EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# An EMA perspective on dialogue with HTA/payer groups: current activities and future considerations

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Safety & Efficacy of Medicines


Land of
HTA Bodies
Land of
Regulators

# Observation: Publications

Clin Pharmacol Ther. 2010 Feb;87(2):152-4.

**Medicines regulation and health technology assessment.**

Breckenridge A, Woods K, Walley T.

Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers

*Hans-Georg Eichler, Brigitte Bloechl-Daum, Eric Abadie, David Barnett, Franz König and Steven Pearson*

**What principles should govern the use of managed entry agreements?**

**Marianne Klemp, Katrine B. Frønsdal**
*Norwegian Knowledge Centre for the Health Services*
**Karen Facey on behalf of the HTAi Policy Forum**
*University of Glasgow*

Pharmacoeconomics. 2010;28(10):915-22. doi: 10.2165/11535400-000000000-00000.

**Comparative effectiveness research: the view from a pharmaceutical company.**

Berger ML, Grainger D.

Curr Med Res Opin. 2010 Sep;26(9):2119-26.

**Addressing the health technology assessment of biosimilar pharmaceuticals.**

Stewart A, Aubrey P, Belsey J.

# Press Release 16 February 2010

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

# Setting the scene

## Decision making

One MA decision valid in 27 Member States (plus EFTA countries) **<=>** Several (30+) decisions across Member States about market access

## Criteria

Different evidential and analytical standards between regulators and HTA bodies

# Marketing Authorisation requirements

28a. *Risk-benefit balance:*

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28, first indent:*

Directive 2001/83/EC

* any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health

**=> In general, key for the benefit-risk decision are data from "controlled clinical trials"**

In the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations.

Regulation (EU) 726/2004,

Recital (13)

# Role of Active Control for Regulators

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1 November 2010
2 EMA/759784/2010
3 Committee for Medicinal Products for Human Use

4 Reflection paper on the need for active control in
5 therapeutic areas where use of placebo is deemed ethical
6 and one or more established medicines are available
7 Draft

Public consultation completed on 31 March 2011

# Relative effectiveness

*Relative effectiveness* can be defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice.*

⇒ **increasingly used by EU member states to help policy makers to identify the most valuable medicine**

* http://ec.europa.eu/pharmaforum/docs/rea_principles_en.pdf

# Objectives for HTA – An example

**2 Ziele der Untersuchung**

Ziele der vorliegenden Untersuchung sind:

- die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich untereinander,
- die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich zu einer Behandlung mit nicht biotechnologisch hergestellten Arzneimitteln,
- die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich zu einer Behandlung ohne Therapieerweiterung (mit oder ohne Placebokontrolle),

jeweils als Zweitlinientherapie bei Patienten mit rheumatoider Arthritis hinsichtlich patientenrelevanter Endpunkte.

Unter Therapieerweiterung ist eine weiterführende Therapie zu verstehen, die ergänzend zur bisherigen Therapie begonnen wird.

Unter Zweitlinientherapie wird im Rahmen der vorliegenden Nutzenbewertung der Einsatz von biotechnologisch hergestellten Arzneimitteln bei Personen, die mit einem krankheitsmodifizierenden Antirheumatikum vorbehandelt sind, verstanden. Hierbei ist der erste Einsatz des jeweils zu untersuchenden Arzneimittels gemäß Zulassungsstatus zu betrachten.

IQWiG: Vorläufiger Berichtsplan A10-01 - Biologika – Zweitlinientherapie bei rheumatoider Arthritis, Version 1.0

# EMA - EUnetHTA Collaboration

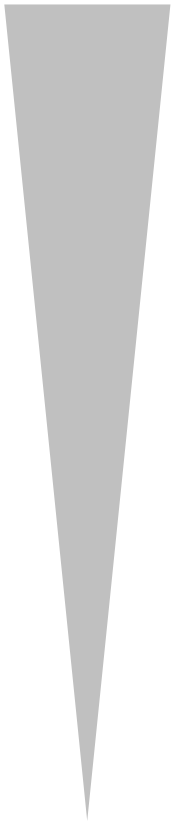
- Mandate from the High Level Pharmaceutical Forum:

> *6.4* Member States, with the involvement of the European Medicines Agency, should continue their efforts to consider how European Public Assessment Report and the National Public Assessment Report can further contribute to relative effectiveness assessments.

