Timely Patient Access to Transformative Medicines: Early Access Strategy

ORPHA STRATEGY Consulting

David Schwicker, Principal

Early and Managed Access Programmes, London Pre-Conference Workshop B, October 24th, 2017
Agenda and Topics Overview

**Early Access**

**Part 1: Strategy**
- Shifting paradigms
- The “rare” challenge
- Early access objectives
- Key strategy elements
- Regulatory landscape
- State of play in Europe
  *Interactive case study*

**Part 2: Value**
- Hurdle to timely access
- Rapid effectiveness assessment
- Value demonstration with fewer data
- Real-world evidence
- OMPs/ATMPs value
  *Interactive case study*

*Networking Break*
Go Round #2

When do you Start with Value/HTA?

Phase I

Phase II (POC)

Phase III (Confirmatory)

Inflection Point Phase I > II

Inflection Point Phase II > III

Pivotal Studies
Timely Patient Access
MA/HTA/P&R is the Hurdle

- EMA: orphan drug regulation, ATMP and SME support, patient engagement
- EC MAA: Centralised procedure
- Market access, HTA, P&R remain national competencies: national healthcare budgets, diverse values, priorities, perspectives, requirements
- Little consensus on the assessment criteria or appraisal process to determine value, particularly for OMPs: unpredictable outcomes
- Approval ≠ access - OHE: only between 40% and 60% of OMPs are fully reimbursed in the UK, France, Italy, and Spain, exception Germany (93%)
- EU5: time from authorisation to final P&R approval is ≈ 15 months
EUnetHTA Forum, September 2017
Rapid Effectiveness Assessments (REA)

• EC advancing HTA harmonisation; public consultation completed, impact assessment report end 2017
• Vision: legislation post 2020, joint REA reports, binding uptake by national HTAs (4 of 9 HTA core domains)
• REAs to be available at CHMP positive opinion
• Roche (Alecensa/ALK+ NSCLC) and Novartis (Midostaurin/AML) leading industry stakeholders; motivation: seat at the table, HTA relationships, competitive head-start post 2020, REAs are incremental work (JA 3 / WP4)
• Pressure from patients: EURORDIS call to payers
EUnetHTA Core Model

EU HTA Harmonisation Post 2020

HTA Core Model DOMAINS

1. Health problem and current use of technology
2. Description and technical characteristics
3. Safety
4. Clinical effectiveness
5. Costs and economic evaluation
6. Ethical analysis
7. Organizational aspects
8. Patient and social aspects
9. Legal aspects

SCOPE

Comprehensive/Full HTA
Rapid REA

Harmonised
National
Timely Patient Access

Uncertainties

- 2016 more than one in three novel medicines approved using at least one of EMA's tools to facilitate early access (7 AA, 8 CMA)
- Early market access with Phase II POC data, surrogate endpoints (e.g. PFS vs. OS), single arm trials, few patients
- Clinical and value outcome uncertainties are anathema to HTA assessment and P&R negotiation: undiscovered risks, lower real-world effectiveness than anticipated
- Increased challenge to get the right drug to the right patient
Ideastorm #2
Early Market Access with Fewer Data

- Call out ideas, concepts
- Fast, no censorship
- Crazy ideas welcome
- Leave comments and discussion for later
1. Start early, very early
2. Document comprehensively and compellingly the burden of disease and the unmet needs of patients
3. Concretise the early promise of your novel medication in addressing some of these unmet needs as compared to existing SOC in an early value proposition
4. Document the degree of innovation of your medication in the disease and therapeutic context
5. Engage early with patient advisors, caregivers, and patient-organisations, identify those issues most important to patients and the sub-populations with the greatest need and potential benefits
6. Develop a full-spectrum value evidence generation plan in coordination with the CDP (RCTs plus RWE)
7. Explore early parallel EMA/HTA consultations, including patient advisors, to, ideally, agree on one set of studies that are relevant to both HTA/P&R as well as the regulatory perspective
8. Describe the benefits of the immediate availability of your medication to the stakeholders
9. “Pressure test” your early market access value story and documentation against recognised value assessment and HTA guidelines, e.g. ORPH-VAL for OMPs
10. Proactively highlight remaining uncertainties in clinical and value outcomes and document how these will be addressed with continued evidence generation post-authorisation
11. Develop proposals for flexible managed entry agreements (MEAs) based on emerging evidence
12. For SMEs, document resources and finances to fulfil post-authorisation commitments
Biopharmaceutical Industry
RWE vs. RCT Status Quo

