislation by the EMA in 2012:

Collection of key information on medicines (2/2)

3. Post-Authorisation Safety and Efficacy Studies:		
Implementation of the PASS procedure for protocols approval and results management for CAPs		• Started July 2012
Consultation on scientific guidance for PAES		• Awaited
4. Electronic submission of core medicine information by MAHs ('Article 57'):		
Start validation of received information		• Joint implementation group (Oct 2012)
5. Reporting by patients:		
Cooperation with Member States to provide information to patients on direct reporting		• Core data fields agreed by Member States (June 2012)

Implementation of the pharmacovigilance legislation by the EMA in 2012:

Better analysis/understanding of data and information (1/2)

1. EudraVigilance and signal detection		
Operation of revised signal detection process for CAPs		• Started July 2012
Support Member States to operate the new EU signal detection processes for NAPs		• Started July 2012 • Signal work-sharing list published (Oct 2012)
Start of signal management through the Pharmacovigilance and Risk Assessment Committee (PRAC)		• Started Sept 2012
Continuation of maintenance work for the current EV system including data quality		• As planned
Implementation of web-publishing of adverse reaction data (further to the EV Access Policy)		• Delivered in May 2012

Implementation of the pharmacovigilance legislation by the EMA in 2012:

Better analysis/understanding of data and information (2/2)

2. Additional monitoring:		
Develop and publish the list of medicines with additional monitoring status		• Initial list likely to be published in March/April 2013
3. IT systems to support processing and analysis of data:		
Finalisation of business requirements for enhanced IT systems		• On-going

Implementation of the pharmacovigilance legislation by the EMA in 2012:

Regulatory action to safeguard public health

1. Scientific committees and decision-making:		
Establishment of new committee (PRAC) and new responsibilities for CMD(h)		• Established July 2012
2. Strengthening referral procedures:		
Operation of new referral procedure (Urgent Union Procedure)		• First referral launched in Oct 2012

Implementation of the pharmacovigilance legislation by the EMA in 2012:

Communication with stakeholders

1. Online publishing of information:		
Publication (on EMA website) of agendas, minutes, assessments, approvals, recommendations, opinions and decisions of PRAC, CMD(h) and CHMP.		• Started July 2012 for PRAC agendas and minutes
2. Coordination of safety messages:		
Operation of the coordination of Member States' safety announcements for non-CAPs.		• Started July 2012
3. Public hearings:		
Introduction of public hearings in the context of Urgent Union Procedure		• Definition of public hearings on-going

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Presentation no. 6

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PROTECT

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

PROTECT: Pharmacoepidemiological Research on Outcomes of Therapeutics by an European ConsorTium

Presented by: Steffen Thirstrup

PROTECT is receiving funding from the European Community's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu).

PROTECT Goal

To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods

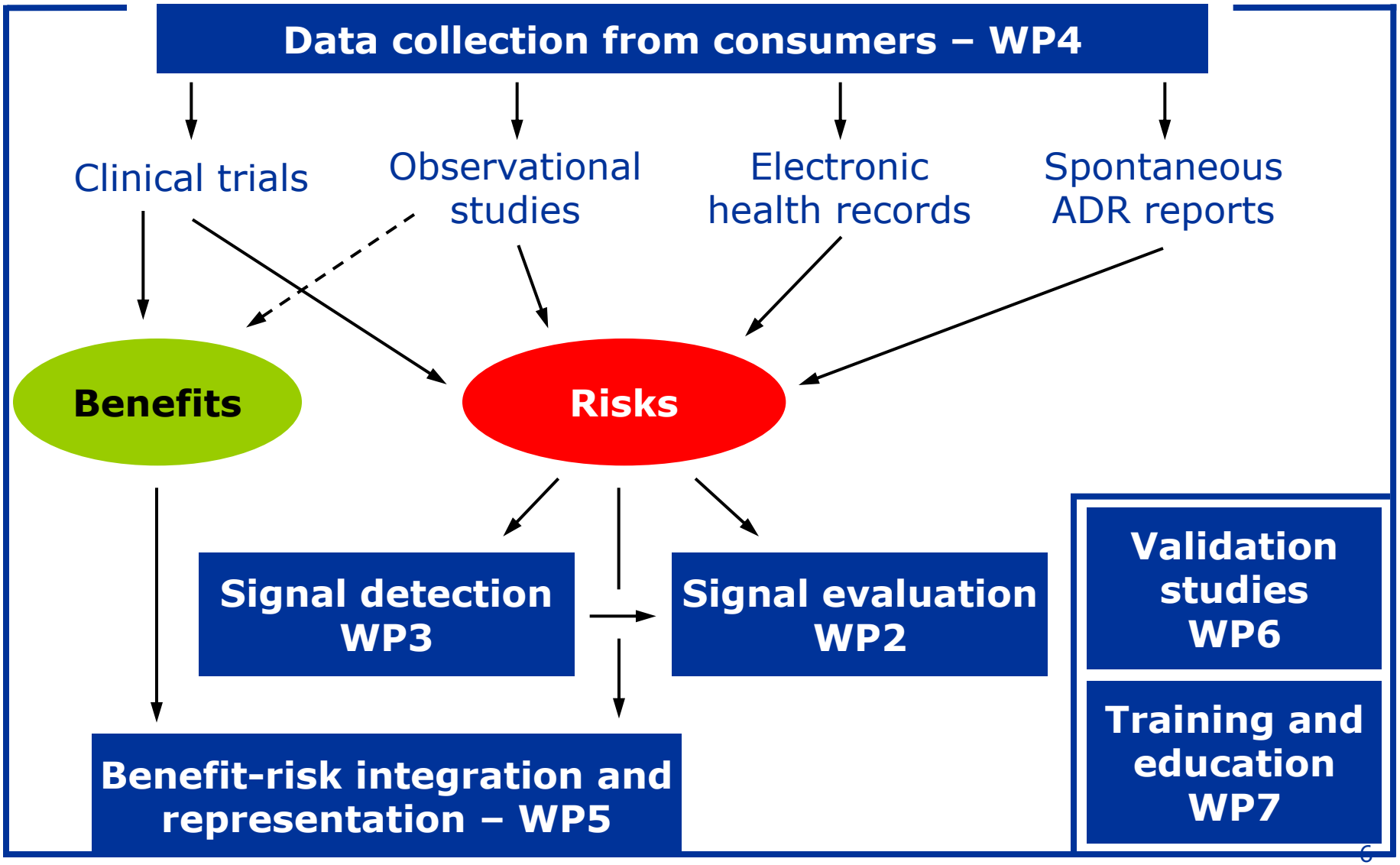
to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

to enable the integration and presentation of data on benefits and risks

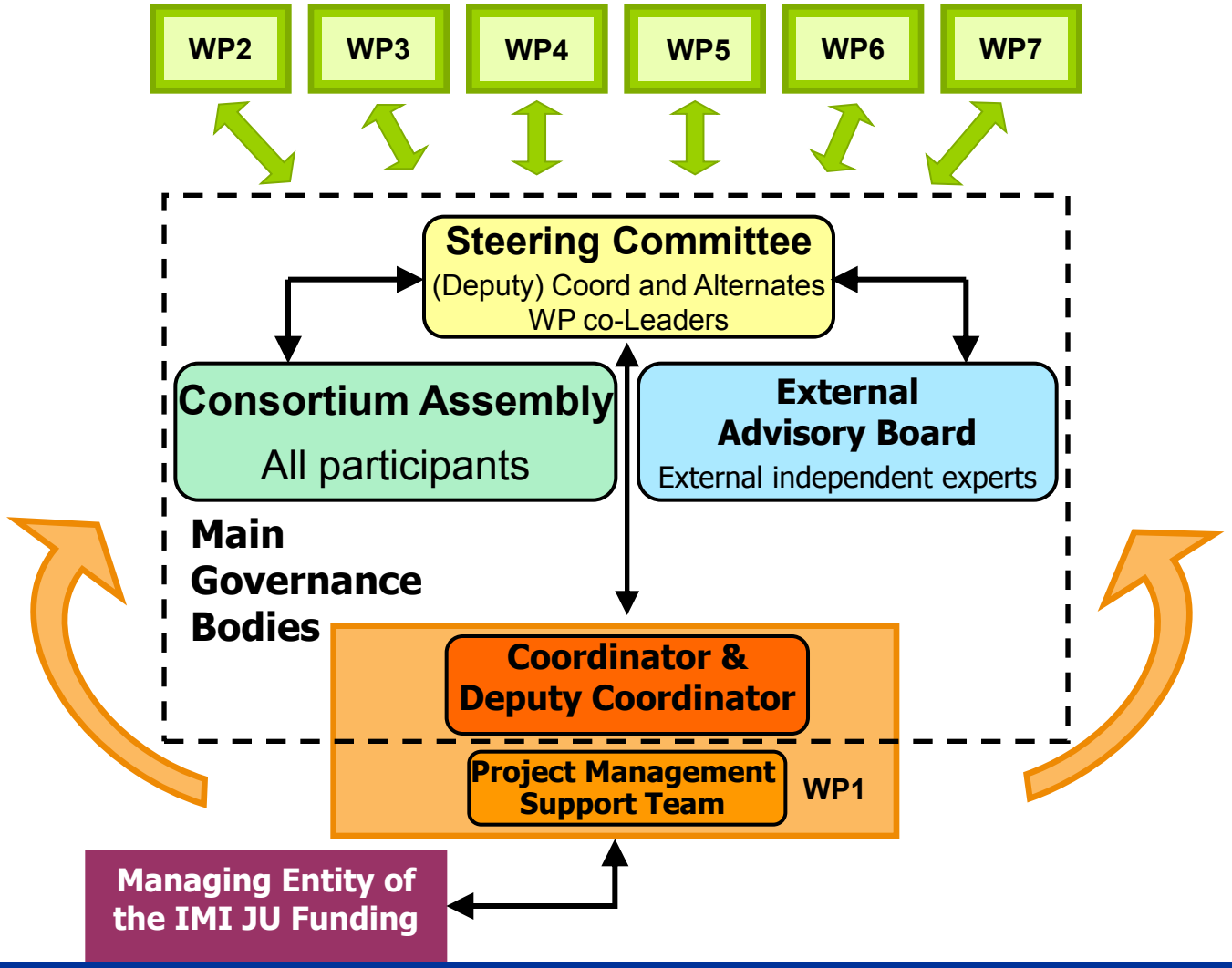
These methods will be tested in real-life situations.

Work Packages

1. Project management and administration
2. Framework for pharmacoepidemiological studies
3. Methods for signal detection
4. New tools for data collection from consumers
5. Benefit-risk integration and representation
6. Validation studies involving an Extended Audience
7. Training and Communication


Data collection from consumers – WP4
Clinical trials
Observational studies
Electronic health records
Spontaneous ADR reports
Benefits
Risks
Signal detection WP3
Signal evaluation WP2
Validation studies WP6
Training and education WP7
Benefit-risk integration and representation – WP5

Management structure



Partners

Public

Regulators:
EMA (Co-ordinator)
DKMA (DK)
AEMPS (ES)
MHRA (UK)

Academic Institutions:
University of Munich
FICF (Barcelona)
INSERM (Paris)
Mario Negri Institute (Milan)
University of Groningen
University of Utrecht
Imperial College London
University of Newcastle Upon Tyne

Others:
WHO UMC
GPRD
IAPO
CEIFE

SMEs:
Outcome Europe
PGRx

Private

GSK (Deputy Co-ordinator)
Sanofi- Aventis
Roche
Novartis
Pfizer
Amgen
Genzyme
Merck Serono
Bayer Schering
Astra Zeneca
Lundbeck
NovoNordisk

Members of the External Advisory Board

Name	Affiliation	Expertise
Corinne De Vries, PhD	Department of Pharmacy and Pharmacology, University of Bath, UK	Pharmacoepidemiology
Trevor Gibbs, MD	Former Head of Global Pharmacovigilance and Product Safety, GSK, UK; Chief Medical Officer at ii4sm	Pharmacovigilance, Health Outcomes, Public Health
David Haerry	European AIDS Treatment Group (EATG), Brussels, Belgium	Public Health Patients' preference
Vicky Hogan, PhD	Director, Office of Risk Management and Science, Marketed Health Products Directorate (MHPD), Health Canada	Benefit-risk assessment
Michael Lewis, MD	EPES Epidemiology, Pharmacoepidemiology and Systems Research GmbH, Berlin, Germany	Pharmacoepidemiology
Allen Mitchell, MD	Slone Epidemiology Center, Boston, USA	Perinatal epidemiology Pharmacoepidemiology
Marcus Müllner, MD	Head of AGES PharmMed (Austrian Medicines and Medical Devices Agency), Austria	Benefit-risk assessment Clinical epidemiology Pharmacovigilance
Gerald Dal Pan, MD, M.H.S.	Director, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), USA	Pharmacovigilance, Drug development, Public Health & Risk management
Munir Pirmohamed, MD	Department of Pharmacology and Therapeutics, University of Liverpool, UK	Pharmacology Pharmacovigilance
Samy Suissa, PhD	Department of Epidemiology/Biostatistics, McGill University, Montreal, Canada	Biostatistics Pharmacoepidemiology

More information?