- Involvement of EMA including representatives from CHMP/COMP, EUnetHTA Joint Action as well as the EC
- Primary objective to improve EPARs:
  - Revised template as of October 2010 ✔
  - Review of implementation: mid 2011
- Other areas for exchange of information TBD (e.g. methodological guidelines, comparators/endpoints)

# Comments from HTAs on the EPAR

- Deviations form the standard template
- Harmonisation of structure and level of detail
- Use of tables and standardisation of their format
- Consistency of data presentation
- Presentation of patient flow-charts
- Presentations of median/means
- Link of conclusions to the product information
- Justification for choice of comparator
- Acceptability of surrogate/composite endpoints
- Acceptability of non-comprehensive data set
- etc



**Format**

**Content**

**Criteria**

# Objectives of the Template Revision

- Formal aspects of the presentation
- Clarification of areas for discussion
- Introduction of a summary table for main efficacy data

⇒ **Mostly affecting the clinical sections**, particularly through extended guidance for Discussion on Clinical Efficacy

⇒ Revisions with regard to presentation (details / clarity / standardisation) but **no change in evidential standards**

**Table XXX. Summary of Efficacy for trial <*trial*>**

| | | | | |
|---|---|---|---|---|
| **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 concealment, 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> | | | |
| **Results and Analysis** *{present the result separate for each analysis that is considered relevant for the conclusion on the trial; in any case the pre-specified primary analysis should be presented}* | | | | |
| **Analysis description** | **Primary Analysis** | | | |
| Analysis population and time point description | <Intent to treat> <Per protocol> <other: specify> *{consider adding a brief description of the definition of the population}* <time point> | | | |
| Descriptive statistics and estimate variability | Treatment group | <group descriptor> *{as per above terminology}* | <group descriptor> *{as per above terminology}* | <group descriptor> *{as per above terminology}* |
| | Number of subject | <n> | <n> | <n> |
| | <endpoint> *{label as above}* (<statistic>) *{e.g. mean, median, etc}* | <point estimate> | <point estimate> | <point estimate> |
| | <variability statistic> *{e.g. standard deviation, confidence interval, etc}* | <variability> | <variability> | <variability> |
| | <endpoint> (<statistic>) | <point estimate> | <point estimate> | <point estimate> |
| | <variability statistic> | <variability> | <variability> | <variability> |
| | <endpoint> (<statistic>) | <point estimate> | <point estimate> | <point estimate> |
| | <variability statistic> | <variability> | <variability> | <variability> |
| Effect estimate per comparison *{add as many rows as needed to describe the relevant statistical testing performed}* | <Co->Primary endpoint | Comparison groups | <group descriptors> *{as per above terminology}* | |
| | | <test statistic> *{e.g. difference between groups}* | <point estimate> | |
| | | <variability statistic> *{e.g. confidence interval, etc}* | <variability> | |
| | | P-value *{indicate statistical test used, e.g. ANOVA}* | <P-value> | |
| | <<Co->Primary> <Secondary> <other: specify> endpoint *{indicate endpoint using terminology as per section "Endpoint and definitions}* | Comparison groups | <group descriptors> | |
| | | <test statistic> | <point estimate> | |
| | | <variability statistic> | <variability> | |
| | | P-value | <P-value> | |
| | <<Co->Primary> <Secondary> <other: specify> endpoint | Comparison groups | <group descriptors> | |
| | | <test statistic> | <point estimate> | |
| | | <variability statistic> | <variability> | |
| | | P-value | <P-value> | |
| Notes | <free text> *{consider amongst others the following information: – reasons for drop-outs – critical findings with regard to the analysis}* | | | |
| **Analysis description** | **<Secondary analysis> <Co-primary Analysis> <Other, specify:>** *{also indicate if the conduct of the analysis was pre-specified}* | | | |
| *{repeat all the above sections for each analysis that is considered relevant}* | | | | |

# Exchange on Evidence Requirements

- Opportunity for dialogue between regulators and HTA/payer groups not only at time of licensing but early in the development process
  ⇒ **Parallel scientific advice for a particular project**

- Experience in various jurisdictions on a national level
- First pilot meetings in the context of trans-national SA procedures with representation from SAWP members, HTA/payer groups and applicants held
- Further experience to be gained

