Generating the Right Evidence to Drive Market Access

Anke van Engen & Louise Parmenter

Webinar
18th September 2012
Your Presenters

Anke van Engen
Consulting Director, Market Access
Ms. Anke van Engen joined Quintiles Consulting in 2001 and is dedicated to helping life sciences companies maximize the commercial success of products through early market access strategy and real-world value demonstration.
Anke has over 11 years of experience in advising global pharmaceutical, biologics and medical device firms on strategic concerns regarding new product development, pricing, reimbursement, health technology assessment and comparative effectiveness research.
Experience covers nearly all therapeutic areas and all major European countries.
Anke holds a Master’s degree in Chemistry from the University of Leiden. She has co-authored, contributed to and reviewed numerous international health economics models and dossiers and has published in peer review medical and scientific journals. As an active ISPOR member she is a scientific abstract reviewer since 2003

Louise Parmenter
Senior Director, Strategic Operations, Real-world & Late Phase Research
Dr Louise Parmenter is accountable for strategy and planning for Quintiles’ Real-world & Late Phase Research. Louise has spent 20 years in the pharmaceutical industry and her specialist area of focus is peri-approval research where she has significant global strategic design and operational knowledge gained from time spent based in Europe and the USA
Louise supports ENCePP (European Network for Centres for Pharmacoepidemiology and Pharmacovigilance) and the TRANSFoRm (Translational Medicine and Patient Safety in Europe) consortia. Louise has a PhD in Neurophysiology, and a BSc in Physiology with Biochemistry from Southampton University, UK. Louise is currently studying for an MSc in Epidemiology run by the London School of Hygiene and Tropical Medicine through the University of London International Programmes.
Contents

• European Market Access Evolving Landscape and Needs
  > Anke van Engen

• Generating the Right Evidence
  > Louise Parmenter
Today’s Webinar Audience

- Academia
- Biostatistician
- Clinical Operations
- Epidemiology
- Health Economics
- Market Access
- Medical Affairs
- Risk Management
- Other
Polling Questions

• A small number of polling questions have been added to today’s webinar to make the session more interactive
European Market Access
Evolving landscape and needs

Anke van Engen
Market Access = Convincing the Payer

*Payers include any organisation or individual with an interest in the costs of healthcare*

Multiple tiers are creating increased sophistication and complexity
National Approaches to HTA

Payers Have Different Notion of Value

Polling Questions

• Which market do you find most difficult to access Today?
  > France
  > Germany
  > UK
  > Spain
  > Italy
Market Access is Changing

Local and regional challenges are increasing

PAST
National – often government - bodies whose role is to negotiate price and/or reimbursement

SINGLE
Negotiation: Internal or external referencing

PRESENT
Local and regional bodies with responsibility for determining how health-care funds should best be spent

MULTIPLE
Evaluation: HTA, guidelines, substitution

FUTURE
Proactive investment into health-care areas of focus or relevance

ONGOING
Investment decisions: Commissioning, payer funded trials

France Germany Italy Spain UK
Polling Questions

• Which country do you think will be most difficult to access in the future?
  > France
  > Germany
  > UK
  > Spain
  > Italy
The Global Market Access Challenge

What do payers say they want?

**Sweden:** “Our goal is to get as much health benefit as possible for the tax money that goes to drugs and dental care”

**UK:** “Patient Oriented Evidence that Matters”

**Argentina:** “Improve the accessibility and quality of health care, encourage the appropriate use of technology and reduce unnecessary health care costs”

**Germany:** “Evidence of an additional benefit over Standard of Care”

**Russia:** “Decisions of HTA agencies serve as recommendations about inclusion or exclusion of the technology from the list of drugs reimbursed by the government.”

**Poland:** “In its work, Polish Agency refers to the scientific evidence primarily with regards to patient safety and efficacy.”

**Australia:** “We don’t buy technology, we buy health gain”

In a value-based pricing marketplace, data is king. Products must demonstrate direct benefit compared with competitors if they want to come out on top.
European Payer Environment

Key focus points

• **Patient segmentation:**
  Manufacturers must show positive efficacy (statistically significant) in the study population, which should be the same as the intended indication population.

• **Relative effectiveness:**
  Depending on the desired positioning it is recommended to include an active control, because indirect comparisons will likely cause issues with making superiority claims.

