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Session:

The European framework on added therapeutic value and the effects on P&R decisions (HTA)

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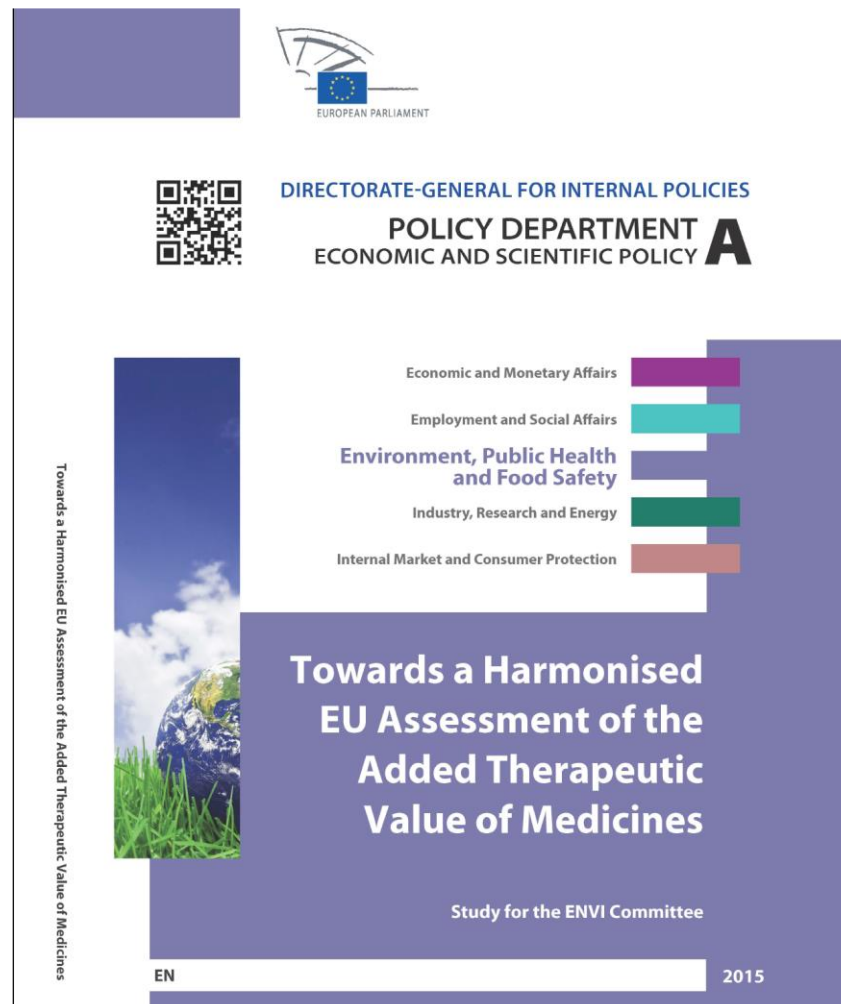


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[http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU\(2015\)542219_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf)



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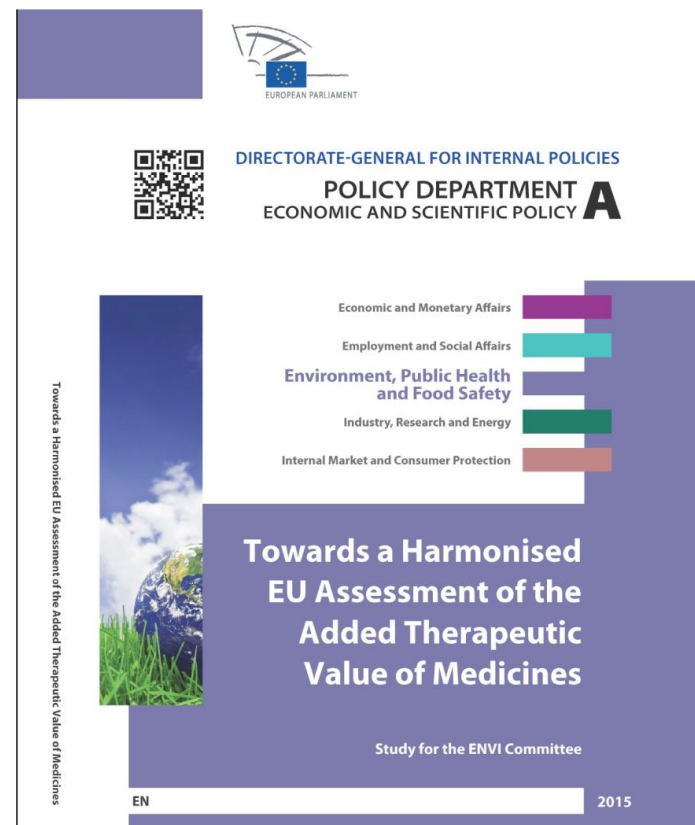
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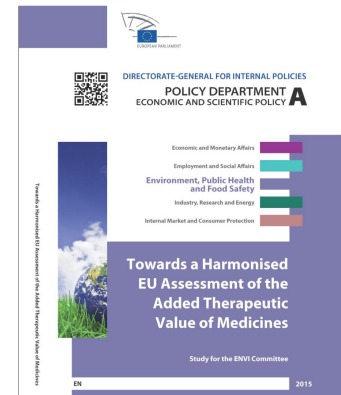
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The present study was undertaken upon request of the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament.