# Key Areas for Exchange

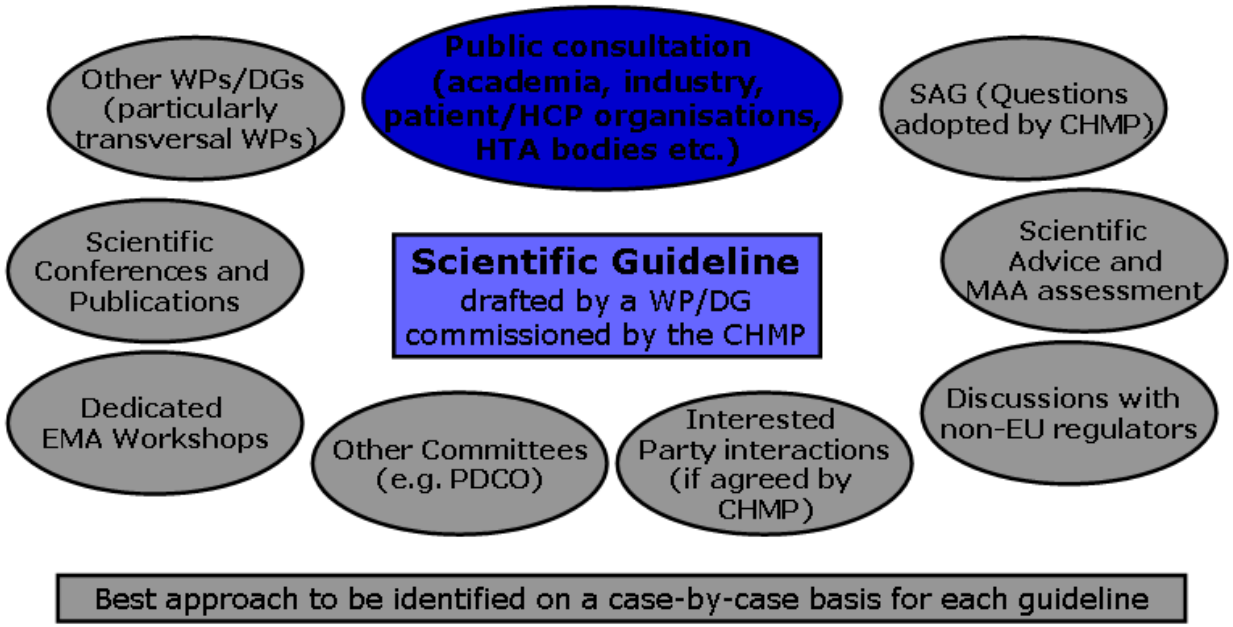
**=> Pre-authorisation requirements - Design elements of the pivotal clinical studies:**

- Endpoints (e.g. surrogate, composite)
- Comparator
- Patient population
- Duration of the study


**=> Post-licensing generation of data of mutual interest – post-marketing research programme**

# Beyond Individual Advice: Guidelines

EMA/CHMP Guidelines under public consultation with HTA groups as potential interested party:



# Methodological Guidelines for HTA

EUnetHTA Methodological Guidelines under development as part of Work Package 5 "Relative Effectiveness Assessment of Pharmaceuticals":

WP5 Objective:

| Title | Description | Indicators |
|---|---|---|
| Development of HTA tools and methods for Relative Effectiveness of Pharmaceuticals ) REA);<br><br>Application and field testing of developed tools and methods | To develop principles, methodological guidance as well as functional online tools and policies for REA by identifying areas where methodological guidance is needed and by providing it, suggesting ways to integrate REA of pharmaceuticals as a special version of the Core Model. In addition to test and implement a REA of (a group) of pharmaceuticals in line with the core HTA development. | Outcome indicator:<br><br>1. Recommendations on the Assessment of Relative Effectiveness identified and published<br><br>Target: Publication of the recommendations in an international journal (submitted). |

Source: http://www.eunethta.eu/Public/Work_Packages/EUnetHTA-Joint-Action-2010-12/JA-WP5---Relative-Effectiveness-Assessment-of-Pharmaceuticals/

# REA - Draft Background Review


Public consultation until 13 May 2011

# Harmonisation Efforts

**How far should we go to harmonise the differences?**

- Not necessarily *all* endpoints
- May need to resolve outstanding issues by way of adaptive trials, secondary endpoints, etc…
- But sufficient to enable one single development program that meets information needs of both communities

HG Eichler: Can we harmonise endpoints for licensing and reimbursement, DIA March 2011

# Considerations for Future Activities

1. **New Pharmacovigilance Legislation**
   - Integration of benefit-risk
   - Strengthened risk management planning
   - New legal basis for Post-authorisation Safety Studies and Post-authorisation Efficacy Studies

