Timely Patient Access to Transformative Medicines: Early Access Strategy

ORPHA STRATEGY Consulting

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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*

Networking Break

Part 2: Value

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

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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

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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

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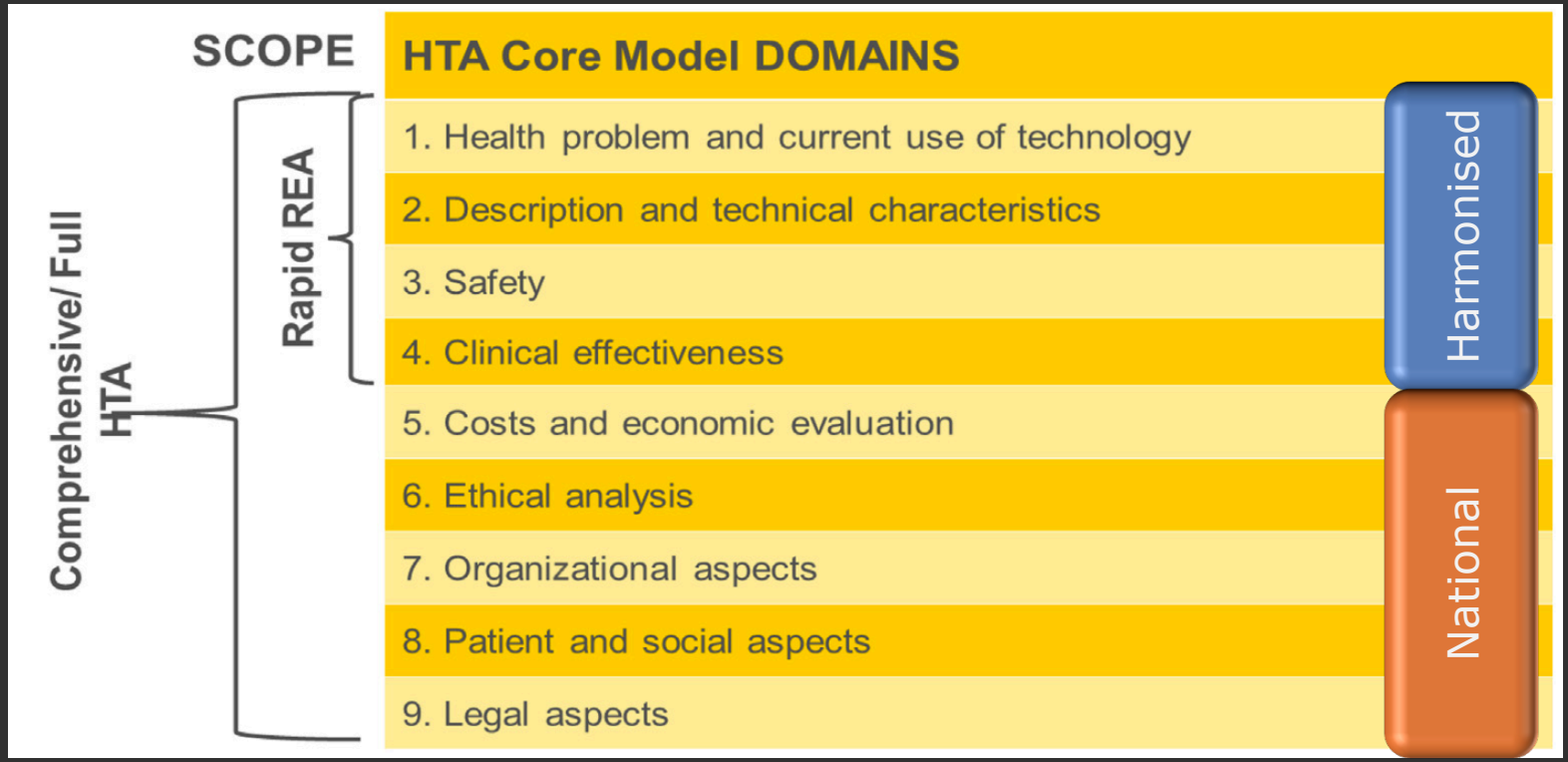
EUnetHTA Core Model
EU HTA Harmonisation Post 2020