Electronic Data
0% 25% 50% 75% 100%
RWD

Investment
100%
RCT
Strongly Enhanced Interest in Real-World Evidence

Real-World Evidence (RWE) ≠ Real-World Data (RWD)
Real-World Evidence (RWE) = Real-World Data (RWD) × Well Understood, Fit for Purpose Analytical Methods
Real-World Evidence

The Current “State of the Art”

- 80% of RWD is unstructured, not interoperable, not research ready, highly complex and not well understood
- Bewildering array of observational analytical methods
- Overcoming the notion that RCTs and RWE are polar opposites, rather they exist on a continuum, are complimentary (the right study for the right question)
- Overriding objective: utilising the full evidence spectrum linking interventions with health and value outcomes to improve health care decision-making and patient care
Real-World Evidence
The Current “State of the Art”

• ISPOR: good practices for RWD studies of treatment and/or comparative effectiveness, Value in Health, 2017
• Exploratory treatment effectiveness studies
• Hypothesis evaluating treatment effectiveness studies (HETE) – evaluating the presence and magnitude of a pre-specified effect – closer to causality, reducing bias
• Recommendations: a-priori determinations, publish protocol, publish results, enable reproducibility, address methodological criticisms, include key stakeholders
RWD/RWE remains a highly divisive issue for HTAs

- Con: GBA/IQWIG, ZIN; Pro: HAS, AIFA

- EMA pushing: RWE will be increasingly crucial, particularly for rare diseases, OMPs and ATMPs

- Post-Licensing Evidence Generation (PLEG): first HTA cross-boarder collaboration on RWE (JA 3 / WP5B)

- Closely aligned with the EMA Registries Initiative
RWE Applications
Unprecedented Opportunities

- Faster Research & Development
- Accelerated Marketing Authorisation
- Earlier Market Access & Pricing
- Post-Marketing & Life-Cycle
RWE Regulatory and HTA Applications

Accelerating Clinical Development
- Faster, smaller RCTs
  - Patients with the greatest unmet need
  - Better defined, smaller populations
  - Decreased screening failures
  - Enhanced recruitment
  - Single-arm studies with historical controls
  - RWE supplementing RCTs in fragmented, rare populations
  - Hybrids: EHR/registry based RCTs

Accelerated Marketing Authorization
- Adaptive Pathways
  - Iterative, life-cycle approach to evidence generation
  - Expanded toolbox: pragmatic and observational studies complement RCTs
  - Early patient engagement
  - Conditional marketing authorization (EMA)
  - Accelerated approval (FDA)

Earlier Market Access and Reimbursement
- Value Demonstration
  - Early value proposition
  - Early dialogues with payers and HTAs
  - Parallel scientific/HTA advice: one set of studies to satisfy both regulatory and HTA perspectives
  - Comparative effectiveness
  - Adaptive pricing/reimbursement
  - Innovative value-based contracts

More Efficient Post-Marketing Commitments
- PASS + PAES
  - LCM: population & indication expansion
  - Increased due diligence and speed
  - Reduced costs
  - Data-driven trial management
    - patient identification
    - screening
    - recruitment
    - centralized consent
    - e-monitoring and safety reporting

Orpha Strategy
Collaborative, multinational RWD networks, including EHDN, EMIF, OHDSI, with numerous cohorts of interest

Hybrid data sources: combining biobank/genomic data with EHRs; matching patient generated data (wearables/social media) with EHRs to create a complete patient journey and personal care pathway

RCT/RWD/pragmatic hybrid studies

Making use of data collected on placebo patients in RCTs (and linking to EHRs)
Orphan Medicinal Products (OMPs)

Current Trends in Europe

- OMP-specific value assessment frameworks are gaining traction: ORPH-VAL, MoCA-OMP, Innovation Algorithm
- Holistic approaches that favour innovation & sustainability
- Address accelerated and conditional marketing authorisation
- Focus on joint and early EMA/HTA scientific advice
- Clinical development strategies and decision-making should increasingly take these criteria into account
**ORPH-VAL Guide to Core Elements of OMP Value**

**Patient Level**
- Survival/life expectancy
- Morbidity
- Patient experience/QoL
- Patient economic burden
- Existing treatment options
- Side effects
- Convenience