     => Implementing Measures under development

2. **ENCePP studies database**
   - Potential to explore needs of HTA bodies

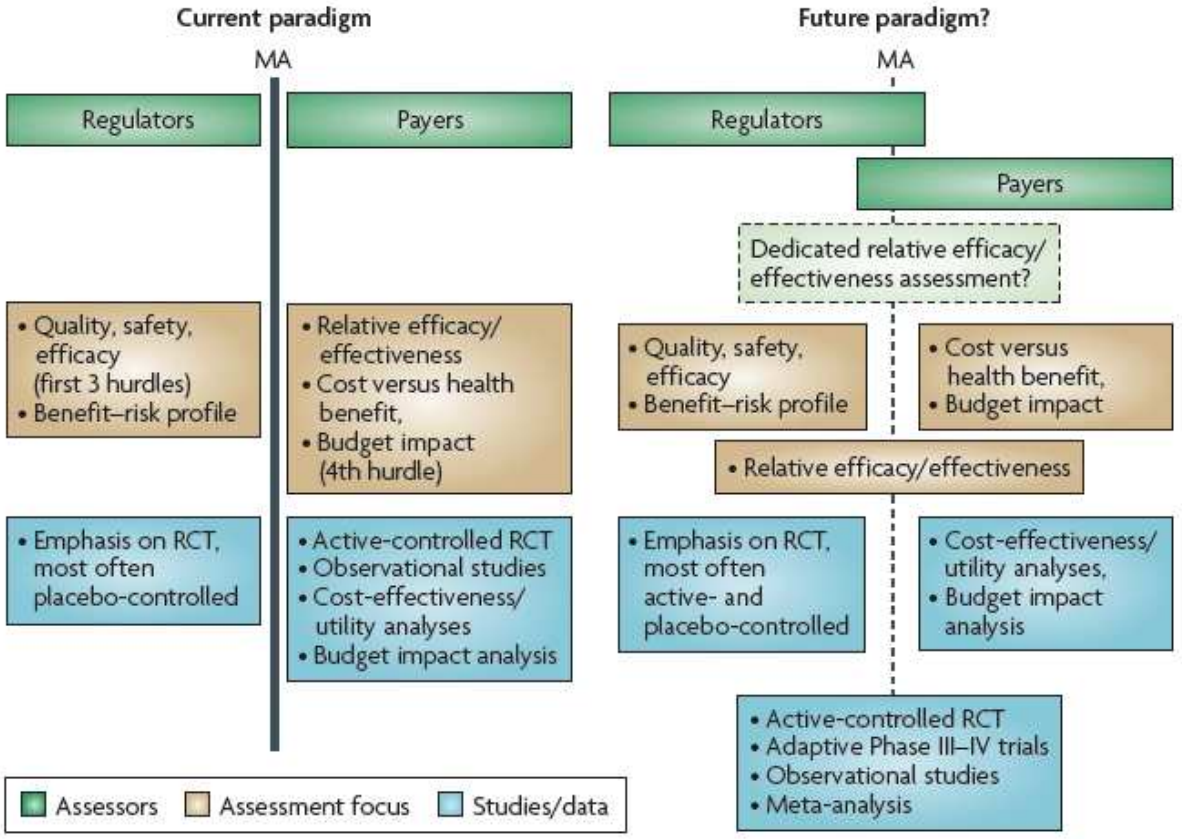
3. **Other activities**
   - E.g. Cross-border Directive, CAVOD initiative, …

# EMA Task Force

**Dialogue with HTA/payer groups in the context of Drug Regulation and Health Technology Assessment**

- Led by the Senior Medical Officer (Hans-Georg Eichler)
- Members of the EMA and its concerned scientific committees (CHMP/COMP)
- Overall co-ordination and communication
- Follow-up on agreed action items in the dialogue with EUnetHTA

# Perspectives




Eichler et al, Nat Rev Drug Discov. 2010 Apr;9(4): 277-91

# Perspectives (cont.)

"Limitations as to what can be achieved with HTA and limitations to the availability of evidence of comparative effectiveness at the time of market authorization provide ongoing challenges to all stakeholders. However, embracing CER [Comparative Effectiveness Research] is regarded as an essential step for the innovative pharmaceutical industry, as companies strive to more clearly demonstrate the effectiveness of their pipeline products with evidence that is compelling to payers and HTA agencies."

Berger et al, Pharmacoeconomics. 2010;28(10):915-922

# Perspectives (cont.)

"Health technology assessment (HTA) is as important as regulation to allow patients access to new medicines, and there are demands that the two processes should be carried out more closely together in time. Although the methods used by the regulator differ from those used by the health technology assessor, there is scope for synergies that would be useful to both parties. By providing scientific advice to sponsors of new medicines, both regulators and health technology assessors can also provide support for drug innovation."

Breckenridge et al, Clin Pharmacol Ther. 2010 Feb;87(2):152-154

# Conclusions

- There is a need to ensure that valuable medicines get to the patients – **Regulators and HTA bodies are accountable to patients**
- Dialogue is necessary between Regulators and HTA bodies respecting their different remits - **Exchange on scientific / methodological principles beneficial to avoid double-standards**
- Several initiatives are ongoing - **An EMA Task Force has been created to facilitate such dialogue**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