Website: www.imi-protect.eu

Email: Protect_Support@ema.europa.eu

Presentation no. 7

eunethta

Rapid model for REA, pilot and future developments

i.e. possibilities to streamline the timelines of rapid pilots with EMA assessments

***Wim Goettsch**, PhD. Project leader of EUnetHTA WP5 JA1 and JA2;*
Deputy Secretary of the Medicinal Products Reimbursement Committee;
Health Care Insurance Board (CVZ), the Netherlands

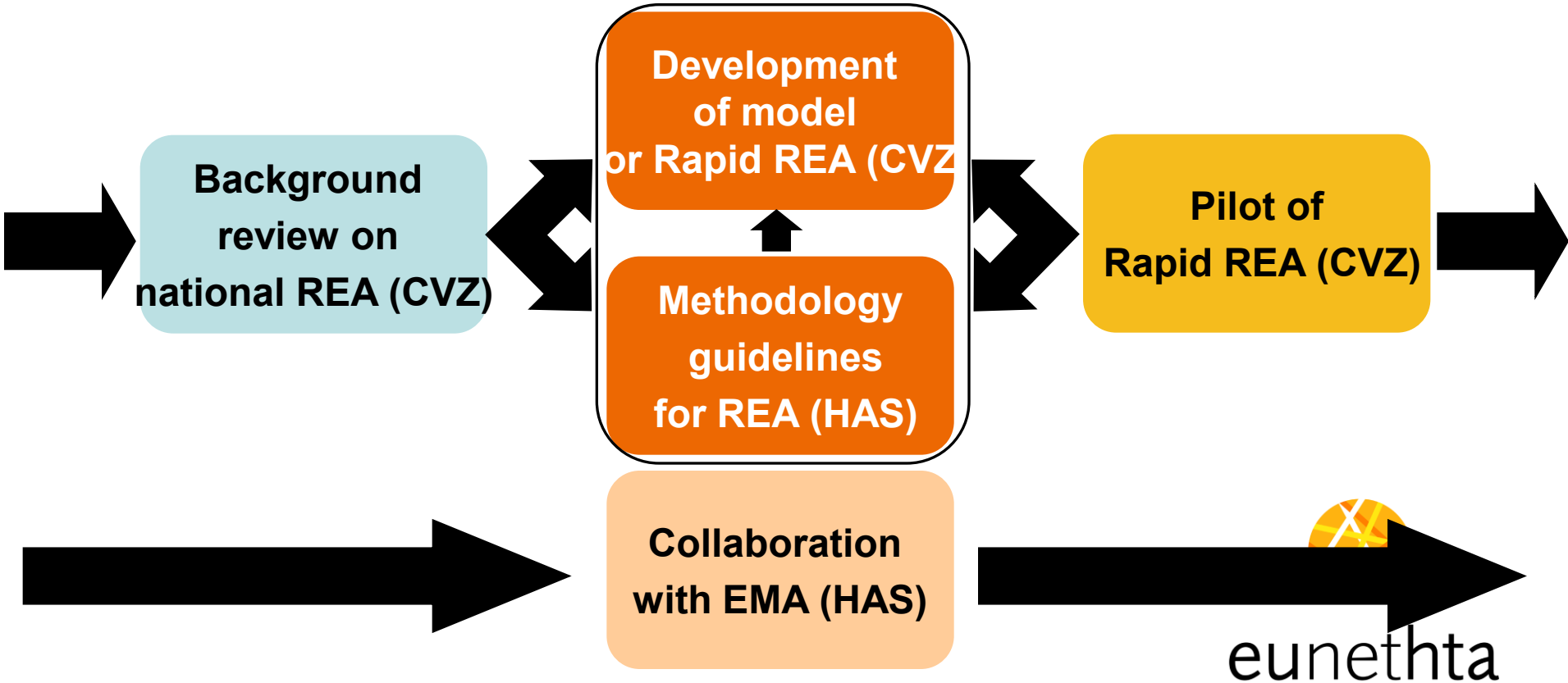
Framework of the presentation

- Short summary on Results WP5 JA1
- WP5 – Joint Action 2 - Objectives and principles
- Work process Strand A
- Suggested mode of operation in pilots of WP5 JA2
- Collaboration model HTA agencies
- Collaboration with MAH
- Topic selection procedure
- **Discussion – questions for EMA**

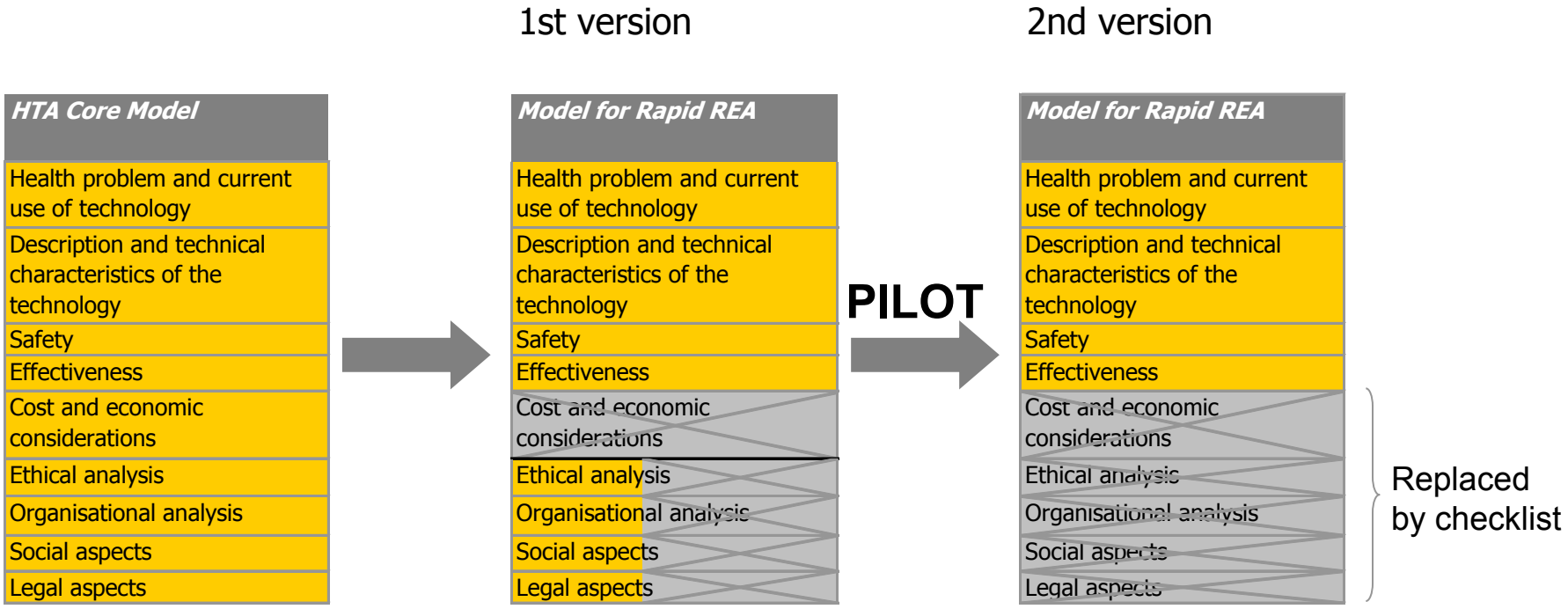
eunethta

EUnetHTA WP5 REA Pharmaceuticals

Objective:
Development of HTA tools and methods for REA



Model for Rapid REA of Pharmaceuticals



Public consultation is ongoing (1 Oct – 15 Nov 2012):

http://www.eunethta.eu/Public/Work_Packages/EUnetHTA-Joint-Action-2010-12/EUnetHTA-JA-Public-Consultations/Public-consultation-of-the-HTA-Core-Model-for-Rapid-Relative-Effectiveness-Assessment-of-Pharmaceuticals-/

eunethta

Guidelines on methodological issues (HAS)

Guidelines	EMA and Public consultation
• Choice of comparator • Composite EP • Surrogate EP • Applicability	**June 29 – Sept. 10**
• Direct and indirect comparisons • Clinical EP • HRQoL • Safety • Internal validity	**Aug. 27 – Oct. 30**

eunethta

First pilot rapid assessment (1)

Topic selection:

- List was produced of all pharmaceuticals that received market authorization between June 2010 and February 2011, selection made based on exclusion criteria
- Manufacturers approached for willingness to provide submission file (2 out of 4 were willing) --→ Pazopanib for the first-line treatment of metastatic renal cell cancer.

Basic documentation:

- Manufacturer submission file
- Model for Rapid REA
- Methodological guidelines developed in WP5

Process:

- Traditional model of collaboration in core-HTA was used
- Domain teams with participants from different organisations
- Synthesis of data after the collection of data in the different results cards

WP5 – Joint Action 2 – rapid assessments

Work plan – Objectives and principles

- **Output (products) oriented work package in order to prove the capacity of cooperation for increased efficiency of European HTA-production**
- **Pilot reports will be produced in order to critically review the applicability of the work done by JA1 WP5 and WP7B**
- **The work package will be divided into two major subgroups:**
  - STRAND A: assessments on pharmaceuticals (10 pilot reports);
  - STRAND B: assessments on other medical technologies such as medical devices, surgical interventions or diagnostics (4 pilot reports)
- **APs will further be split into active groups and less active groups**

eunethta

WP5 – Joint Action 2 – rapid assessments

Work plan – Work process Strand A

1. Specific deliverables:

- 10 pilot assessments (i.e. REAs)
- 2-3 national reports per REA
- Adaption of the 'Model for Rapid REA of pharmaceuticals'
- Testing of the submission file template for marketing authorisation holders developed by WP7

WP5 – Joint Action 2 – rapid assessments

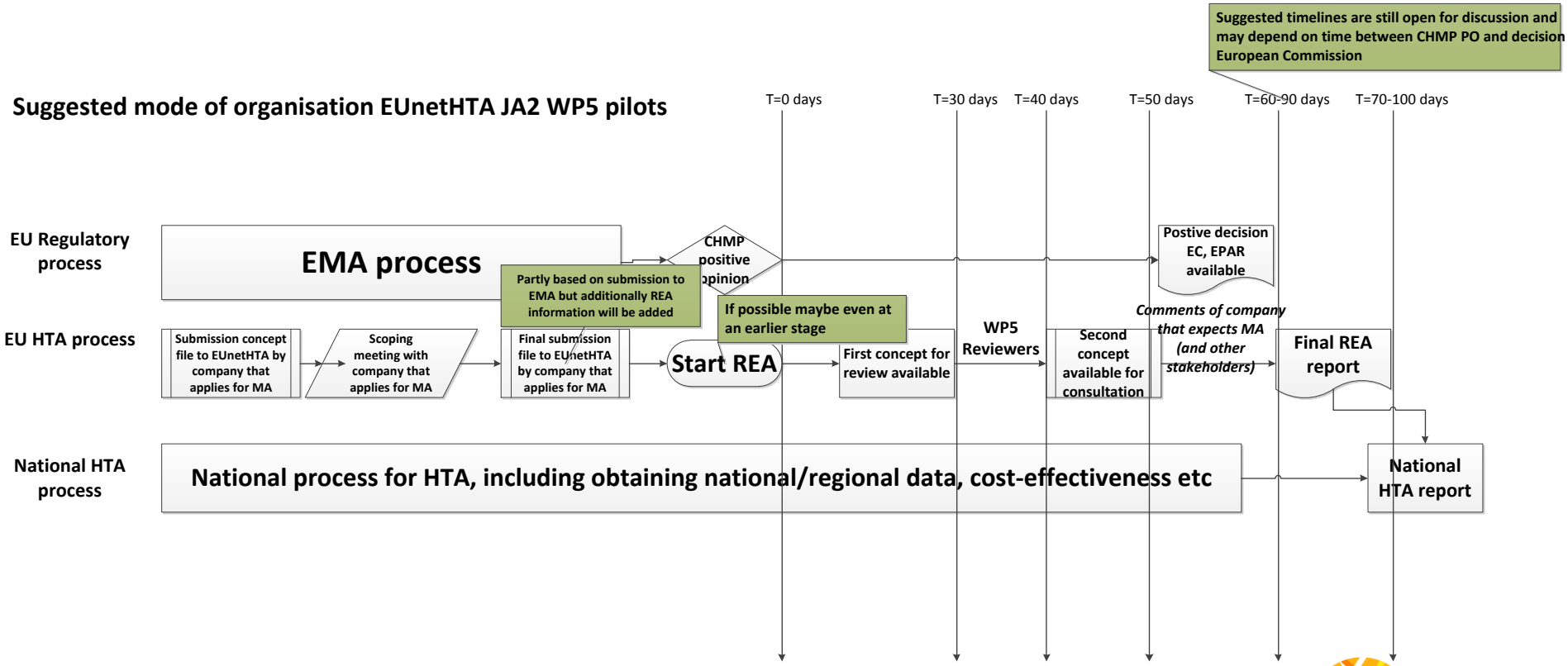
Work plan – Work process Strand A

2. Documentation and tools

- Model for Rapid REA (version 3) & guidelines on methodological issues (version 5) produced within Joint Action 1 (JA1) WP5
- Procedure manual and templates for doing the assessments
- **European Public Assessment Report (EPAR) or the draft EPAR**
- Submission file of marketing authorisation holder (if possible)
- Whenever possible, the online tool will be used for the pilot assessments