**Healthcare System Level**
- Healthcare system resources
- Healthcare system budget
- Healthcare system organisation

**Societal Level**
- Rarity
- Small budget impact
- Sustainability of innovation
- Societal preferences
- Uncertainty of quality of evidence
- Uncertainty around value parameters

**Uncertainty & Considerations Beyond OMP Value**
- Family/carer quality of life
- Family/carer economic burden
- Societal economic burden

**DISEASE & TREATMENT**
### MoCA-OMP Transparent Value Framework

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Lower Degree</th>
<th>Medium Degree</th>
<th>High Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available Alternatives/Unmet Need, including non-pharmaceutical treatment options</td>
<td>yes, new medicine does not address unmet need</td>
<td>yes, but major unmet need still remains</td>
<td>no alternatives except best supportive care - new drug addresses major unmet need</td>
</tr>
<tr>
<td>(Relative) Effectiveness, Degree of Net Benefit (Clinical Improvement, QoL, etc. vs. side effects, societal impact, etc.) relative to alternatives, including no treatment.</td>
<td>incremental</td>
<td>major</td>
<td>curative</td>
</tr>
<tr>
<td>Response Rate (based on best available clinically relevant criteria)</td>
<td>&lt;30%</td>
<td>30-60%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Degree of Certainty (Documentation)</td>
<td>promising but not well-documented</td>
<td>plausible</td>
<td>unequivocal</td>
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## The New AIFA Innovation Algorithm

<table>
<thead>
<tr>
<th>DIMENSION</th>
<th>STATUS / IMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UNMET THERAPEUTIC NEEDS</strong></td>
<td></td>
</tr>
<tr>
<td>MAXIMUM</td>
<td></td>
</tr>
<tr>
<td><em>Absence of therapeutic options</em></td>
<td><strong>MAXIMUM</strong></td>
</tr>
<tr>
<td>IMPORTANT</td>
<td></td>
</tr>
<tr>
<td><em>Alternatives lack relevant clinical impact</em></td>
<td><strong>IMPORTANT</strong></td>
</tr>
<tr>
<td>MODERATE</td>
<td></td>
</tr>
<tr>
<td><em>Alternatives have uncertain safety / clinical impact</em></td>
<td><strong>MODERATE</strong></td>
</tr>
<tr>
<td>POOR</td>
<td></td>
</tr>
<tr>
<td><em>Alternatives with high impact on outcomes are available</em></td>
<td><strong>POOR</strong></td>
</tr>
<tr>
<td>ABSENT</td>
<td></td>
</tr>
<tr>
<td><em>Alternatives that modify history of disease are available</em></td>
<td><strong>ABSENT</strong></td>
</tr>
</tbody>
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**COMMERCIAL IMPLICATIONS**

- Funded via "innovative drugs fund"
- No payback mechanism
- Immediate regional formulary inclusion
- Benefit duration period of 36 months

- Immediate regional formulary inclusion
- Benefit duration period of 18 months

- No benefits
References & Further Reading

https://www.orphastrategy.com/early-access/
ISPOR Glasgow Issue Panel #21
Adaptive Pathways and RWE

The Patients’ Voice
Nicola Bedlington
Secretary General, European Patients’ Forum and Co-Founder, The Patient Access Partnership PACT, Brussels, Belgium

Health Technology Assessment Perspectives
Ad Schuurman
MA, Head of the International Department, National Health Care Institute (ZIN), AH, The Netherlands

The Biopharma Viewpoint
Rob Thwaites
MA, MCom, Senior Director, Takeda, London, UK

ISPOR 20th Annual European Congress, Glasgow, Scotland, Wednesday, 8th November 2017, 10:00-11:00
Pros and Cons Brainstorming

RWD Collection in EAPs

• Call out PROS
• Call out CONS
• Additional issues of interest
• Group discussion
# EAP / CUP RWD Pros and Cons