• **Endpoints:**
  Focus on hard endpoints, health related quality of life

• **Economic evaluation:**
  Direct comparison for efficacy and safety will be required. Only for more restricted indications and patient sub-populations indirect efficacy and safety comparison may remain acceptable. Manufacturers should try to limit uncertainty around the outcomes by choosing the correct comparator, correct comparator dosage and substantiate additional benefits over comparators.
## Generating the Right Evidence

**Reasons for approval or rejection**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Reasons for Rejection</th>
<th>Reasons for Approval</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• Less than or equally effective to comparator</td>
<td>• More effective than placebo</td>
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<tr>
<td></td>
<td>• Less than or equally effective to placebo</td>
<td>• At least as effective or more than comparator</td>
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<tr>
<td></td>
<td>• Appropriate comparator/s not used</td>
<td>• Acceptable comparator used</td>
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<tr>
<td></td>
<td>• Administration not as convenient as comparator</td>
<td>• More convenient administration than comparator</td>
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<td></td>
<td>• Lack of long term data</td>
<td></td>
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<tr>
<td>Safety</td>
<td>• Failure to use the most appropriate comparator/s</td>
<td>• Acceptable comparator used</td>
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<tr>
<td></td>
<td>• Safety concerns from observed or lack of data</td>
<td>• Fewer adverse events than the comparator</td>
</tr>
<tr>
<td></td>
<td>• More or worse adverse events than comparator</td>
<td>• No serious adverse events reported</td>
</tr>
<tr>
<td>Economic</td>
<td>• Limitations in economic model</td>
<td>• Suitable economic model presented</td>
</tr>
<tr>
<td></td>
<td>• Not cost effective</td>
<td>• Considered cost effective</td>
</tr>
<tr>
<td></td>
<td>• Absence of correct or robust economic model</td>
<td>• Price or risk share successfully negotiated</td>
</tr>
<tr>
<td>Study Cohort</td>
<td>• Study population did not match the indication population</td>
<td>• Study population was an accurate reflection of the intended indication population</td>
</tr>
<tr>
<td></td>
<td>• Population not specifically identified</td>
<td></td>
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<tr>
<td>Other</td>
<td>• Not enough supporting evidence</td>
<td>• Study population reflected indication population</td>
</tr>
<tr>
<td></td>
<td>• Flaws in study design, power, etc</td>
<td>• Clinical imperative meeting observed critical medical unmet need</td>
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<td></td>
<td>• Extrapolation of findings beyond that supportable by the data</td>
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What Can We Learn from HTA’s

The example of oral antidiabetics

Reasons for Acceptance

• Agents that received agency acceptance presented clear evidence of positive clinical benefit.
• Clearly defined patient population with the evidence available for this particular patient group was necessary to obtain positive HTA opinion.

Reasons for Rejection

• The lack of longer term trial data (≥1 year) to demonstrate sustained efficacy and safety.
• The lack of controlled studies against standard of care (SOC), associated with a low acceptability of superiority claims based on trials without direct comparisons.
• The lack of sufficiently convincing data to demonstrate additional benefits over SOC (e.g. weight reduction, positive effect on lipid profile).

Source: HTA Watch, Quintiles’ online searchable database monitoring HTA activity of >80 agencies worldwide.
Generating the Right Evidence

The example of oral antidiabetics

- Extended follow-up & extrapolation
- Intended indication population
- Active comparator
- Use validated model; collect EQ-5d
- HbA1c; weight; micro- and macrovascular outcomes

Value

- Patient segmentation
- Relative effectiveness
- Time horizon
- Economic evaluation
- Endpoints
Polling Questions

• Has your company ever used real world data in a HTA submission?
  > No
  > Yes but not often
  > Yes often
  > Don’t know
Demonstrating Real-World Value

Payers opinions differ – Nordics among leading supporters of real world data

IQWIG refers to the discussion on pragmatic trials and views RCTs as feasible means to generate real-world data, depending on the appropriate trial design. Hence, with regard to the benefit assessment as a precursor for the cost-benefit-assessment, IQWIG is confined to RCTs if available but flexible with regard to the proximity of the trial design to routine care conditions. Real-world data generated by study designs other than the RCT are only taken into account by the institute if there is no alternative.

HTA agencies in Scandinavia are proactive in encouraging the development of real world evidence and like to see as much as possible in their submissions.

