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# Is a single evidence base possible across Europe?
## *How should evidence generation efforts be focused to meet payer requirements for market access?*

By RJW&partners

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# Panel Participants

Panel Member:
Timm Volmer

Panel Member:
Wil Toenders

Panel Member:
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Moderator:
Ad Rietveld


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# Executive Summary (1/3)

- While European regulatory requirements have become harmonized via EMA approval, there remain differences in payer evidence expectations across countries.
- In the early 1990s, efforts to harmonize pricing and reimbursement procedures was resisted by EU member states due to a desire to retain autonomy on pricing. Instead the focus shifted to transparency of decision-making.
- Manufacturers are able to create a pan-European evidence base for regulatory approval. In contrast, payers take a broader perspective and require country-specific insights into relative effectiveness, benefits in practice, clinical relevance of these benefits, disease severity and comparison to market relevant (standard of care) treatment.
- Despite a clear rationale for harmonization, there are three main methodological challenges for joint relative effectiveness assessments:-
  - Payers across countries may request different clinical comparators given differences in national guidelines, medical practice, market shares of individual products and acceptance of off-label comparators.
  - There are differing opinions on the acceptance of intermediate and/or surrogate endpoints across countries.
  - Some payers only focus on data from RCTs, but some countries also take observational studies into consideration.

# Executive Summary (2/3)

- Harmonization can be addressed at two levels: (1) utilisation of the evidence base for reimbursement (2) rigour of scientific methodology and approach to decision-making.
- The debate on the need for co-operation between payers not only takes place between EU Member states but also within individual countries – particularly in countries with strong regional autonomy such as Spain and Italy.
- Irrespective of the level at which co-operation is discussed, a key question is what level of harmonization is considered possible and desirable within Europe:-
  - EU Member states, but also regions within a country, have differing levels of GDP and healthcare expenditure, and therefore access to different levels of resource
  - Different levels of financial resource and differing local population needs lead to different priorities - this encourages national and regional/local payers to be autonomous in their decision-making without interference from other countries and/or EU bodies like the European Commission.
- Although countries with a less well-established assessment procedure could derive the most benefit from European co-operation, there is the perception among payers that harmonisation may give rise to unsustainable healthcare demands on EU Member states with the smallest healthcare budgets.

# Executive Summary (3/3)

- Unlike the regulatory authorities, ultimately payers think more in terms of effectiveness rather than efficacy, and the sustainability of their individual healthcare systems is paramount from their perspective.
- Although organizations such as EUnetHTA exist, there is unlikely to be a central reimbursement institute that parallels the EMA in the foreseeable future since sustainability and the retention of autonomy over decision-making takes priority over a willingness for scientific collusion.

# Question: Is there a mismatch between EMA and Payer Evidence Requirements?

- Although there is considerable overlap, EMA's requirements can be different to those of payers:
  - EMA does not focus on financial sustainability – which is the ultimate aim of any payer organisation.
  - EMA does not accept off-label comparisons – which are often requested by payers.
  - Dependent on the disease area, regulators may accept surrogate parameters while payers are more and more looking for health outcomes data
  - EMA does not require national studies but clinical practice may vary between countries and can have a major impact on the type of data payers expect.
  - EMA is ultimately driven by industrial interests, whilst payers are responsible to the sustainability of the various healthcare systems.
- Evidence requirements may also differ between international regulators – for example in oncology, the FDA and EMA are taking different approaches to what is acceptable.

*"It is not a surprise there is a mismatch, it is a colliding situation of different interests. It has been stated by EMA that they have to look after industrial interests, then countries **don't** see their interests reflected in those decisions. There is no sustainability built into EMA decision-making* " Oriol Sola-Morales

*"The standard of therapy within each country is often a stumbling block; for example, with EMA off-label comparison is unacceptable, however, for several EU pricing and reimbursement authorities this is acceptable.*" Wil Toenders

*"We talk about a mismatch between the EMA and payers – but it is important to recognise that there is also a mismatch between regulators in the US and EU on the acceptable evidence base."* Tim Volmer

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# Question: What can companies do to tackle the situation?

- Companies have to accept that the risk in developing medicines has increased:
  - Achieving regulatory approval does not guarantee sales.
  - Companies can seek advice for their clinical development programme from the various official payer advice services who may make recommendations which are not commercially attractive – there is also a danger the advice will be invalid as new comparators enter the market.
  - An alternative approach is to develop an evidence base which is more commercially attractive – companies can seek advice from ex-payers and in-market experts to optimise market access without going through official channels.
- Crucially, whichever route companies decide to take, the advice (official or unofficial) must be sought whilst there is still time to influence the clinical trial program.
- Ultimately, payers have to make a reimbursement decision on the evidence base available to them and companies must do everything possible to address payers' biggest fear – uncertainty.

*"When you join the club, you have to accept the rules of the club – the rules are very well established. The only solution is to acknowledge from the very beginning that regulation of the market is not the end of your journey – this is just the beginning."* Oriol Sola-Morales

*"When you look at the tax authorities, they always have some information number that you can call about how to pay your taxes – but they will never tell you how not to pay. To me the same applies to market access."* Ad Rietveld

*"The authorities cannot help that between the time that the advice is given and the trial finishes, that new comparators come to market and the therapeutic paradigm might have changed."* Wil Toenders

*"Companies need to understand the Government (payers') mindset – there remains a question if they will get a return on their upfront investment. How do you help them manage this uncertainty?"* Tim Volmer

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# Payers increasingly focus on the value and health outcomes of new drugs relative to existing treatments rather than on regulatory data

## Germany

- German system has two steps: (1) Evidence Generation (2) Price Negotiation.
- Definition of the comparator essential – influenced by clinical practice in Germany – comparator has to be within label.
- Strong correlation is required for an intermediate outcome to be accepted as a surrogate.
- Close monitoring of 'standard of care' is important to maintain validity of the trial for evaluation.
- Care context determines the efficacy of a comparator.

## The Netherlands

- In oncology, progression free survival data are no longer enough and overall survival and QoL data are expected.
- Comparators can be off-label
- New chronic medicines face great challenges in the absence of evidence on hard endpoints.
- Orphan medicines with scarce clinical evidence will no longer get the ebnefit of the doubt.
- Budget impact and cost per QALY will play a much more prominent role than in the past.
- Manufacturers are encouraged to interact with Zorginstituut: scientific advice contacts.

## Spain

- Payers think about effectiveness rather than efficacy.
- Budget impact is vital and this applies at the national and regional level.
- A compelling evaluation would have clinically relevant outcomes, epidemiological certainty (stress on certainty), safety and critically budget impact.
- It is important to acknowledge the system requirements and get advice and insight early to optimise market access.

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# Thank you and please do get in touch!


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