The German Healthreform and IQWiG Update

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- The New AMNOG Process
- Key Elements of the Law
- The Industry Dossier
- IQWiG Methods 4.0 Draft
Optional Prefiling consultation of JC

- Before start of phase III possible
- Studies Design
- Comparator
- Endpoints

Before Submission
- Time until Submission remains untouched

- Comparator
- Format and Content of Dossier

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AM-NutzenVO: Regulations for benefit assessment

Overview for value dossier

- Approved therapeutic indication
- Medical benefit & additional medical benefit compared to appropriate comparative therapy
- Number of patients and patient groups who benefits
- Costs of therapy for SHI
- Requirements for quality assured application
Scope of benefit assessment, § 35a SGB V

- For each innovative agent:
  - Launch (Lauer-Taxe) = Value dossier
  - Extension of therapeutic indication

In-line products:
- Only, if requested by JC
- Extension of therapeutic indication for evaluated pharmaceuticals
- Focus on pharmaceuticals competing with evaluated pharmaceuticals

Exception:
- Expected SHI Volume ≤ 1 mio € /year
- Orphan-drugs
  - Additional benefit proved by marketing authorization, but magnitude of effect and costs for the SHI
  - Dossier and benefit assessment by more than 50 mio € /year SHI-volume

- Additional Benefit
  - Industrie has to prove additional benefits against the comparator
  - Comparator will be determined by JC
    - FRP Drug
    - Endpoint studies
    - EBM
  - Additional benefit based on SPMC and clinical studies with patient relevant endpoints according to EBM
  - Patient relevant endpoints (Mortality, Morbidity QoL)
  - Prefarable H2H RCT
  - Indirect comparison are an option
  - If no studies are available JC can ask for new studies
Modul 1

- Summary
  - Foundation of the Negotiations

Modul 2

- Active agent, ATC code, PZN, packaging size, etc.
- Mode of action
- Authorized areas of application
- Other authorized areas of application in Germany
- Status of authorization internationally
**Modul 3**

- **Therapy cost for the GKV**
  - Costs in pharmacy sales prices
  - Costs of additional GKV payments according to SPCM
    - (e.g. only monitoring costs which are mentioned in SPCM will be counted)
  - Calculation of the annual costs of therapy

- **No Modeling**
  - No QUALY
  - No Cost Effectiveness Analysis
  - No Budget Impact Model

- **Paper and Pencil Analysis based on SPMC and direct Costs**

- **Foundation for negations**
  - no influence on additional benefit
  - Is reviewed by IQWiG

**Comparative treatment**

- appropriate comparative treatment
  - EBM based, with Endpoint Studies, FRP

- Reason for the choice:
  - Minutes of the advice of GBA
  - Reason

**Epidemiology**

- Description of the disease, characterization of the target population
- Unmet need
- Prevalence and incidence in Germany
- **Number of patients with significant additional benefits**
**Modul 4**
- **Benefit and Additional Benefit**
  - Systematic Review
    - Bibliographical research + Study register search + Industry IIR
  - Assessment of the Evidence (biometric quality of the study)
  - Patient relevant Endpoints, Design
  - Summarizing the Studies in Meta-analyses
    - Random Effect Model
    - If heterogeneity not large no pooled effect should be calculated
    - subgroups and the effect modifying variables
  - If no H2H studies available Indirect Comparison may be accepted
  - Non Randomized studies may accepted
    - Reason, why it is impossible or inappropriate to implement RCTs
    - Reasons why the observational study are not biased
    - Non Randomized study will have little value in the process
  - Surrogate Endpoints may not be accepted

**Modul 5**
- Clinical Study Reports
- Common Technical documents
  - CTD 2.5 2.73 2.74
- EPAR
- Modul 4 is not confidential
- Modul 5 confidential parts could be flagged
### Classification (AM-NutzenV)