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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

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Ideastorm #2
Early Market Access with Fewer Data

- Call out ideas, concepts
- Fast, no censorship
- Crazy ideas welcome
- Leave comments and discussion for later

Early Market Access Value Demonstration

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

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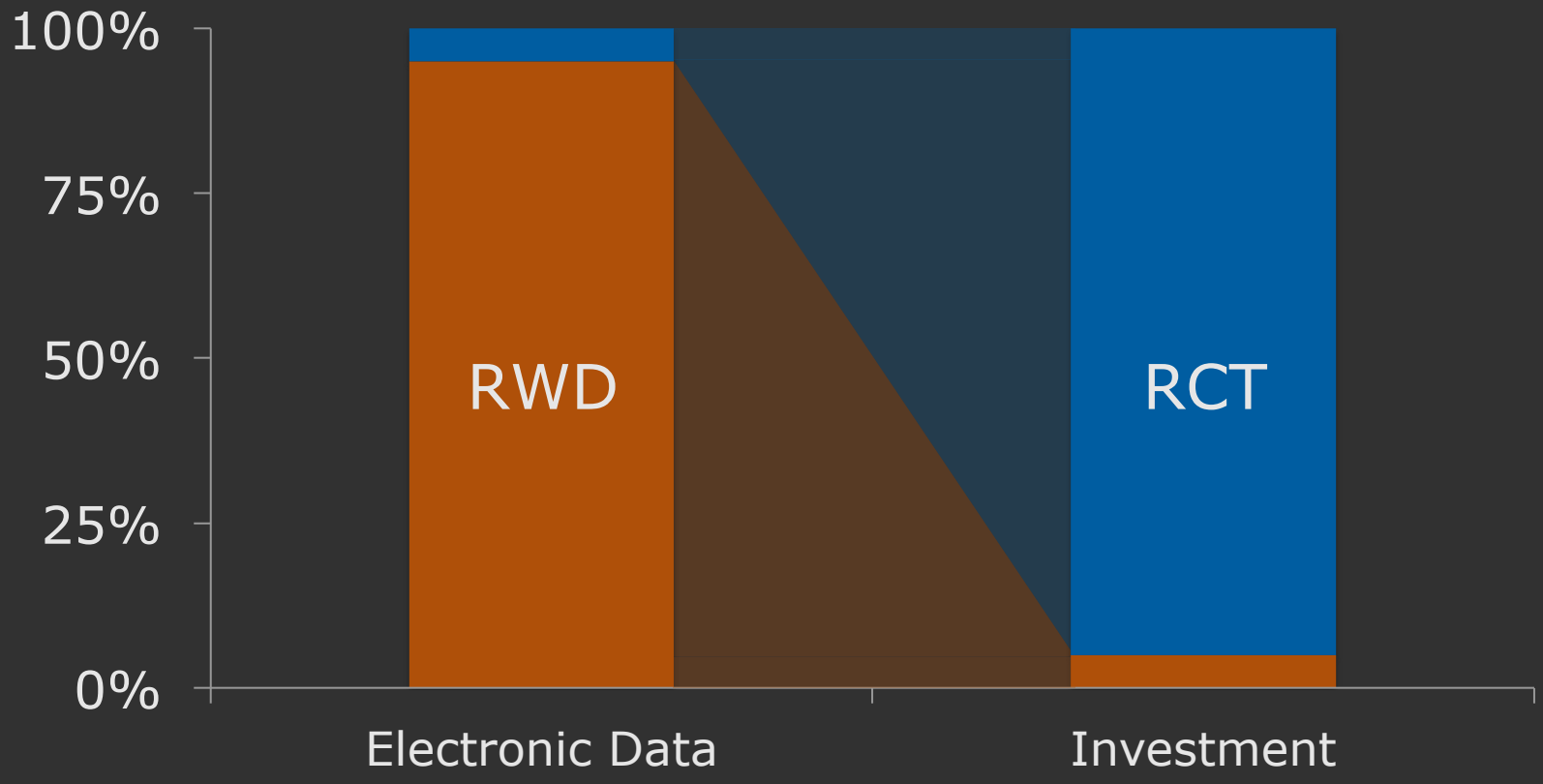
Biopharmaceutical Industry
RWE vs. RCT Status Quo