The aim is **to investigate the feasibility and opportunity of introducing a harmonised EU approach concerning the assessment of the added therapeutic value (ATV) of medicines in the European Union.**



►EU assessment of ATV / background in P&R

- **Transparency Directive (TD):** P&R decisions must be taken in a *transparent, objective and verifiable way* with respect of *strict timelines* (maximum of 180 days from submission to decision).

The Council of the European Communities, Dir. 89/105/EEC. OJ 1989;L40:65-71.

- The **High Level Pharmaceutical Forum (HLPF)** provided definitions of relative effectiveness and efficacy and endorsed the scientific nature of REA. The HLPF recommended implementing good practice principles in REA and to reward valuable innovation.

<http://bookshop.europa.eu/en/high-level-pharmaceutical-forum-2005-2008-pbND3008692/>

- The **Cross Border Directive / Art. 15:** the Union shall support and facilitate cooperation between national authorities or HTA-bodies

The European Parliament and the European Council. Dir. 2011/24/EU. OJ 2011;L88:45-65

- The **Joint Action initiatives / JA1** (methods), **JA2** (pilots) & **JA3** (implement)

http://ec.europa.eu/health/technology_assessment/cooperation_hta/index_en.htm

- **Relative Efficacy/Effectiveness Assessments (REA)** assessments are the main tools used to estimate ATV.

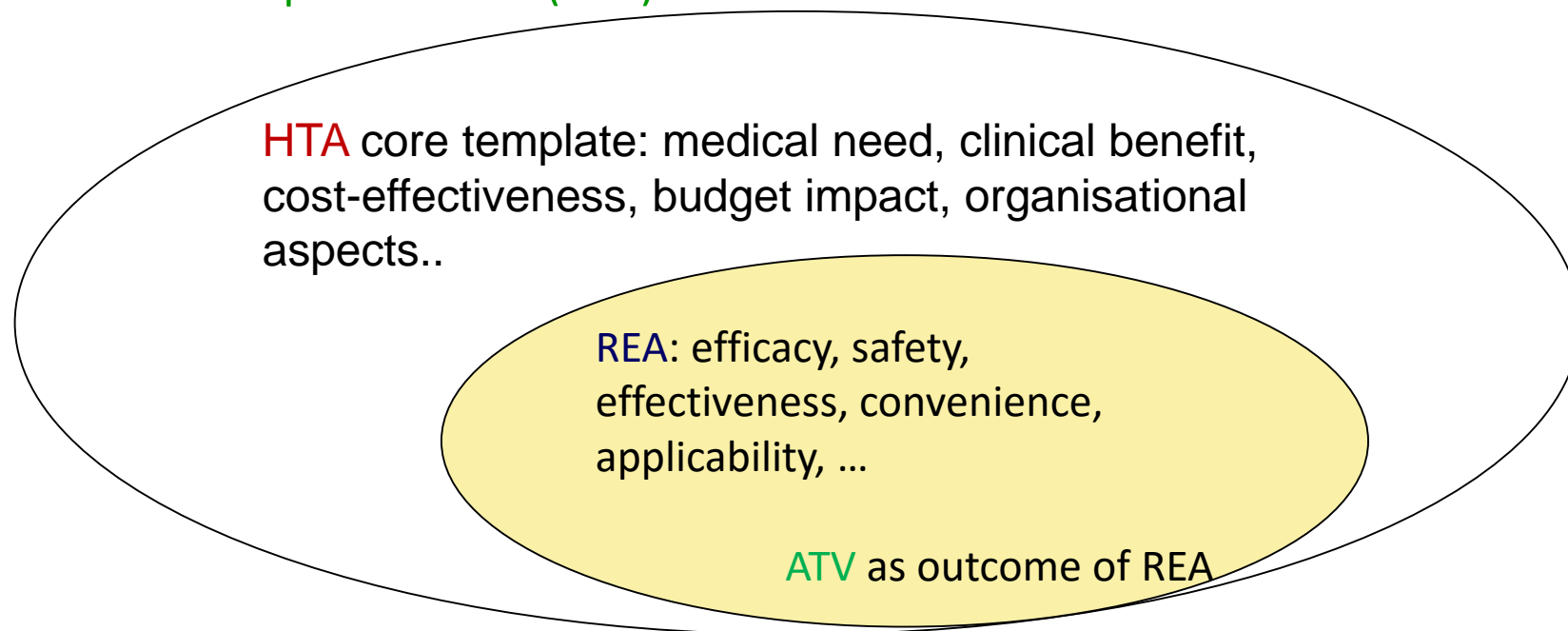
Relative efficacy and effectiveness are respectively the extent to which an intervention does more good than harm compared to one or more alternative interventions, either under ideal circumstances (usually controlled clinical trials) or under the usual circumstances of health care practice (daily practice).