France and Netherlands open-minded to real-world evidence and in separate cases provide conditional reimbursement until the supportive real-world evidence becomes available.

Real world data are advantage but not an absolute requirement in the UK

NICE advises that registry data can be useful for utility data mapping, defining baseline data for patient subgroups, etc. However if data from registries/observation studies are supplied to show that effects from clinical trials can be replicated in the real world – is not required.

Though not fully embraced, payers are slowly beginning to turn to observational data to help understand a particular therapy. Registry data is not currently used to determine coverage or reimbursement decisions. There is an emerging interest and slow trend amongst payers in utilizing observational data for coverage decisions. As more real-world data becomes available, payers tend to consume more and demand more.

Quintiles Confidential
A Hopeful Example

**NCCHTA study to support NICE’s decision**

**Background:**

The standard treatment for symptomatic uterine fibroids is hysterectomy.

During the mid-1990s a minimally invasive uterus-conserving treatment was described known as uterine artery embolisation (UAE).

Evidence from a few small randomised controlled trials comparing the two treatments suggested that UAE is a safe, effective treatment up to 12 months.

Long-term safety and efficacy remain unknown.

HOPEFUL is a pragmatic observational study that has investigated and compared the two treatments in the medium term.

**The HOPEFUL study**

Multi-centre retrospective cohort study. Data were collected locally from patients' hospital records and also from patients themselves by postal questionnaire. Questionnaire data included free-text comments and this qualitative material was analysed using constant comparison. A two-stage probabilistic decision model was designed to estimate UK NHS costs and health outcomes in terms of quality-adjusted life-years (QALYs).

The research findings from this NCCHTA study directly influence decision-making bodies (NICE).

UAE is an effective treatment for some women with fibroids and HOPEFUL trial supports the National Institute for Health and Clinical Excellence (NICE) guidance that it should be made available as one of the options for treatment, with a possible reduction in the need for hysterectomy as the first-line treatment. (Results published in 2008)

NICE has published “Uterine artery embolisation for fibroids” guideline in November 2010, where UAE was endorsed for use.
Polling Questions

• Where do you see the data gaps in gathering the right evidence?
  > Effectiveness against the right comparator
  > Data on the right endpoints
  > Evidence in a sub-population
  > Long-term data
  > Evidence of cost-effectiveness data
While perception sometimes is that payers are only interested in cost, we see that the single thing which influences payers most is superiority of clinical effectiveness.
European Market Access

Generating the Right Evidence

Louise Parmenter
Decision Makers on the Road to Market Access

Regulatory Agency  Payer / HTA Body  Prescriber  Patient as Payer

Drug Candidates  Market and Patient Access

- Does the drug do more good than harm in a defined group of patients?
- What are the health and cost consequences associated with this drug relative to other interventions?
- How does the drug perform relative to other interventions in this patient?
- Am I willing and able to pay for this treatment out-of-pocket?

“Typical” Hierarchy of Research Designs

- Meta-analyses & Randomized Controlled Trials
- Prospective Observational Cohort Studies & Pragmatic Trials
- Case-control studies
- Case-reports
- Expert opinion
Spectrum of Research Approaches

- Meta-analyses & Randomized Controlled Trials
- Prospective Observational Cohort Studies & Pragmatic Trials
- Case-control studies
- Case-reports
- Expert opinion

Real-world
“Hierarchies of evidence should be replaced by accepting – indeed embracing – a diversity of approaches.”
Polling Questions

• When does your company formulate a Market Access Plan?
  > Phase II
  > Phase III
  > Phase IV
Evidence Planning & Generation for Market Access Should Start Early in the Product Life Cycle

- **Preclinical R & D**
- **Clinical Development**
  - Phase I
  - Phase II
  - Phase III
- **Regulatory Submission**
- **Approval**
- **Post-approval**

Optimization of Randomized Controlled Trials

Evidence Planning & Generation for Market Access
### Opportunity vs Consideration

<table>
<thead>
<tr>
<th>Opportunity</th>
<th>Consideration</th>
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<tbody>
<tr>
<td>Head-to-head comparator</td>
<td>Methodological issues may make data difficult to interpret e.g. superiority vs non-inferiority, choice of comparator (2 arms, 3 arms with placebo). Increase in size and complexity</td>
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<tr>
<td>Patient Reported Outcomes</td>
<td>Early planning is important to ensure validated instruments are available. Important data for payers with some increased complexity of study conduct.</td>
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### Opportunity Consideration