eunethta

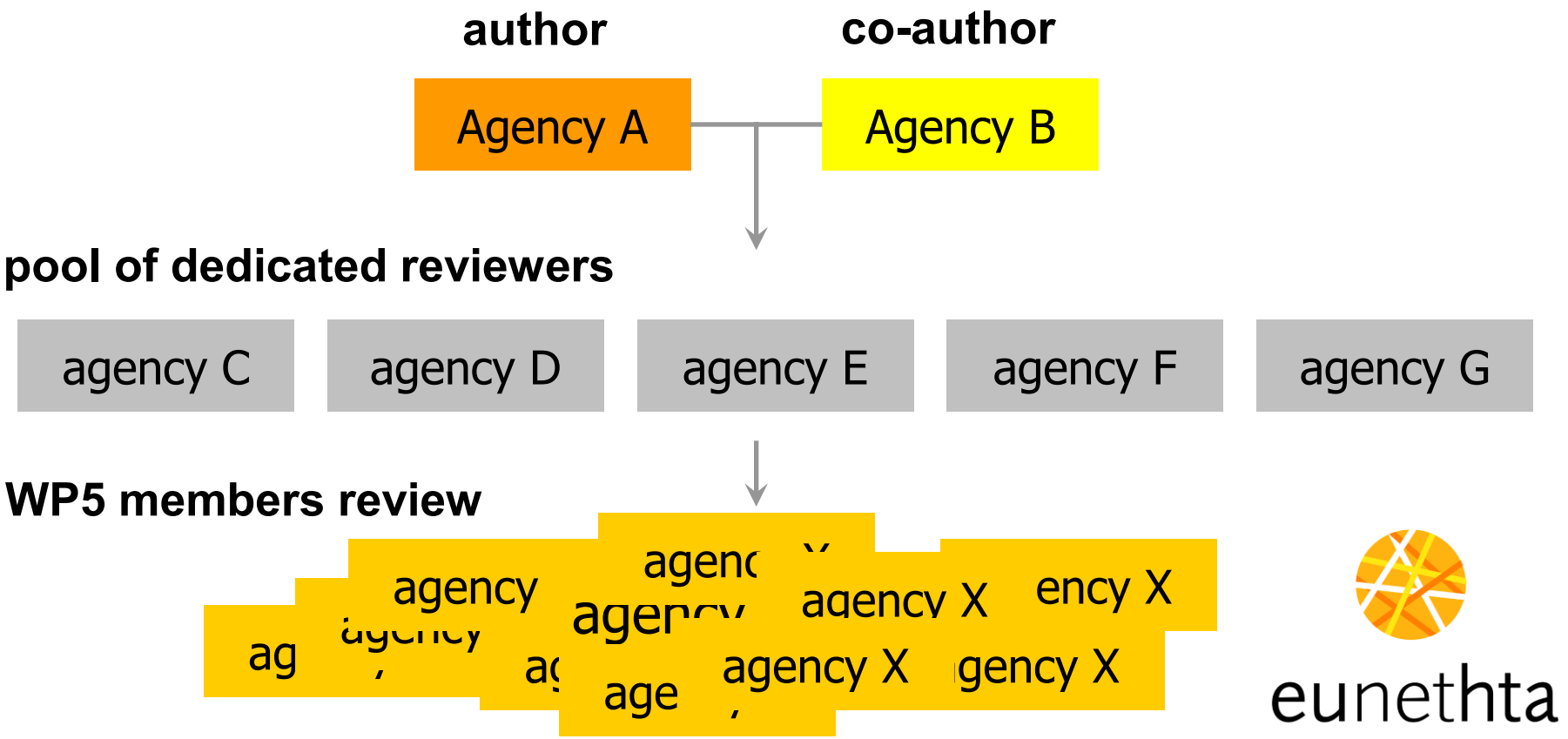
Suggested mode of operation in pilots of WP5 JA2



eunethta

Collaboration model HTA agencies

Anticipated collaboration model:



Collaboration with marketing authorisation holder (MAH)

- Pre-meeting regarding submission file (Scoping)
- Submission file provided by MAH
- Review of draft report by MAH

- MAH that have products for which is foreseen that they will receive market authorisation between 2013 and 2015 are asked to voluntarily participate in these pilots

eunethta

Topic selection procedure (1)

- Pipeline of the authoring agencies should be a relevant selection criterion
- **Collaboration with European Medicines Agency (EMA)**
- Collaboration with marketing authorisation holders (MAHs)

eunethta

Topic selection procedure (2)

- **Development of the preliminary list of pharmaceutical companies that are willing to participate in a pilot**
- **Many contacts with industry to engage them in the pilots:**
  - Letter was send to EFPIA
  - Contacts with specific companies: Lilly, Roche, Astrazenaza, J&J, Sanofi, Bayer, Novartis, Daiichi-Sankyo, Pfizer, MSD, BMS, MerckSereno
  - In general positive, some already have specific compounds for pilots in 2013 and 2014
  - Meeting with small orphan drug companies (SME) in January 2013

eunethta

Discussion – questions for EMA

- **Possibility of early availability of CHMP report soon after positive decision of CHMP?**
- **Is it possible to have indication on a possible decision before final CHMP so we can start our pilots even earlier?**
- **Is it possible to use the EMA submission file of the manufacturer before decision CHMP ?**
  - do we need approval of the manufacturer?
- **Is it possible to have any indication on the exact duration between the CHMP positive advise and the final availability of the EPAR for specific products?**

eunethta

Thank you for your attention!

Any questions???????

W.G. Goettsch (Wim); PhD

Deputy Secretary of the Medicinal Products Reimbursement Committee AND Project leader of the WP5 of EUnetHTA on relative effectiveness assessment of pharmaceuticals Health Care Insurance Board (CVZ) P.O. Box 320 1110 AH Diemen, The Netherlands

T: +31207978057
F: +31207978992
M: +31651134099
E: wgoettsch@cvz.nl

eunethta

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

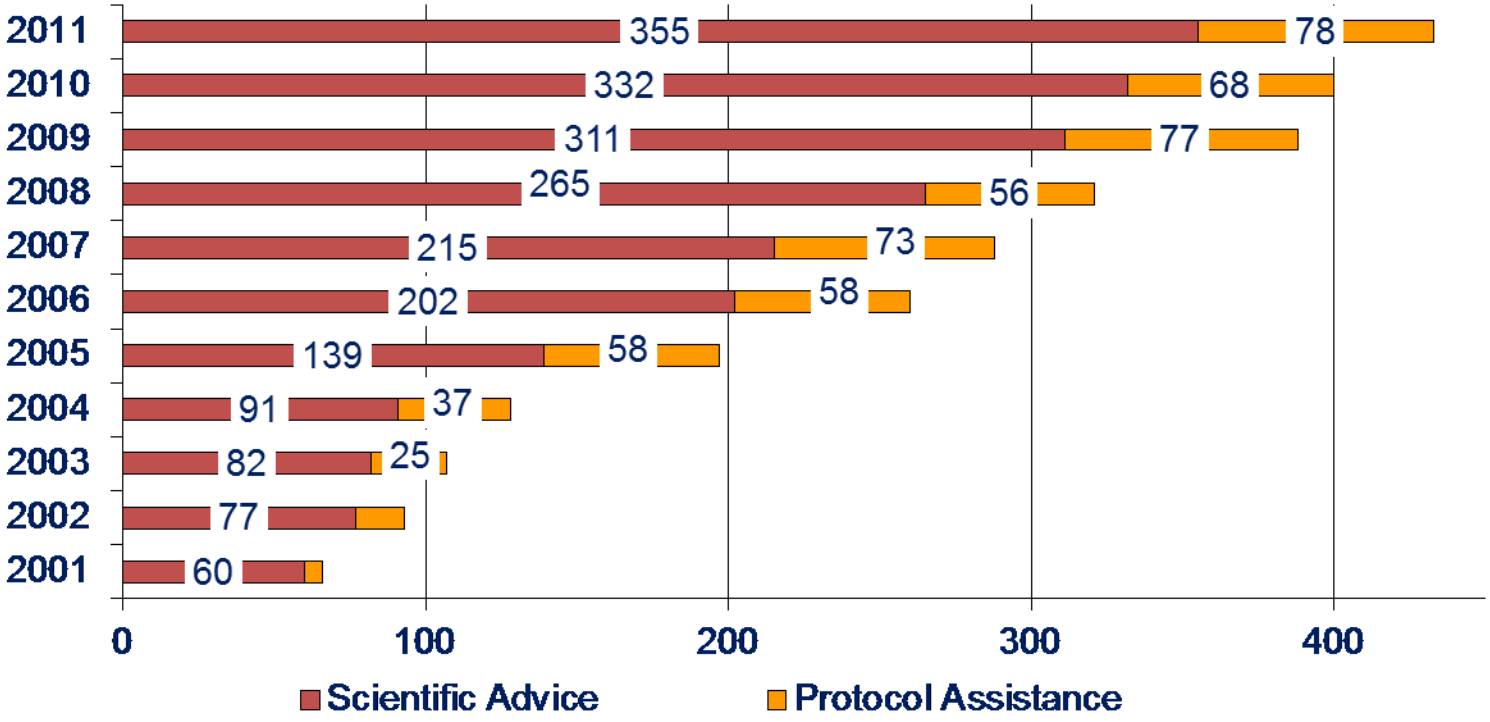
Presentation no. 8

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HTA-EMA Scientific Advice

Presented by: Spiros Vamvakas (spiros.vamvakas@ema.europa.eu)
Head of Scientific Advice

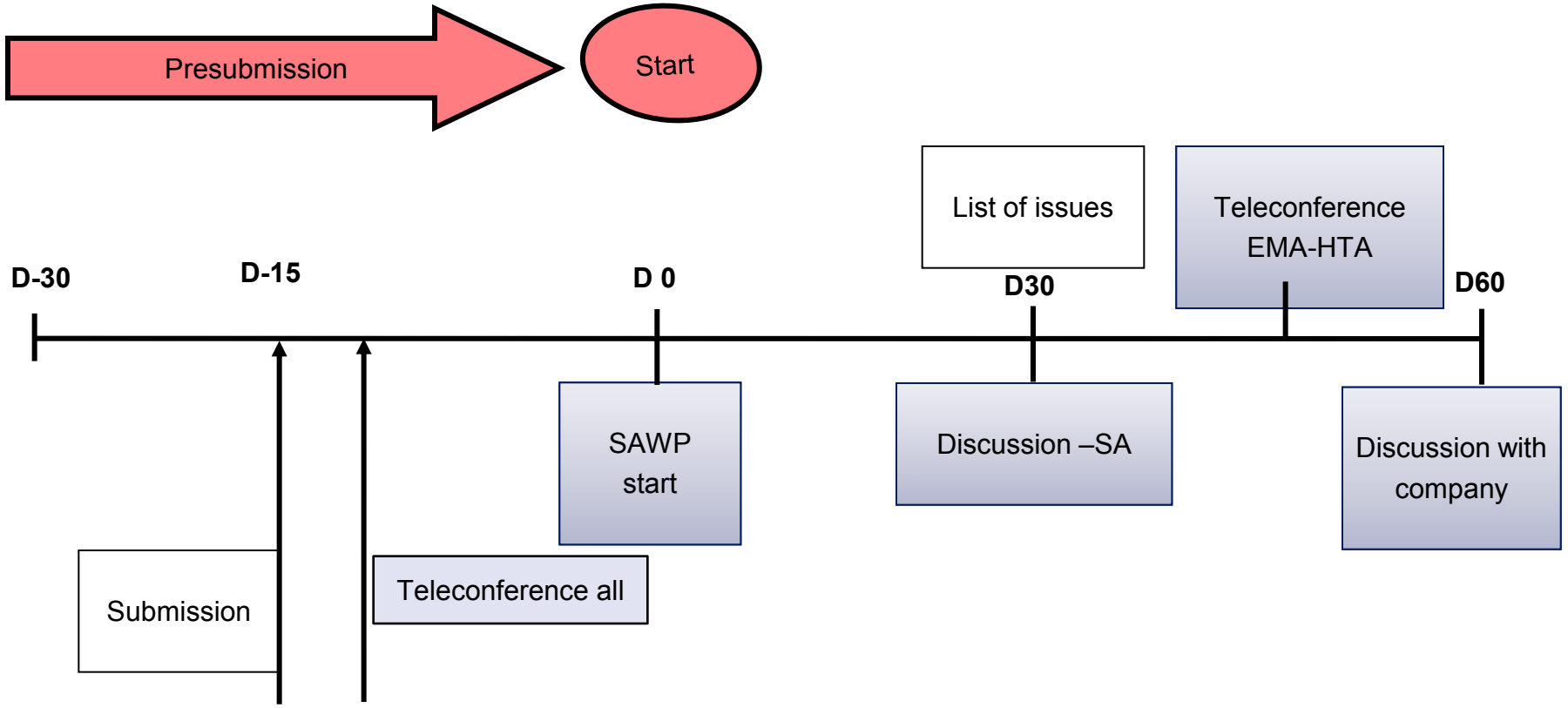
Scientific advice is given by the Committee of Medicinal Products for Human (CHMP) on recommendation of the Scientific Advice Working Party (SAWP)



Scientific advice working party

- 27 members and alternates from national authorities, universities and hospital, 10 scientific secretariat;
- expertise spanning across quality, non-clinical pharmacology and toxicology, all major clinical fields and statistics;
- monthly face-to-face meetings (3 days);
- during the face-to-face meeting discussion of 30-40 new products based on drafted reports;
- during the face-to-face meeting also ~ 20 discussion meetings with companies related to products discussed the previous month.