High Level Pharmaceutical Forum 2005-2008. Final Conclusions and Recommendations of the High Level Pharmaceutical Forum.

- The **therapeutic value** can be defined in terms of various patient-relevant endpoints and relevant levels of effectiveness, efficacy and safety^{ISDB}.
- There is no universally agreed definition of **added therapeutic value**.

►EU assessment of ATV / ENVI-study / METHODS

- Added therapeutic value (ATV):



ATV has not been defined by the HLPF; but the HLPF endorsed the aim of REA to compare health technologies according to their ATV.

In this context ATV can be understood as the outcome of the REA.

►EU assessment of ATV / ENVI-study / **METHODS**

- Only analysis of the ATV-assessment in the P&R-context.

Marketing Authorisation Application (MAA)

1. European Centralized or MRP/DCP
2. Dossier based on
 - Efficacy
 - Safety
 - Pharmaceutical quality
3. Benefit/risk balance of the drug on its own

European Public Assessment Report
EPAR

Reimbursement Decision

1. Per member state
2. Evaluation builds on MAA-elements:
 - + Effectiveness, Convenience, Applicability
 - + Medical need
 - + Price and Budget impact...
3. Relative therapeutic value as compared to alternatives
4. Relative economic value as compared to alternatives $\Delta C / \Delta E$

National Assessment Reports

2 distinct phases in the study

- A mapping exercise on the use of ATV in 28 EU Member States (MS) by extensive review of the available (ENG) literature
- In-depth review of ATV practices in 6 selected countries:
 - Member States France, Italy, Austria, Poland, Slovakia and Sweden
 - Study flow:
 - Desk research
 - National country reports
 - Discussion with national HTA-experts (EU Joint Action on HTA)
 - Validated national reports

... in 3 months time!

►EU assessment of ATV / ENVI-study / RESULTS

Table 3: Overview of the use of ATV in the EU-28

Country	With what is the new medicine compared?	ATV classification levels	ATV impact on price	Assessment of cost effectiveness
Austria	The most similar comparator according to Anatomical Therapeutic Chemical (ATC) level, as long as this is reasonable. This is mostly all pharmaceuticals within a therapeutic class; however, it can also deviate from this	No added benefit (generics), analogous or similar therapeutic benefit, added therapeutic benefit for a subgroup of patients, added therapeutic benefit for the majority of patients, important added benefit for a subgroup of patients, important added benefit for the majority of patients	Medicines with important added benefit (for a majority of a subgroup of patients) are entitled to negotiate a price above the EU average price	Yes

►EU assessment of ATV / ENVI-study / **RESULTS**

Country	With what is the new medicine compared?	ATV classification levels	ATV impact on price	Assessment of cost effectiveness
France	Best standard care ⁷⁸	<p>ASMR I: Major improvement,</p> <p>ASMR II: Significant improvement,</p> <p>ASMR III: Modest improvement,</p> <p>ASMR IV: Minor improvement,</p> <p>ASMR V: No improvement.</p>	Medicines with ASMR I to III are entitled to a price premium, determined by the manufacturer and benchmarked to foreign prices. The same applies to medicines with ASMR IV with limited market potential.	Yes