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Strongly Enhanced Interest in Real-World Evidence

Real-World Evidence (RWE) ≠ Real-World Data (RWD)

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Strongly Enhanced Interest in Real-World Evidence

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

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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

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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

EUnetHTA Forum, September 2017
Real-World Evidence

- 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

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RWE Applications
Unprecedented Opportunities

Faster Research & Development

Accelerated Marketing Authorisation

Earlier Market Access & Pricing

Post-Marketing & Life-Cycle

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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

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i-HD/EMIF Meeting, September 2017
"Next-Level" EU RWE Developments

- 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

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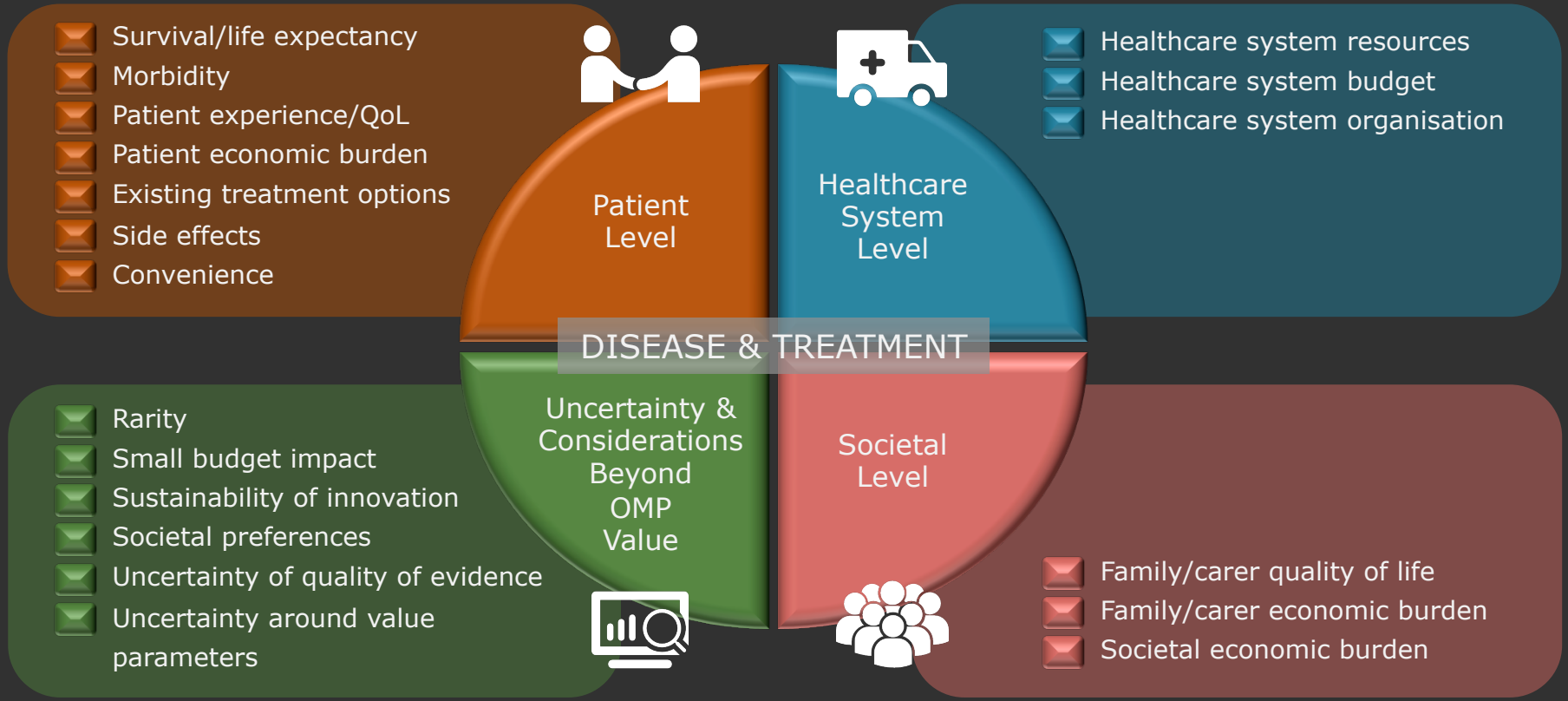
ORPH-VAL Guide to Core Elements of OMP Value