Scientific advice – HTA procedure



Outcome

CHMP SA letter

Minutes circulated by the company commented upon and agreed by all participants.

Parallel HTA-EMA SA experience so far: Sept 2010 – Nov 2012

- 17 procedures, 15 finalised, 2 ongoing;
- diabetes, heart failure;
- Alzheimer's, depression;
- lung cancer, breast cancer, melanoma, pancreas-ca, mesothelioma;
- asthma, rheumatoid arthritis;
- multi-resistant infections;
- food allergies;
- orphan condition.

- The majority new mechanisms of action in the respective area, new monoclonal antibodies, new chemicals, tumour vaccines.

Parallel HTA-EMA SA experience so far

- HTAs and payers from UK, Sweden, France, Italy, Netherlands, Spain, Germany, Belgium;
- 6 procedures facilitated through Tapestry, 11 individual companies directly with EMA and HTAs;
- 15 big companies, 2 SMEs.

When - early

Very early with non-clinical proof of concept and no clinical data:

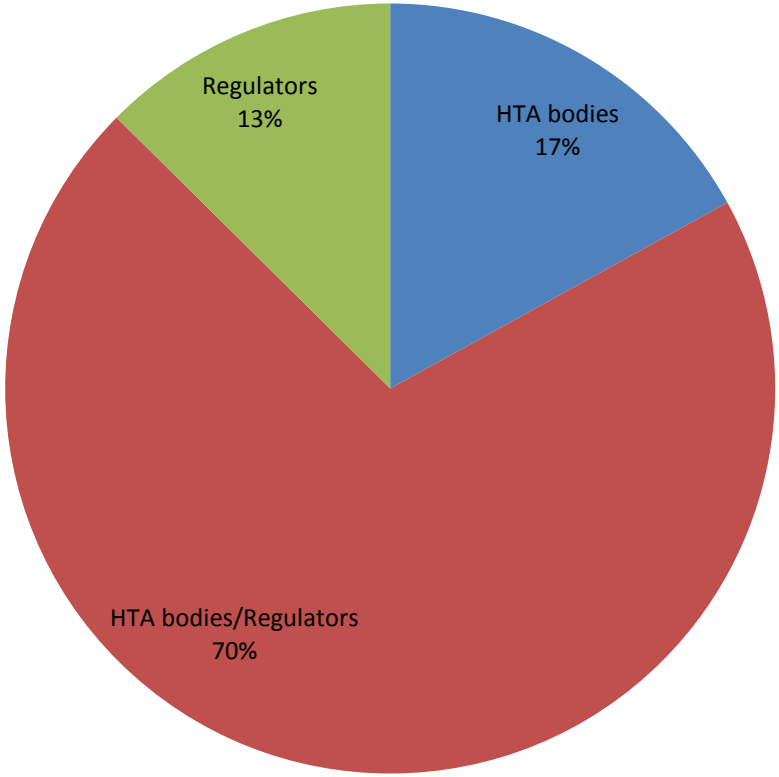
- Only general responses but company can benefit from orientation of what would be needed and the multi-stakeholders view on the pharmacological concept and general study design.
- A red light can be as useful as a green light (companies reflection).

When - later

When exploratory clinical data are available:

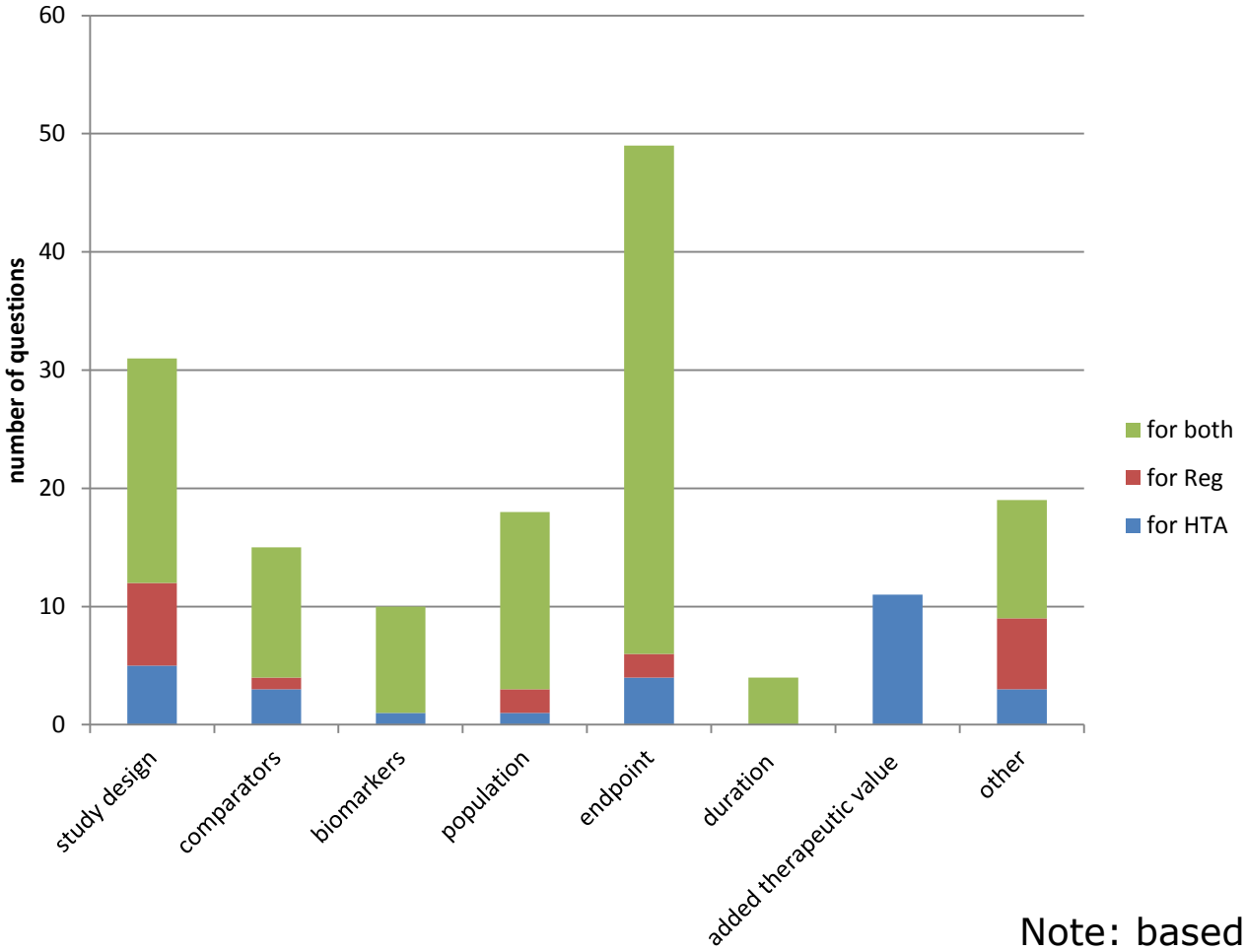
- Precise responses on which end-points, duration, comparators, size of the trial and statistical plans are important for the stakeholders.
- Precise idea on what / how much is required and what is feasible.

Questions raised by applicants



Note: based on finalised 15 procedures

Topic areas



Note: based on first 15 procedures

Shared discussions

- Cardiovascular death and number of rehospitalisation's can be included in the same trial as endpoints.
- What is the value of MRI imaging as indicator of progression of atherosclerosis?
- If final data on cardiovascular events cannot be provided for diabetes preauthorisation what alternatives are there for the company from the regulators and HTA point of view?

Shared discussions

- Is this an acceptable approach to qualify circulating tumour cells as prognostic markers for progression free survival or overall survival from the regulators and HTA point of view?
- Value of a new not validated endpoint from the regulators and HTA point of view; e.g. radiographic progression free survival to include bone events in breast cancer as compared to the standard PFS per RESIST which does not include bone events?

Shared discussions

- Do the stakeholders consider the impact to the caregiver (e.g. time assisting or supervising patient) an important piece of the value proposition when evaluating a treatment for prodromal Alzheimer disease?
- Do the stakeholders agree with the selection of instruments in the clinical trial to capture the burden to the caregiver (dependence scale)? Are there any other data that should be collected?

HTA discussion

The cost-effectiveness of the product will be strongly influenced by the extent to which treatment prolongs the prodromal Alzheimer disease phase, delaying progression to more costly states associated with potentially lower quality of life and greater cognitive impairment. This would potentially result in a greater proportion of residual life being spent with lower disability and lower medical costs. However, delaying progression may also extend life expectancy and time in the moderate and severe disease states, which could result in higher total lifetime costs and reduce the cost-effectiveness of treatment. Modelling will be necessary to project out the implications of potential post-trial scenarios. Do you agree with the approaches taken to establish the most plausible scenario and what data or analyses will be required to support the plausibility of the scenario?

HTA discussion

Company believes that appropriate use of new, higher acquisition cost antibiotics as initial empiric therapy delivers greater overall benefits to health systems than holding them in reserve. Whilst doing so may result in short term increases of drug acquisition costs, this approach will minimise longer-term societal costs due to a reduction in the emergence and growth of resistance, and the potential to prolong the utility of all antibiotics. What is the view of the participant HTAs?

HTA discussion

We recognize that RA patients cycle through various treatments due to inefficacy and intolerance, especially anti-TNFα inhibitors. How can we demonstrate the economic burden associated with this prescribing pattern? Do HTAs agree that it is now valuable to switch patients to a new class of biologics with associated efficacy and safety benefits instead of sequencing patients through multiple anti-TNFαs? How will HTAs determine which biologic class to use in specific RA patient populations after TNF failure?

The future

EMA and the EU regulators would very much like to engage in more parallel procedures together with HTAs.