<table>
<thead>
<tr>
<th>Opportunity</th>
<th>Consideration</th>
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</thead>
<tbody>
<tr>
<td>“Piggyback” Evaluations of Economic Outcomes</td>
<td>Convenient and timely. Need to be mindful of representativeness and duration</td>
</tr>
<tr>
<td>Pragmatic Approaches</td>
<td>Difficult to incorporate into development with more opportunities in phase IIIB &amp; IV</td>
</tr>
<tr>
<td>Patient Sub-populations</td>
<td>May need increased sample sizes to ensure adequate representation of sub-populations Additional consideration for inclusion/exclusion criteria and country and site selection choices.</td>
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Limitations... trial sample may not be representative

"A clinical trial is the best way to assess whether an intervention works, but arguably the worst way to assess... who will benefit"
Limitations...bias towards no difference

“Clean”, explanatory or efficacy trial

“Noisy”, pragmatic or effectiveness trial

- Eichler Accelerating the development of comparative effectiveness information: does phase IIIb represent an opportunity? ISPOR meeting, June 2012
Definition of Real-world Research

- Real-World Research is evaluation of effectiveness, safety and quality of care in settings and populations that are representative of practice including those not generally captured in traditional clinical trials. It can be characterized by:
  - Type of Outcome e.g. Clinical, Economic, Patient Reported
  - Research Approach e.g. Observational Studies, Pragmatic Trials, Database Studies
Polling Questions

• When, in the development life cycle does your company run real-world studies?
  > Do not run real-world studies
  > Phase II
  > Phase III
  > Phase IV
  > Across all phases
Evidence Planning & Generation for Market Access Should Start Early in the Product Life Cycle

Preclinical R & D

Clinical Development
  Phase I  Phase II  Phase III

Regulatory Submission

Approval

Post-approval

Optimization of Randomized Controlled Trials

Evidence Planning & Generation for Market Access

Incorporation of Real-world Studies
Real-world Studies can Support Market Access

• Prelaunch (product not included):
  > natural history of disease
  > burden of illness
  > treatment patterns
  > competitor products
  > disease management
• to inform development, launch strategy, and market access

• Post-launch:
  > brand usage (on and off-label)
  > safety & effectiveness
  > compliance, adherence, persistence
  > treatment satisfaction
  > competitor brands
  > comparative effectiveness
  > disease management

…and have value across the life cycle
### Some Considerations for Observational Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Consideration</th>
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</table>
| Retrospective Database Studies (EMRs, insurance claims) | Able to assess extremely large populations  
Quick and relatively inexpensive  
Good for assessing rare outcomes and long latencies.  
Emerging availability of routine databases across all of Europe although some world-class EMR sources exist e.g. Nordic countries, UK |
| Registries and Prospective Observational Cohort Studies | Able to assess extremely large populations  
More expensive than database studies although less expensive than clinical trials  
May form a backbone for country specific sub studies       |
Generating the Right Evidence for Market Access

Time

Accepted Evidence Standard

Cost
Summary

• The European Market Access Landscape is complex and changing
• Payers have different notions of value
• Insights can be identified by evaluating HTA decision trends
• Generating the right evidence for market access requires forward planning
• …and understanding how the product life cycle can be augmented to capture the right evidence, at the right time, for:
  > Regulators,
  > HTA & payer bodies,
  > Providers
  > Patients
“Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.”

Upcoming Events

Webinar

• Generating the Right Evidence for Market Access in the US: How to Successfully Navigate Against a Constantly Changing Roadmap
  • 10:00-11:00am EDT, October 11, 2012
  • Eric Faulkner, Director, Global Market Access, Quintiles
  • Dr. Louise Parmenter, Senior Director of Strategic Directions, Quintiles Outcome
  • Register online: https://www1.gotomeeting.com/register/792321721

Key Topics:
• Understanding how pharmaceutical and device manufacturers need to change approaches to evidence development and value communication to support successful product access
• Key drivers of market access strategy in the United States, including accountable care organization (ACO) models, health exchanges, health plan consolidation and diversification, comparative effectiveness, real-world data, coverage with evidence development, and risk-sharing?
• What key drivers are most important?
• How will these factors impact market access strategy and potential?