►EU assessment of ATV / ENVI-study / RESULTS

N = 28 MS Differences were found in:

- Definition and choice of comparator(s); 'current standard'
- The use of ATV as a distinct parameter: FR, IT, BE... >< UK, SE
- The level of measurement:
 - Ordinal scale: e.g. IT, FR, DE, NL
 - Categorical: e.g. BE, CZ
 - Interval scale: SE (QALYs)
- The impact on decisions:
 - Probability of listing as reimbursable medicine e.g. IT, FR
 - price premium only if ATV: in BE, FR, NL, DE...
 - Need for pharmaco-economic analysis may be dependent on ATV

N = 6 MS Main findings:

- HTA-agency: different structure, resources, objectives and scope
- Differences in
 - the ATV-assessment methodology, its documentation
 - Publication of ATV-assessment results
- Focus on clinical end-points and direct H2H-comparisons
- Assessment is dependent on manufacturer's data
- No or limited QC-procedures of the assessments
- REA often preceding CEA

+/- similar aim and approach

but

major differences in methods and implementation process

1. Recommendation on the need of ATV as a distinct and specific outcome

Added therapeutic value should be assessed as a distinct outcome of relative efficacy assessments, separately from cost and other economic considerations.

2. Recommendations on the use of ATV in a reimbursement setting

ATV definition and composition

A product has ATV if the incremental health benefit is clinically relevant. To this end, the therapeutic value of a medicinal product should refer to items such as efficacy, safety and effectiveness. The weighting given to the specific elements will be dependent on the disease characteristics and the available treatment options.

2. Recommendations on the use of ATV in a reimbursement setting (cont.)

ATV measurement scale

The measurement scale for ATV should be harmonised. Preference is given to an ordinal scale.

ATV estimate as the outcome of REA

Strengthening further the cooperation between the various competent authorities, EUnetHTA and other stakeholders. The interactions happening in the Joint Action programme will help to identify all sources of heterogeneity among the assessors and might facilitate the development of a stepwise approach towards good practices to reduce this variability.

The interpretation of the clinical benefit of the new medicinal product will depend on:

- the assessor's understanding of good clinical and statistical practice
- the importance given to the primary and secondary end-points; the acceptability of surrogate end-points; the clinical relevance of a statistical significant difference; the applicability of indirect treatment comparisons
- the uncertainty relating to the incidence of adverse events (which are seldom a primary end-point)
- the possibility to interact with other experts;
- the importance given to patient input;
- the understanding of the particularities of an R&D programme for orphan diseases
- The availability (and endorsement) of sound methodology and guidelines etc.

3. Recommendations on the organisational level

Assessment by experts versus stakeholders

A multi-disciplinary expert panel instead of a panel of stakeholders should perform the REA.

The HLPF made a clear statement on “...the scientific assessment of the relative effectiveness of medicinal products...”.

3. Recommendations on the assessment level (cont.)

Assessment by international joint committee of experts

For reasons of local expert resource capacity issues, of the scientific nature of REA and of the similar objectives in REA between Member States, preference is given to an international European joint committee which performs the REA of medicinal products near to market authorisation, prior to local reimbursement submission.

4. Recommendations on transparency and quality assurance of the REA methods and ATV estimation

On the methodological level, the competent authorities should increase their efforts to develop good practices in the field of REA.

Authorities and applicants should formally endorse standards for REA.

REA methods and REA assessment reports should be made public.

The applied assessment process should be compliant with the endorsed assessment standards and should be subject to quality control.

►EU assessment of ATV / ENVI-study / **ATV & P&R decision**

REA results + medical need + price + cost-effectiveness + impact on the healthcare budget + ... = affecting the P&R-decision

> < *But the Transp.Dir?*

Example (Belgian reimbursement data, 2002-2007):

$$*P_{[\text{pos decision}]} = a_1 \cdot \text{ATV} + a_2 \cdot \text{Budget Impact} + a_3 \cdot \text{ICER}$$

* Binary logistic regression model explaining 58% of the variance in the reimbursement decision :

- Which *remaining elements* explain residual variance?
- What *if repeated to actual medicinal product* submissions?
- What if...

Bormans V, Van Wilder P. Effectiveness, efficiency and budget impact affect the Belgian drug reimbursement decision (DRD). Value in Health 14 (2011):A233-A510. Abstract HT1.

Many thanks for your attention!

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