Presentation no. 9

NICE Scientific Advice Projects in collaboration with EMA

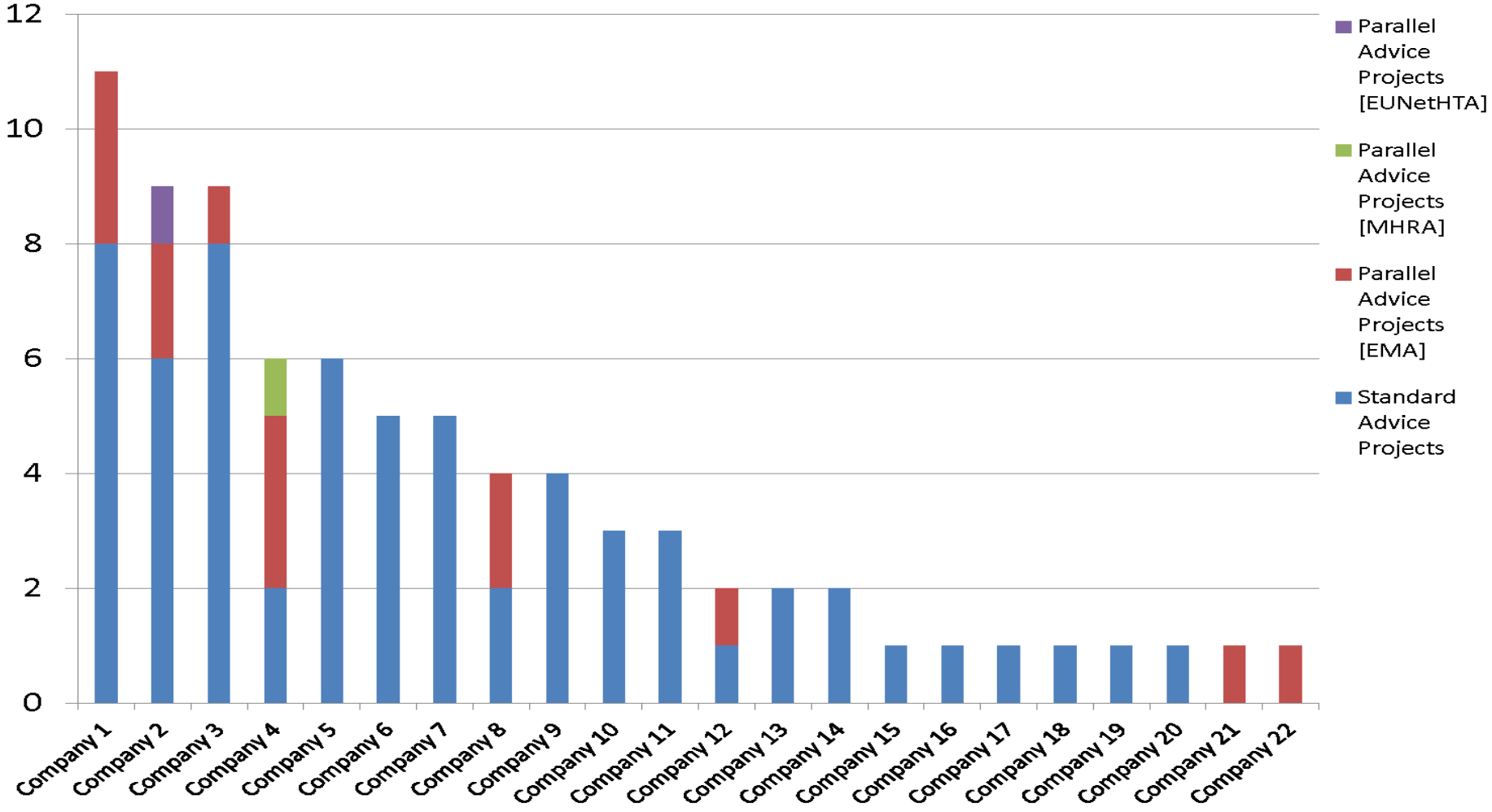
Carole Longson

National Institute for Health and Clinical Excellence

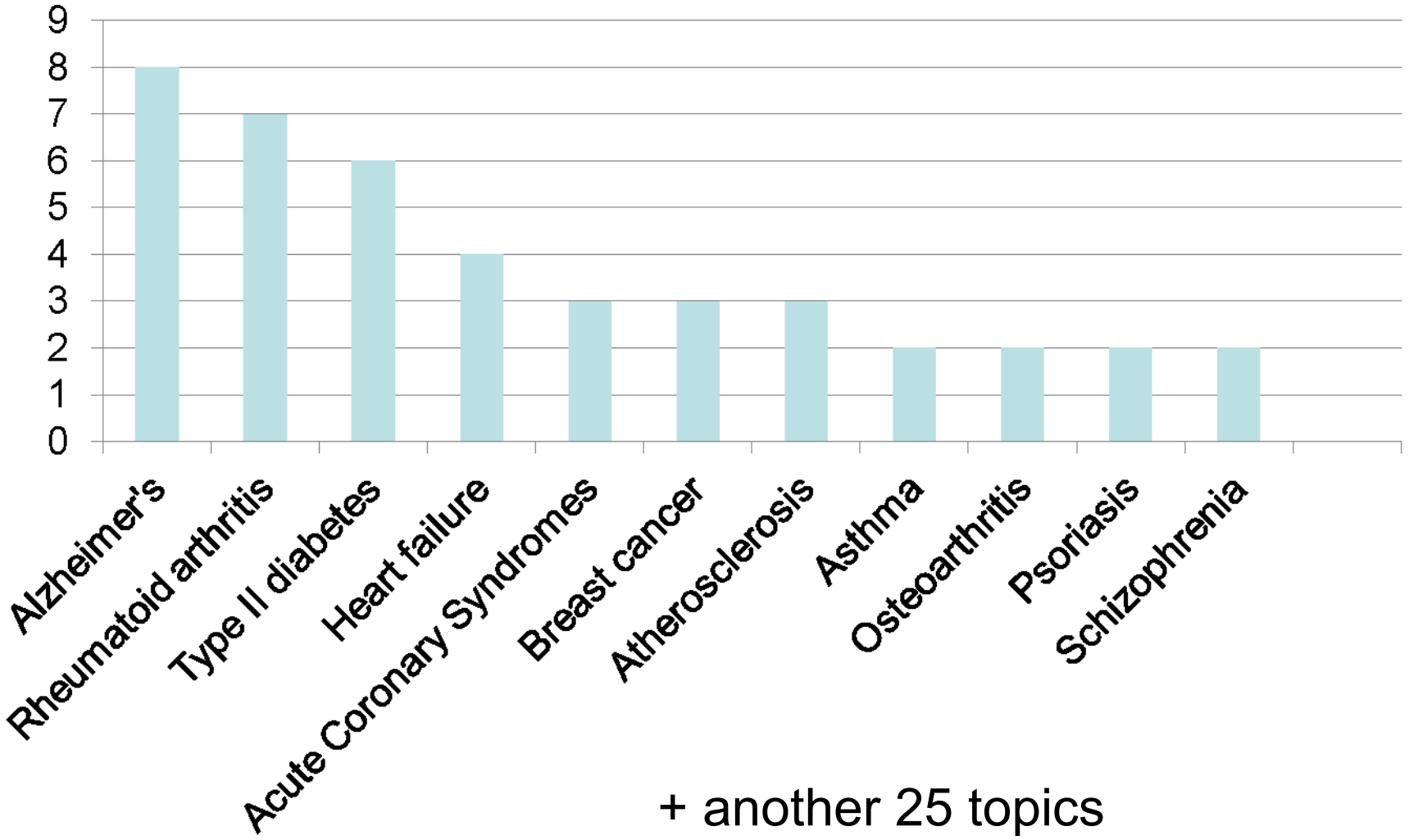
NICE Scientific Advice Products

Product	Format of advice
Standard Advice	Written advice report.
Advice alongside the MHRA	Modified standard advice process. Written advice report.
Advice alongside the EMA	Advice offered verbally at face-to-face meeting. NICE comment on company minutes. Written advice when undertaken alongside modified standard advice process.
Advice alongside other HTA agencies	Advice offered verbally at face-to-face meeting. NICE comment on company minutes.

Advice Projects by Company



Requests by Specific Disease



+ another 25 topics

Advice alongside the EMA: Procedure

1. Initial contact with NICE to check availability
2. Submit Letter of Intent to EMA and NICE
3. Sign contract with NICE
4. Submit pre-validated briefing package to EMA and NICE
5. Pre-validation teleconference with EMA and NICE
6. Submit revised briefing package to EMA
7. Send EMA-validated briefing package to NICE
8. Send face-to-face meeting slides to EMA and NICE
9. Face-to-face meeting
10. Send minutes from meeting to NICE for review

Observations
EMA/HTA Projects

- Each participating organisation is able to provide advice in accordance with their own procedures
- Work programme collaboratively organised in advance
- Advice is given in the light of meaningful interactions and understanding of respective views
- From NICE perspective the interactions are important and have been extremely useful
- Work is in progress to develop an efficient and acceptable procedure for the provision of ‘parallel’ written advice
- We need to explore how best to involve both regulatory and HTA experts in the advice meetings

Presentation no. 10

eunethta

Early dialogues (multi-HTA scientific advice)

EMA – EUnetHTA Meeting
20 November 2012
Copenhagen

New EUnetHTA initiative on Early dialogues

- **One of the European Commission priorities**
- **Part of EUnetHTA JA2**
- **JA2 WP7 "improvement of evidence generation for all HT":**
  - early dialogue
  - disease-specific guidelines for technology developers
  - general methodology guidelines
  - additional evidence generation

eunethta

Preparatory pilot early dialogues

- **2 preparatory pilots conducted before start of JA2**
  - 1st pilot early dialogue meeting: **30 May 2012**
  - 2nd pilot early dialogue meeting: **2 July 2012**
- **Coordinated and hosted by HAS**
- **Participating HTA organisations: IQWIG, GBA, KCE, INAMI, HVB, CVZ, AIFA, NICE and EC representative**
- **Experience on 2 drugs in oncology**
  - Innovative products (biotech, new mechanism of action)
  - one small and one big company

eunethta

Preparatory pilot early dialogues Preliminary experience

Successful

First experience gained on:

- Feasibility, including draft procedure
- HTA bodies collaboration/governance issues,
- HTA prospective thinking on evidence requirements based on 2 examples
- Consolidated view/agreement/transparency on the choice of comparators and endpoints for REA

Help to prepare JA2 WP7

Feed-back on the procedure from participating HTA bodies and 2 companies **– amended draft procedure**

More formal feed-back (survey) planned after 5-6 pilots (end 2013)

eunethta

HTA Early dialogue pilots draft procedure

- HT with supposed **added benefit** for patients
- One indication per procedure
- Development strategy, cost-effectiveness studies: planned (not ongoing) studies
- Prospective questions (and position) pertaining to clinical relative effectiveness, economical and other aspects, relevant for the development plan
- Non binding and confidential

eunethta

HTA Early dialogue pilots draft procedure

- Draft briefing document (ToC, summary, questions / company's position and background documentation) sent to the coordinator **2.5 months** before the FTF meeting with HTA bodies.
- 1st review by coordinator: 5 days
- Company to complete le dossier: 10 days
- The revised dossier sent to participating HTA bodies **2 months** before the FTF meeting

eunethta

HTA Early dialogue pilots draft procedure

- **Teleconference with HTA** bodies **1,5 month** before FTF meeting to identify missing information in the dossier
  - ➢ **list of main issues** to be addressed by the company either in writing and/or at the FTF meeting
- **D-30:** Submission of **additional information/clarification** by the company
- **D-7: HTA bodies send short written answers to company's questions to the coordinator**
- **D-3: Compiled document with all answers released to participating HTAs**

eunethta

HTA Early dialogue pilots draft procedure

- **D 0: Early Dialogue Meeting**

  One-day meeting (from 10.30 a.m to 17.30 p.m) organised by the coordinator and taking place at the HAS, France

  - Preliminary discussion (without the company)
    - Coordinator to present product/indication, questions and company's proposal, highlighting key issues or possible disagreements among HTA bodies

  - **FTF meeting with the company and HTA organizations – 3h**
    - Company to address each question with position, including additional issues identified by HTAs at teleconference
    - **Followed by opinion of each HTA body**
    - Open dialogue, discussion on alternative approach

  - Conclusions (without the company)

eunethta

HTA Early dialogue pilots
draft procedure

- **D+7: Draft detailed minutes** including common answers/positions and positions of each HTA body on each question to be provided by the company
- **End of procedure:**
  - Finalization of detailed minutes - reviewed and validated by all HTA bodies participants
  - If remaining issues: clarification teleconference may organized by coordinator

eunethta

Early dialogue pilots JA2
WP7 (co-ordinator HAS)

Drugs AND non-drug technologies

- Waiting list: pharmaceuticals and other technologies
- 6 pilots for drugs planned for end 2012-13: meeting in Dec., Feb., April, June, Sept., Nov.
- 1 pilot for a medical device/procedure in 2013

→ Feed-back and input from companies and HTA bodies expected end of 2013 (survey) to improve the process

Involved HTA bodies: WP7 partners

Cooperation with EMA to be put in place

EC financing additional early dialogues

eunethta

Early dialogue vs scientific advice
Current situation

Early dialogue HTA:

- **Several HTA bodies, no EMA representative**
- Participating HTA bodies - EUnetHTA network
- Transparent, detailed HTA advice: common/divergent views expressed orally and in writing (procedure)

Parallel EMA – HTA scientific advice:

- **EMA (regulatory European) advice + independent national HTA advices**
- 2 or 3 participating HTA bodies
- No step within the procedure dedicated for discussion/exchange between HTA bodies and between SAWP and HTA representatives

eunethta

Early dialogue vs scientific advice
For discussion/approval

- EMA: observer(s) in HTA early dialogue?
- Towards a parallel EMA – EUnetHTA scientific advice / early dialogue?
  - Main steps and timelines are similar
  - Briefing book: similar for regulators and HTAs
  - Questions: similar (common), specific for EMA, specific for HTA,
  - Final documents: to be validated/reviewed by both EMA and HTA bodies and to be shared?

eunethta

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Presentation no. 11

Mutual commenting on Guidelines – Current status

EMA-EUnetHTA meeting, 20 November 2012, Copenhagen

Presented by: Michael Berntgen
Head of Rheumatology, Respiratory, Gastroenterology and Immunology