<table>
<thead>
<tr>
<th>Level</th>
<th>Description (AM-NutzenV)</th>
<th>Examples (AM-NutzenV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Extensive additional benefit</td>
<td>• Cure</td>
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<td></td>
<td>• Sustainable and benefit not yet achieved</td>
<td>• Extensive extension of life span</td>
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<td></td>
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<td>• Long lasting suppression of heavy symptoms</td>
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<td>• Avoidance of severe side effects</td>
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<tr>
<td>Level II</td>
<td>Significant additional benefit</td>
<td>• Soothing of severe symptoms</td>
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<tr>
<td></td>
<td>• Benefit not yet achieved</td>
<td>• Moderate extension of life span</td>
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<td>• Perceptible relief</td>
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<td>• Other significant</td>
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<tr>
<td>Level III</td>
<td>Marginal additional benefit</td>
<td>• Soothing of mild symptoms</td>
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<td>• Moderate or only small benefit</td>
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<tr>
<td>Level IV</td>
<td>Additional benefit not quantifiable</td>
<td>• Scientific data do not allow quantification of additional benefit</td>
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<td>• Not detailed in AM-NutzenV</td>
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<tr>
<td>Level V</td>
<td>No additional benefit</td>
<td>• Not detailed in AM-NutzenV</td>
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<tr>
<td>Level VI</td>
<td>Less benefit than comparable therapy</td>
<td>• Not detailed in AM-NutzenV</td>
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**Frankreich**

[Map of Europe highlighting France]
France: 70% of the drugs have no additional benefit.

- IQWIG will Review the dossier
  - According standards of EBM and IQWiG Methodpaper
  - Validity and Completeness
  - Quality of Design and Analysis
  - Is the additional benefit demonstrated?
  - How strong is the Evidence?
  - Certainty of the Results
  - Magnitude of the Effects?
  - IQWiG Conclusion can differ from Industry conclusion
Surrogate Endpoint

- (see also Rapid Report: Surrogate Endpoints in Oncology)
- Not patient relevant
- Validation through Meta Analyis of several RCTs with Surrogate and Endpoints. (Indication and Intervention)
- If no Validation possible (R to low) STE (Surrogate Treshold Effect) approach should be maintained
- STE- minimal Treatment effect to assure effect concerning the patient relevant endpoint
Statistical Significance is not enough

Figure 1. Criteria for a statistically significant result using the threshold $\delta$ (dashed line) that defines the minimum clinically relevant effect.
Step-procedure for Clinical Relevance

1. If a valid $\delta$ on for Group Level is available use this for shifted Null hypothesis.
2. If a valid (MID) Responder definition is available use this. Significance is sufficient.
3. If not Available than use SMD (Hedge G) = 0.2 or adapt MID to group level.

Combined Endpoints
- Individual components must all patient relevant
- surrogates only if of Institut as valide recognition
- Components has separately represent
- Are the weights equal
- Is the effect parallel?
- Wasn't relevant endpoints point considered?
- posthoc defines?

Indirect Comparisons
- MTC is in Development
- Accepted for the early Benefit Assesment and Cost-Benefit Assesment
- Evidence of MTC is lower than H2H
Subgroup Analysis

- **Method Paper 3.0**
  - Arbitrary selection of subgroups
  - post hoc Analysis
  - Multiple testing
  - Small Power
  - SGA should not dominate (NS) the primary analysis,

- **Method 4.0**
  - exception social law implications
  - Life specific Characteristics, age sex
  - AMNOG: Identify Supgroups of patients with additional benefit
  - Difference between Studies and Meta Analysis
  - Data of Subgroups should only pooled, if there is no substantiell heterogenity
    - Interaction Test P<5% Proof of Subgroup Effect
    - Interaction Test P<20% Indication of Subgroup Effect
    - **Proof: no pooled Estimator**
    - Indication: Description of Subgroups
    - More than two subgroups – p>20% pool

- **What does this mean ?**
  - For our products
  - For our studies
  - For profession
Module 4 Benefit and Additional benefit

- Price will be function of
  - comparator
  - Disease area
  - Magnitude of effect
  - Evidence