<table>
<thead>
<tr>
<th>Issues</th>
<th>Pros</th>
<th>Cons</th>
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| **Formalized Protocol and CRF/PROs** | Better patient selection and formal data capture  
• Protocol-driven patient screening and selection  
• Clearly defined inclusion/exclusion criteria  
• Formal, legal informed consent procedures  
• Formalized/validation data capture  
• Enhanced quality control and monitoring | Need for speed  
• Compassionate use (CU) driven by patient demand  
• Drafting of protocol, CRFs, selection of PROs, regulatory and PV issues, ethical approvals take time  
• Site selection, training, not all CU sites may be willing/able to participate in a formal study |
| **Use of RWE for Regulatory Purposes, Value Demonstration and HTA** | Formal study/registry a requirement  
• Key benefit: regulators will be open to RWE, e.g. in rare diseases where the collection of data in RCTs is difficult  
• Consider parallel agency/HTA advice, recommendable in non-conventional development approaches: early and enhanced guidance on key issues for development, e.g. target population, endpoint, PROs | Agency/HTA scientific advice requires time  
• Parallel advice meetings add work  
• Limited resources lead to long timelines for meetings  
• Informal RWD collected alongside CU inadmissible for regulatory purposes, may have limited application for HTA, will support hypotheses generation and inform study design |
| **Operational Reputational and Legal Considerations** | Informs the development of P2/3 studies  
• Identification and selection of patients with the greatest unmet need and with the greatest potential for the experimental treatment to have a significant effect  
• Inclusion of endpoints that are actionable for decision-making from a regulatory, patient, and HTA perspective | Cannibalization of P2/3 studies  
• Formal observational study/registry combined with the CU program may direct patients away from RCTs  
• Need procedures in place to direct patients to trials  
Key legal and reputational caveat:  
• A formal study/registry may be seen as off-label promotion, measures to mitigate risks required |
| **EMA Guidelines, Scientific Advice, CHMP CU Opinion** | EMA: explicit proposal to employ RWD in development  
• Single arm studies for rare diseases compared with outcomes inferred from disease registries  
• Collection of efficacy and safety data from early access/compassionate use programs to supplement RCTs in small populations  
• Option of Compassionate Use opinion by EMA/CHMP to harmonize the approach across EU | CU programs remain at the full discretion of EU Countries  
• CHMP CU opinion a non-binding recommendation  
• Individual laws and approaches to compassionate use and RWD collection are to be considered in each of the EU Member States |
| **Adverse Events and Risk Mitigations** | Improved patient selection will help mitigate AEs  
• Decreased risk of impact on the safety profile of the existing label (in case drug is marketed in a different indication) | Off label and CU remains an issue….  
• ….in non-participating countries and sites  
• Possibility of greater capture of serious adverse effects vs. routine off label and CU pharmacovigilance  
• PV requirements may delay study/ethical approvals |
Can support regulatory submissions, and HTA/P&R, in rare diseases where the collection of data in RCTs is difficult, e.g. the safety of ultra-rare paediatric interventions

Exploratory RWD and hypotheses generation for future observational research

Patient-relevant outcomes, HRQoL and satisfaction

Patient and physician/HCP experience: often the first contact with a new medicine in routine clinical practice

Consistency of administration, e.g. for gene therapy, ATMPs
MEA Proposal for Medicines with CMA

- Conditional Marketing Authorisation
- Prior parallel EMA/HTA scientific advice
- Agreement on post-authorisation commitments
- Early HTA assessment and appraisal
- Transparent value assessment framework
- Holistic approach (e.g. MoCA/ORPH-VAL)

**Pricing agreement**
- Based on early promise and the degree of uncertainty
- Full evidence spectrum: RCTs, pragmatic trials, RWE, PASS
- % of drug payment to manufacturer
- % in escrow (e.g. OMP/rare disease fund)

**Post-authorisation studies with due diligence**
- Economic and budget impact analysis
- Benefit/risk and value confirmed full payment to manufacturer
- Early promise not (fully) confirmed partial or no payment

- Re-assessment at set milestone with consistent value framework

- Disease burden
- Unmet need
- Net clinical benefit
- Response rate
- Patient views
- Healthcare system
- Societal preferences
- Innovation

Icons by [http://www.freepik.com](http://www.freepik.com)
Biopharmaceutical Portfolio Offerings
Emphasising Value over Volume

• Targeted/personalised treatment
• Meaningful patient outcomes
• Improved net benefit over SOC

• Smaller, faster RCTs
• Accelerated approval
• Earlier market & patient access

• Market positioning
• Competitive differentiation

• Greater real-world effectiveness
• Increased healthcare efficiency
• Value-based offering to payers
Go Round #3

What are you taking away?

Goal: summarise our learnings as a group

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Please briefly state your primary takeaway point from this workshop

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Summary and slides will be available on https://www.orphastrategy.com
Thank you for the active participation!

"What we call art here, is the application of a knowledge to an action."
René Daumal

Blue hour, view from the Müllerhütte, Stubai Alps, Tirol, Austria, David Schwicker, 2009

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