An agency of the European Union

Meeting in February 2012 - Minutes

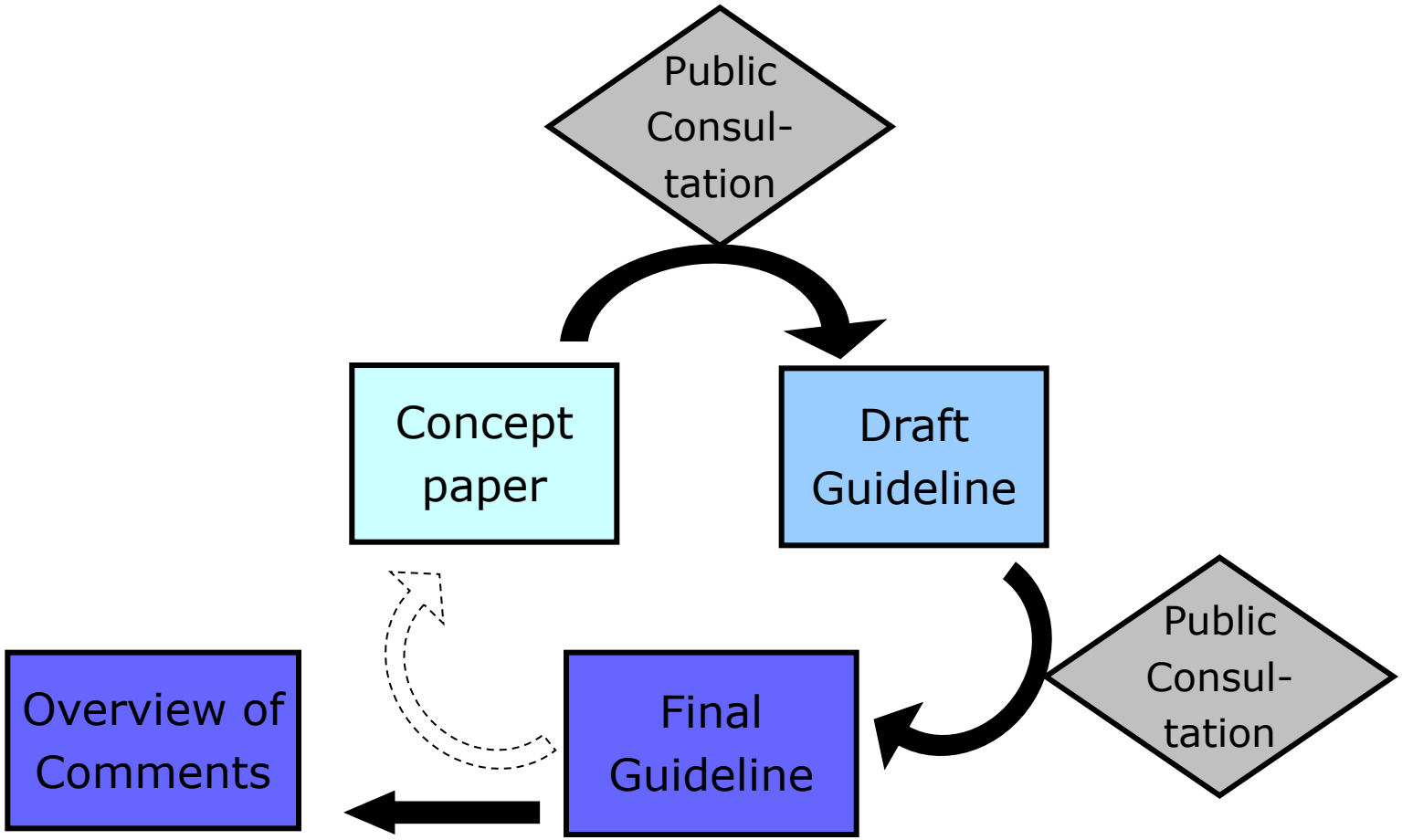
There was a discussion on how the EMA/CHMP and EUnetHTA could mutually contribute to their respective guideline production during the consultation phase:

- Concerning the EUnetHTA GLs, the timelines proposed for the EMA's consultation (2 months) were endorsed. The expectations in terms of comments from the EMA are mainly to check the consistency with the EMA guidelines and to provide scientific input. The primary objective of these GLs is to help rapid assessment of pharmaceuticals. To make this objective straightforward before the consultation phase, it was decided that a general statement on the objective would be mentioned at the beginning of each GL.
- For the GLs produced by the EMA/CHMP and with relevance for HTA organisations (clinical and methodological), the EMA will establish a process to provide EUnetHTA (Finn Børlum Kristensen) with a list of guidelines under public consultation on a regular basis.

EMA Commenting on EUnetHTA Guidelines

Topic of EUnetHTA guidelines	Commenting period	Reviewers
– Composite endpoints – Surrogate endpoints	29 June – 10 September	CHMP, COMP, EMA, PDCO, SAWP
– Clinical endpoint	27 August – 31 October	
– Choice of comparator – Applicability (external validity)	29 June – 10 September	EMA, CHMP, COMP
– Health-related quality of life (HRQoL)	27 August – 31 October	
– Safety	27 August – 31 October	EMA, CHMP, PRAC
– Direct and indirect comparisons – Internal validity	27 August – 31 October	BSWP, CHMP, COMP, EMA

EMA Guideline Development Process



Commenting on EMA Guidelines - clinical

Topics of EMA Guidelines	Commenting period	Comments
Clinical investigation of medicinal product in the treatment of depression	22 March - 31 March	
Evaluation of anticancer medicinal products in man	22 March – 31 May	- NICE (UK)
Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man - methodological considerations for using progression-free survival (PFS) as primary endpoints in confirmatory trials for registration	22 March – 31 May	- NICE (UK)
Guideline on the Clinical Investigation of Medicinal Products in the Treatment of Urinary Incontinence	22 March – 31 May	
Clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis	22 March – 5 June	- NICE (UK)
Reflection paper on the non-clinical and clinical development for oral and topical HIV pre-exposure prophylaxis (PrEP)	30 April – 30 June	
Draft reflection paper on clinical aspects related to tissue-engineered products	30 April – 31 July	- IQWiG (DE)
Concept paper on the revision of the CHMP points to consider on the evaluation of medicinal products for the treatment of irritable bowel syndrome	13 June – 31 August	

Commenting on EMA Guidelines - PhV

Topics of EMA Guidelines	Commenting period	Comments
Post-authorisation safety studies (GVP)	22 March - 18 April	
Risk management systems (GVP)	22 March - 18 April	
Periodic safety update reports (GVP)	22 March - 18 April	
Guideline on good pharmacovigilance practices: Module X – Additional monitoring	5 July – 24 August	
ICH guideline E2C (R2): Periodic benefit-risk evaluation report (PBRER)	30 April – 21 May	

For discussion

- Was the exchange considered useful?
- Should we maintain the regular provision of EMA guidelines?
- Are the processes for the exchange optimal?

Presentation no. 12

eunethta

Methodology guidelines

Mira Pavlovic,

EMA-EUnetHTA meeting, Copenhagen, November 20, 2012

WP5 Methodology guidelines
Initial planning

- **Public consultation finished for all 9 guidelines**
- **Comments received from: industry, public bodies, experts, HTA organizations, EMA**
- **All comments compiled for each guideline and sent to authors**
- **Thorough discussion planned in Budapest with:**
  - **WP5 members (all guidelines)**
  - **EFPIA experts (endpoints guidelines)**
- **Final versions planned for the end of December 2012**

eunethta

WP5 Methodology guidelines
Reality

- Important number of thorough comments received (30 – 40 pages per guideline)
- Important issues raised
- WP5 meeting in Budapest, November 22-23
  - **Comments discussed guideline per guideline**

WP5 Methodology guidelines
Change in programme

- Meeting with stakeholders (EFPIA) **postponed for January 21, 2013**

- Finalisation of guidelines postponed for January 31, 2013
  - Applicability, Internal validity, Direct and Indirect Comparisons, Safety: **December 31, 2012**
  - Choice of comparator, Clinical endpoints, HRQoL, Surrogate endpoints, Composite endpoints: **January 11, 2013**

eunethta

WP5 Methodology guidelines
Comments provided by 20 stakeholders

- **10 – 15 per guideline**
- **HTA bodies:**
  - Canadian Agency for Drugs and Technologies in Health (CADTH), AIFA, OSTEBA, SBU, RCCEEPh (HTA Russia)
- **EMA**
- **European federation of statistics in pharmaceutical industry** (EFSPI/PSIHTASIG)
- **International society of Drug Bulletins (ISDB) and Medicines in Europe Forum (MiEF)**
- **Industry:**
  - EFPIA, EUROPABIO, LEEM, UBC, GSK, Novartis, Pfizer, Bauch+Lomb, Sanofi-Pasteur,
- **HTAi** Patient and Citizen Involvement Interest Subgroup
- **Academy experts**
  - Nicolas Albin (France), Rod Taylor (UK)

eunethta

WP5 Methodology guidelines
General comments for all guidelines

- GL reflect more current thinking based on good practices than recommendations to HT assessors on how to perform REA
- Areas where there is **less consensus** across HTAs in specific methodological aspects should be highlighted (and where strong recommendation cannot be made)
- More relative to efficacy than effectiveness. Should cover how post marketing inputs to REA could address uncertainties inevitable at initial assessment
- Not always designed for **orphan drugs**
- Do not address **non-RCT data** (e.g. post marketing observational studies)
- **Involvement of stakeholder** (including external expert groups, academia, healthcare professionals) necessary **at an earlier stage in the process**

eunethta

WP5 Methodology guidelines
Suggestions for all guidelines

- Specify that the **scope** is mostly on evidence available at the time of launch
- Expand discussion session on what the **key issues** are
- Shorten synthesis of literature
- **Align** EUnetHTA draft guidelines with already existing clinical and regulatory ones
- Consider development of **disease-specific guidelines** to establish consistency in assessment
- EUnetHTA **scientific advice** needed on REA
- Rewrite guidelines to be **more useful** for REA assessors **(primary target)**

eunethta

WP5 Methodology guidelines
Lessons learned

High number and valuable comments from SAG and public consultation

- contribute to improved documents at the end
- BUT: high work burden for authors and EunetHTA

Generating guidelines is extemely useful for increased understanding and harmonisation of assessment:

- among HTA Agencies
- between HTA agencies and stakeholders
- between HTA agencies and EMA
- between HTA agencies, EMA and stakeholders

However it is a very resource and time consuming process that requires more focused attention and time in JA2

eunethta

JA2 WP7: development of consensus on HTA methodologies

EunetHTA JA2 (2012-15): lead HAS, co-lead IQWIG

- **WP7 : Increase the quality of evidence generation (all HT)**
  - Initial evidence:
    - Early Dialogue
    - Disease-specific guidelines
  - Additional evidence : Common core protocols
- **Harmonise methods of assessment (all HT)**
  - Methodology guidelines
  - « Core HTA information »

eunethta

JA2 WP7: Methodology guidelines, all HT
Suggestions for review/revision and new topics

- **Identify needs for JA2: proposals from**
  - WP4, WP5 and WP7 JA2 members
  - EMA
  - stakeholders
- **To discuss at the WP7 JA2 meeting in January 2013**

eunethta

JA2 WP7: Methodology and disease-specific guidelines

Disease-specific guidelines

- Coordinated by HAS
- Topics TBD
- Involvement of stakeholders and EMA in the proposal and development process

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Presentation no. 13

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Significant benefit of orphan medicinal products: concept and experience

EMA-EUnetHTA meeting
20 November 2012

Presented by: Jordi Llinares
Section Head orphan medicines

Criteria for orphan designation

RARITY (prevalence) / RETURN OF INVESTMENT

- Medical condition affecting not more than 5 in 10,000 persons in the Community (around 250,000)

OR

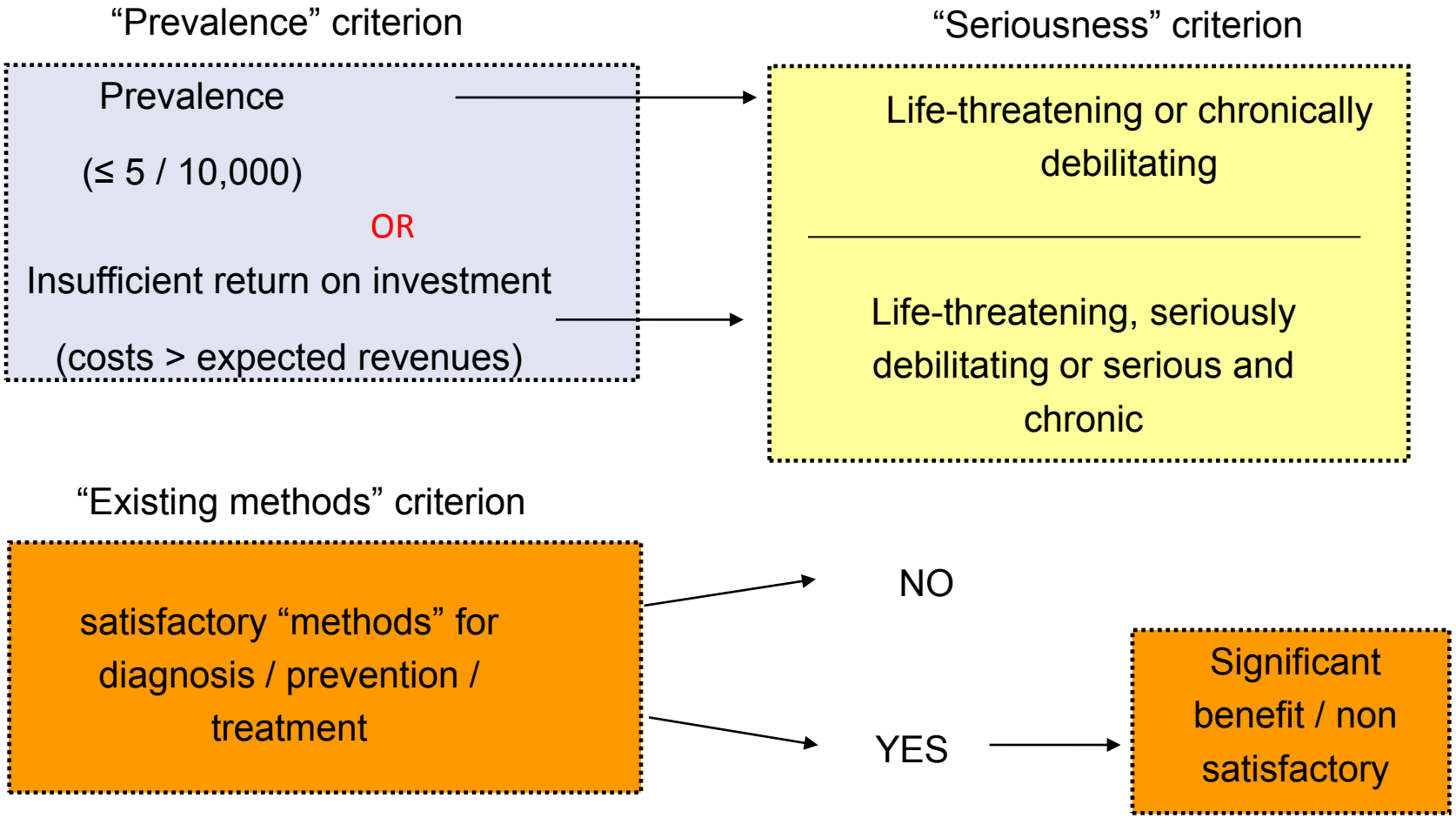
- Without incentives unlikely that marketing would generate sufficient return to justify the necessary investment

SERIOUSNESS

- Life –threatening or chronically debilitating

ALTERNATIVE METHODS AUTHORISED

- If satisfactory method exist the sponsor should establish that the product will be of significant benefit


"Prevalence" criterion
Prevalence
(≤ 5 / 10,000)
OR
Insufficient return on investment
(costs > expected revenues)
"Seriousness" criterion
Life-threatening or chronically debilitating
Life-threatening, seriously debilitating or serious and chronic
"Existing methods" criterion
satisfactory "methods" for diagnosis / prevention / treatment
NO
YES
Significant benefit / non satisfactory

What is significant benefit?

Definition: "A clinically relevant advantage or a major contribution to patient care"

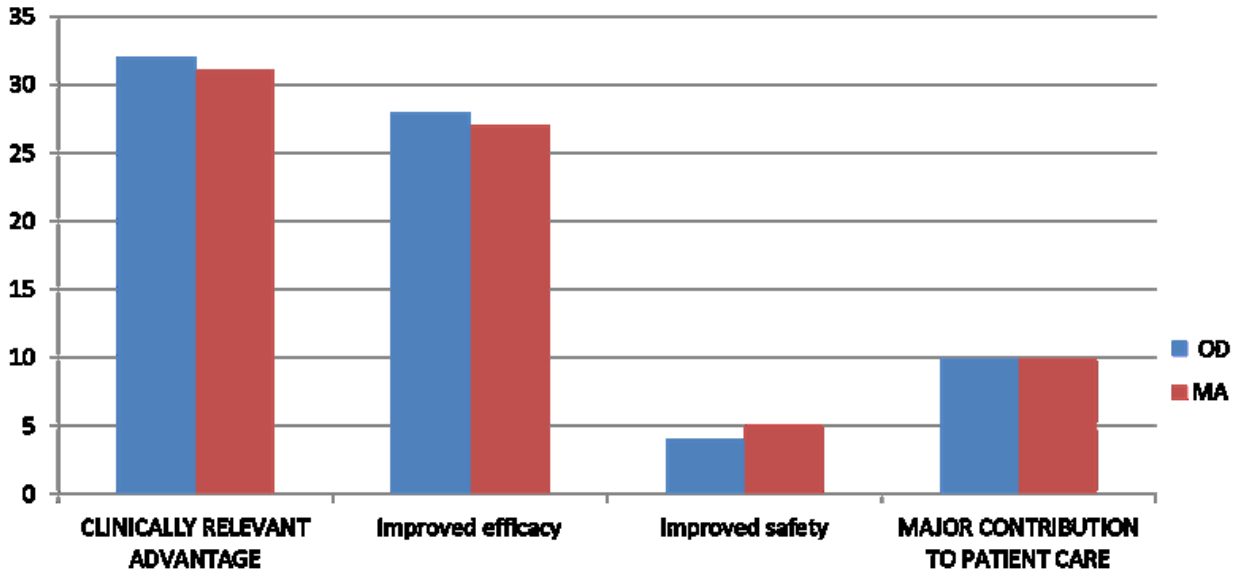
- Significant benefit over **authorised** products (satisfactory methods)
  - Reference medicinal products as defined in approved indication
  - Does not always correspond to "standard of care" e.g. hydroxyurea / siklos in sickle cell disease
- Orphan Designation: justification based on assumptions (sound pharmacological principles)
- At marketing authorisation: confirmation based on data to maintain orphan status
- COMP to assess whether or not sign benefit is supported by available data
- Sponsor can discuss data generation for justification in protocol assistance

Significant benefit applied, summary

Significant benefit	Clinically relevant advantage	Major contribution to patient care	Total
Designation *	350 (80%)	67 (15%)	438 (100%)
Marketing authorisation**	50 (86%)	12 (21%)	58 (100%)

*Significant benefit present in more than 70% of orphan designations; 5% based in combination of criteria (n=608)
**Significant benefit present in 76% of authorised orphan medicines (n=76)

Significant benefit by procedure / type (marketing authorization subset; n=33)



A case of assumption of SB at the time of designation

Clinically relevant advantage based on preclinical and early clinical data

Product for Peripheral T cell lymphoma

Authorised products for treatment:

Table 1. Combination Therapies in Relapsed or Refractory PTCL

Regimen	Comments
CHOP+Denileukin diftitox	ORR 48% (27% CR) (Dearden et al. 2011)
L-asparaginase+methotrexate+dexamethasone (AspaMetDex)	NK/TCL, ORR 78% (CR 61%) (Jaccard et al. 2011)
SMILE (steroid, methotrexate, ifosfamide, L-asparaginase and etoposide)	Extranodal NK/TCL, 38% CR (Suzuki 2010)
DHP (dexamethasone, cisplatin, cytarabine)	ORR 50% (Chau et al. 2001)
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)	NCCN NHL Guidelines v.3 (NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas Version 3 2011)
ICE (ifosfamide, carboplatin, etoposide)	Transplant-eligible, CR in 2 patients (Hertzberg et al. 2003)
GEM-P (gemcitabine, cisplatin, methylprednisolone)	ORR 69% (CR 19%) (Arkenau et al. 2007)

Case SB at time of designation

- antitumoural activity of the product on different tumour cell lines;
- Experimental models T-cell malignancies
  - reduction in tumour volume was demonstrated in combination with rituximab when compared to vehicle;

Case SB at time of designation

- phase 2 study in patients with relapsed or refractory PTCL
- Preliminary evidence of tumour response
  - four responses were achieved among the 8 patients in the PTCL group: 3 CRs and 1 PR
- Targeting aurora A kinase inhibition is a valid therapeutic approach for treating PTCL → pharmacology considered

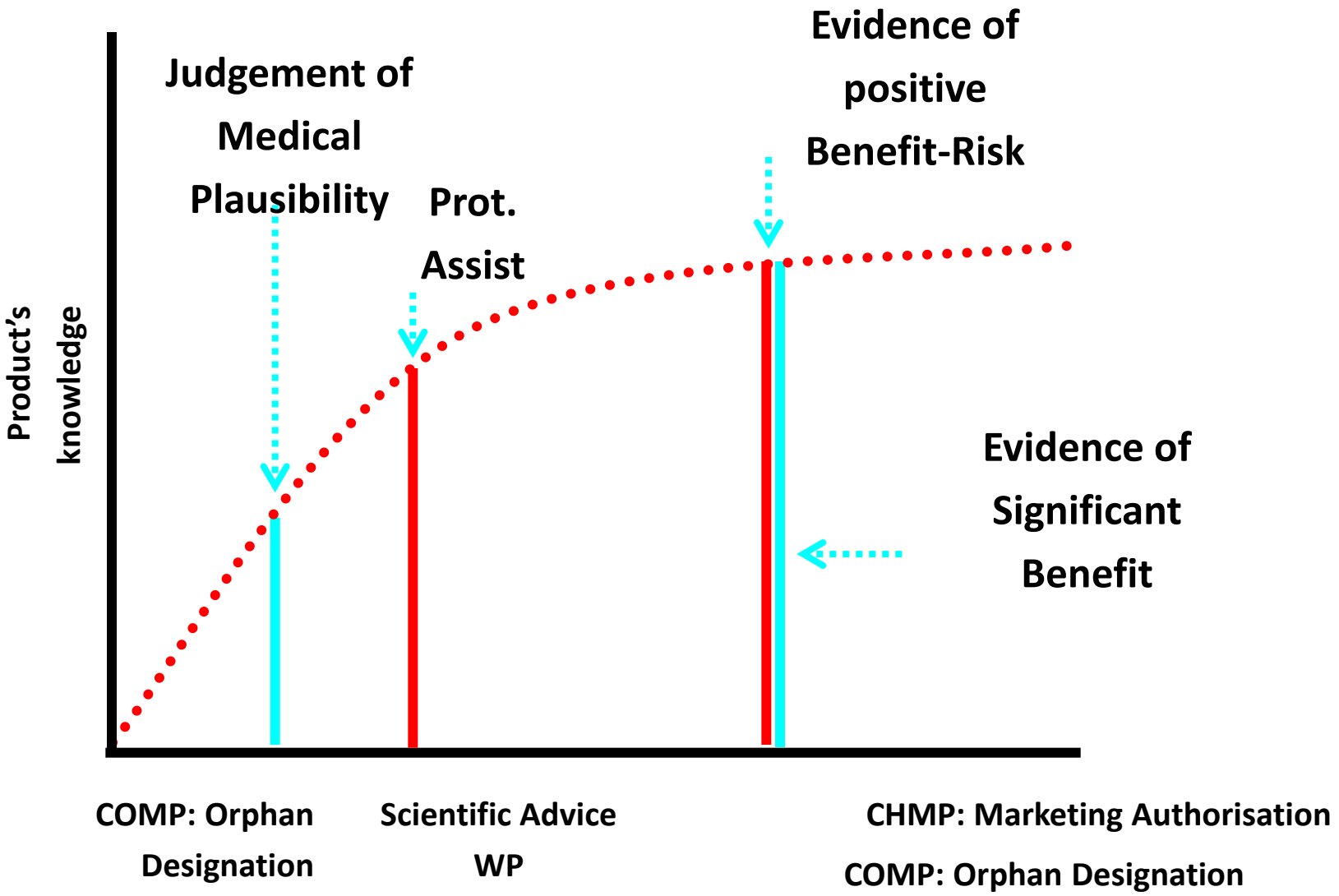
Case SB at time of designation

- sufficient justification has been provided that XXXX *may be* of significant benefit
- potential clinically relevant advantage
  - alternative mechanism of action which has the potential to translate into clinical efficacy
  - early clinical results: complete and partial responses in patients with aggressive relapsing or refractory peripheral T-cell lymphoma

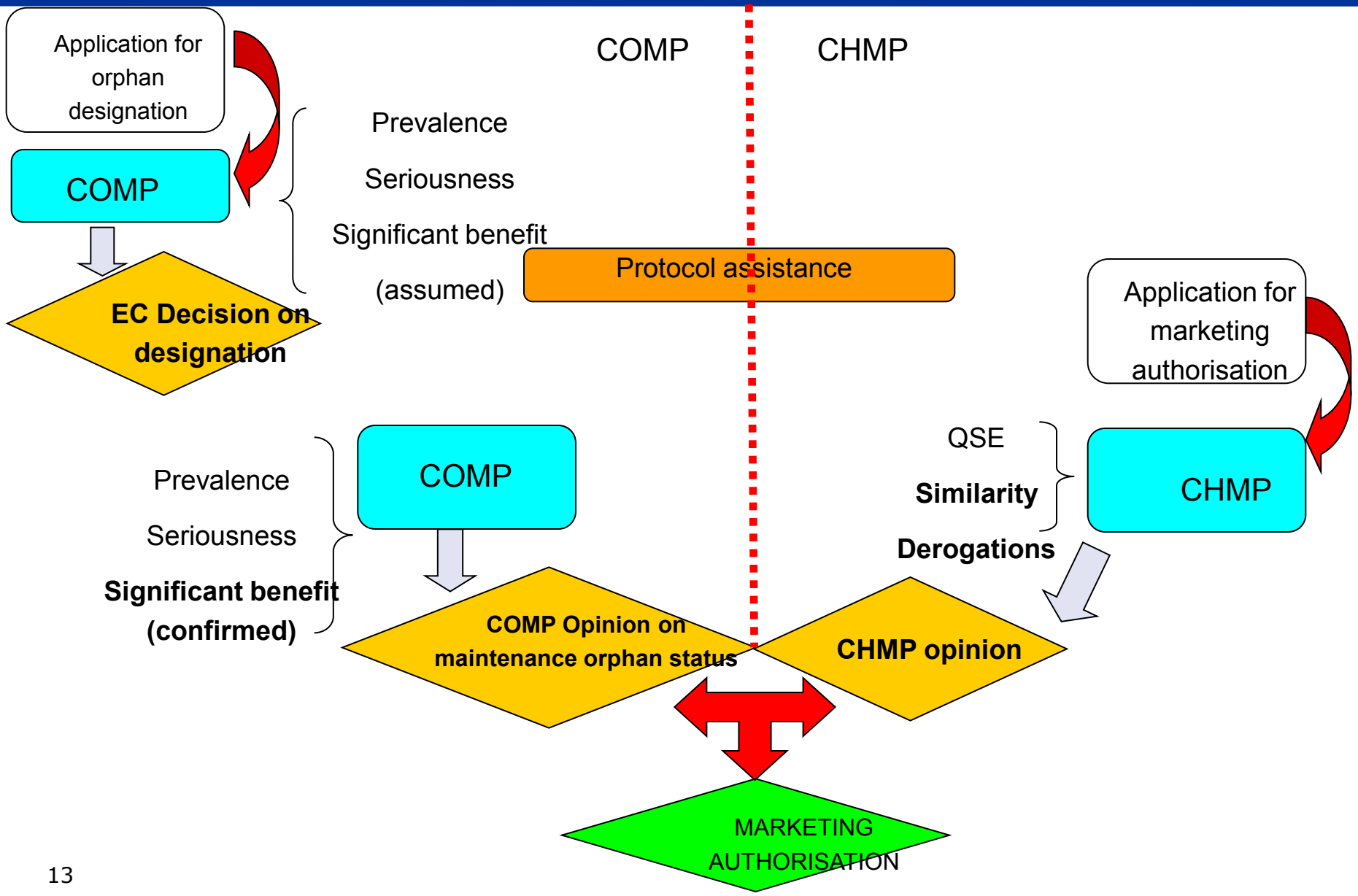
SB at the time of marketing authorisation: confirmation orphan status

CONFIRMATION ORPHAN STATUS → required by the product's orphan designation

- Confirmed: authorisation and [illegible] to marketing exclusivity
- Not confirmed: authorisati[illegible]as non orphan (so, no marketing exclusivity)



COMP and CHMP roles


COMP
CHMP
Application for orphan designation
COMP
Prevalence
Seriousness
Significant benefit
(assumed)
EC Decision on designation
Protocol assistance
Application for marketing authorisation
Prevalence
Seriousness
Significant benefit
(confirmed)
COMP
QSE
Similarity
Derogations
CHMP
COMP Opinion on maintenance orphan status
CHMP opinion
MARKETING AUTHORISATION

Authorised products not showing SB

Product	SB at orphan designation	At marketing authorisation
XXXX for treatment of angioedema	EU-wide availability (major contribution patient care)	Another prodcut approved in 22 member states through mutual recognition
YYYY for treatment of renal cell carcinoma	New mechanism of action and improved efficacy (clinically relevant advantage)	YYYY unable to show a relevant clinical advantage compared to reference treatments
ZZZZ for treatment of gastric cancer	Better efficacy (clinically relevant advantage)	ZZZZ was ”only” non inferior to reference treatment Improved safety claimed could not be supported by data

Authorised products not showing SB

Product	SB at orphan designation	At marketing authorisation
WWW for treatment of angioedema	EU-wide availability (major contribution patient care) and improved PK	Another prodcut approved in 22 member states through mutual recognition Pharmacokinetic characteristics not translated intorelevant clinical advantage
VVVV for treatment of malaria	Oral formulation plus easy administration (major contribution to patient care and potential better efficacy (clinically relevant advantage)	No data valid for EU that justifies clinically relevant advantage (noninferiority to EU standard)

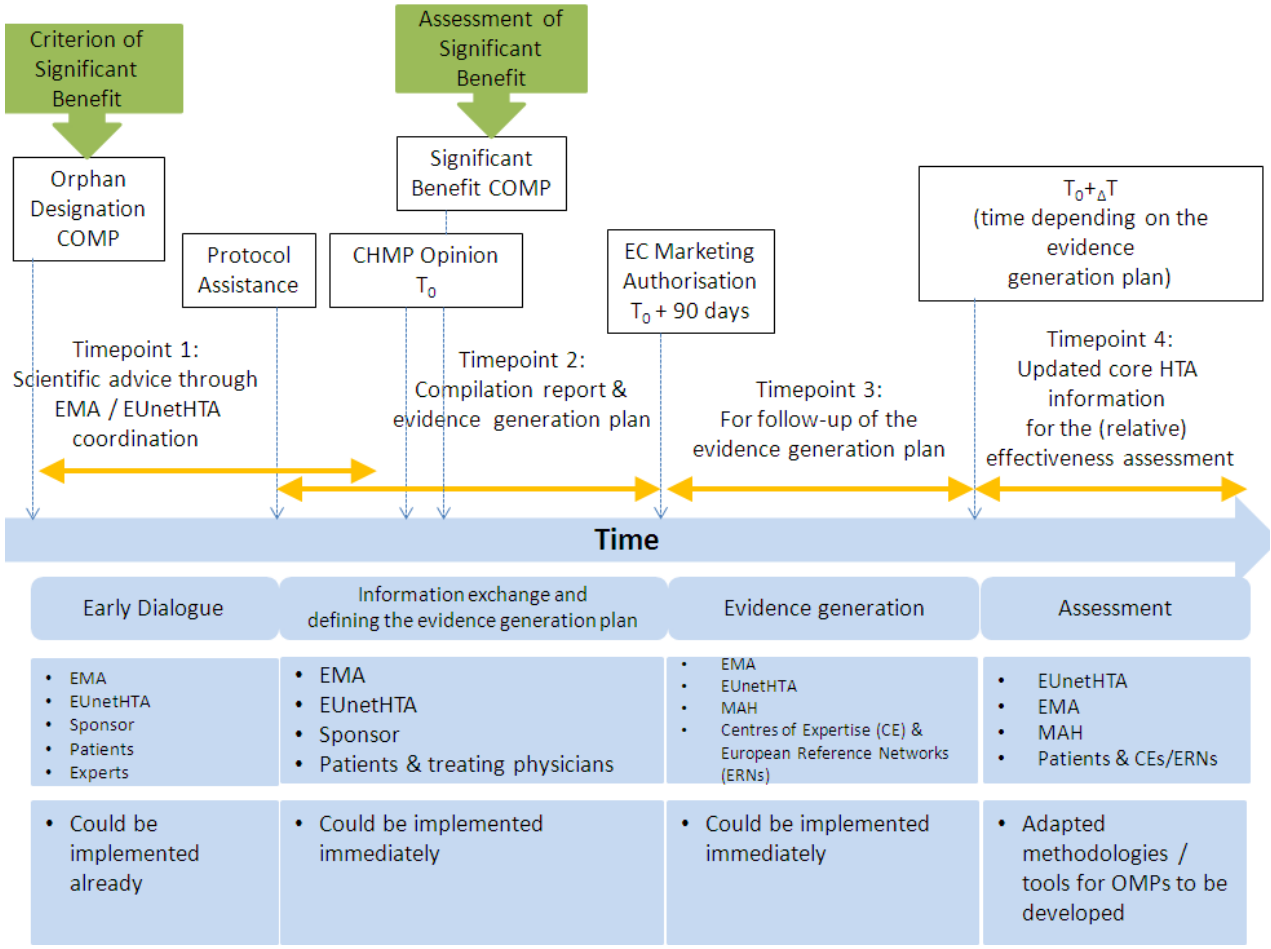
Communicating on significant benefit

- Public summaries of opinion at time of designation and review → Project to increase level of detail (opportunity for collaboration)
- Withdrawal strategy before adoption of opinions → absence of public summary
- Since Sept 2012 publication of COMP minutes
  - → transparency on discussion at the time of marketing authorisation
  - balancing confidentiality and public health interests

Significant benefit: generating and sharing evidence

EUCERD recommendation on CAVOMP

- "continuum of evidence generation that takes place during the life cycle of an individual OMP "
- "ways to facilitate scientific information exchange on orphan medicinal products, in order to support the Member States in their processes of making informed decisions on the scientific assessment of the clinical effectiveness of an orphan medicinal product"
- " **collaboration between the EMA and the EUnetHTA**, (…) such as: early dialogue and scientific advice,(…) assessment of significant benefit, added clinical benefit, and clinical superiority.



http://www.eucerd.eu/?post_type=document&p=1446

Thanks for your attention

Any questions?

Contact: jordi.llinares@ema.europa.eu

More information: http://www.ema.europa.eu; in special topics / medicines for rare diseases

Back up slides

and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final)

Assumption of improved efficacy

a) clinical data absent

- compare effects of authorised treatments or established methods in same pre-clinical models (direct comparison)
- different mechanism of action insufficient by itself
  - must justify MoA → improved efficacy

b) clinical data available

- may not be direct comparative at initial designation
- if not, effects from exploratory studies compared with data from published lit. may be OK

and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final), cont'd

Assumption of improved safety

- Clinical experience
  - (exceptionally, reference to pharmacological properties)

- If no clinical data – if current methods have significant safety problems (documented) and extensive extrapolatable experience from other authorised indication(s)

- Safety issues with current methods must be documented and not theoretical
  - (recombinant/transgenic products)
  - Cannot compare theoretical risk of current method with theoretical risk (or its lack) of product under development

and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final), cont'd

Assumption of major contribution to patient care

- Route of administration more convenient – better compliance
  - supported by data

- Quality of life-improvement
  - supported by data

- Supply/Availability
  - supported by data

Legal basis (I)

Art 5 (12) Regulation (EC) 141/2000

- A designated orphan medicinal product shall be removed from the Community Register of orphan medicinal products:

(…)

(b) if it is stablished before the marketing authorisation is granted that the criteria laid downin Article 3 are no longer met in respect of the medicinal prodcut concerned;

(…)

Legal basis (II)

Commission Communication

(July 2003; 2003/C 178/02)

(B.2) removal on basis of Art 5(12)(b) "must be preceded by a re-evaluation by the Committee for Orphan Medicinal Products of the criteria laid down in Article 3"

"In particular" significant benefit but **not only**

(B.2.1) report on fulfillment of designation criteria to be sent when Sponsor submits MAA

Information to be assessed in parallel to the marketing authorisation assessment

Sponsor may be invited to provide additional information in case of reasonable doubt

Specific requirements MAA

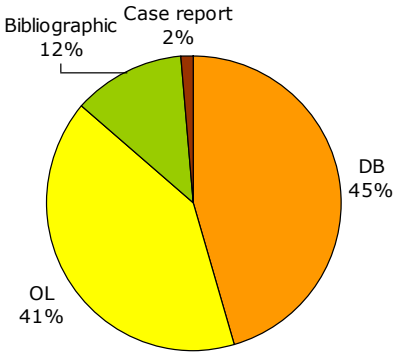
Confirmation designation criteria

- Report to orphan medicines section
  - At time of submission MA
  - Possible to update
- Need to address all designation criteria
- Standard set at time of authorisation
- Assessment by COMP; opinion after MA opinion by CHMP

Level of evidence

Of the granted marketing authorisations:

- 30 (45%) MAAs included double blinded randomised studies
- 27 (41%) MAAs included open label studies
- 8 (12%) MAAs were based on bibliographical data
- 1 (2%) MAAs were based on case reports



Of the rejected marketing authorisations:

- 15 (37%) MAAs included double blinded randomised studies
- 23 (56%) MAAs included open label studies
- 3 (7%) MAAs were based on bibliographical data

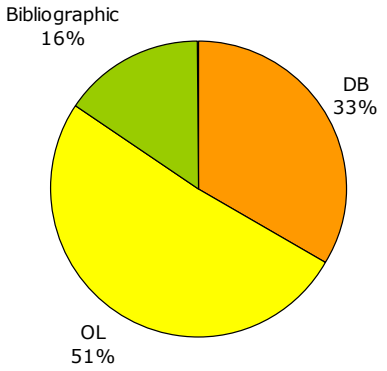


Figure 2.5.1: Survival (Full Analysis Set Population) – Study S1301/FLAGS