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MoCA-OMP Transparent Value Framework

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

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The New AIFA Innovation Algorithm

	DIMENSION			STATUS / IMPLICATIONS	
	UNMET THERAPEUTIC NEEDS	ADDED THERAPEUTIC VALUE	QUALITY OF EVIDENCE	DESIGNATION	COMMERCIAL IMPLICATIONS
RATINGS	**MAXIMUM** *Absence of therapeutic options*	**MAXIMUM** *Greater efficacy / curative relative to alternatives*	HIGH	INNOVATIVE	• *Funded via 'innovative drugs fund'* • *No payback mechanism* • *Immediate regional formulary inclusion* • *Benefit duration period of 36 months*
	IMPORTANT *Alternatives lack relevant clinical impact*	**IMPORTANT** *Greater efficacy / better benefit / risk ratio*			
	MODERATE *Alternatives have uncertain safety / clinical impact*	**MODERATE** *Moderately greater efficacy in subpopulations relative to alternatives / surrogate outcomes used*	MODERATE	CONDITIONALLY INNOVATIVE	• *Immediate regional formulary inclusion* • *Benefit duration period of 18 months*
	POOR *Alternatives with high impact on outcomes are available*	**POOR** *Minimally greater efficacy than alternatives; irrelevant medical outcomes used*	LOW	NOT INNOVATIVE	• *No benefits*
	ABSENT *Alternatives that modify history of disease are available*	**ABSENT** *No greater efficacy relative to alternatives*	VERY LOW		

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References & Further Reading

Early Marketing Authorization and Market Access

Key Features	FDA Expedited Programs	EMA Support for Early Access
Enhanced Early Agency Interaction	**Fast Track** Designation • frequent interactions • assess potential for alternate trial design, endpoints, rolling review and accelerated approval	**PRIME** (Priority Medicines) • "early dialogues" to identify potential for accelerated development, AA and CMA **Adaptive Pathways** (AP) • iterative, life-cycle development concept • pragmatic trials and real-world evidence supplement RCTs • early involvement of stakeholders (patients, HTAs)
Dedicated Agency Resources	**Breakthrough Therapy** Designation • dedicated cross-disciplinary project lead • senior management access • shortened development program	**PRIME** • early rapporteur appointment • dedicated EMA contact person
Earlier Marketing Authorisation / Market Access	**Accelerated Approval** • based on surrogate/intermediate clinical endpoints • rapid clinical development • confirmatory trials post-marketing	**Conditional Marketing Authorisation** (CMA) • on the basis of less complete clinical data • comprehensive evidence generation post-authorisation **Compassionate Use Opinion** (CHMP before MA/CMA)
Reinforced Scientific Advice	Fast Track Designation Breakthrough Therapy Designation Accelerated Approval Parallel EMA/FDA scientific advice (PSA)	PRIME and Adaptive Pathways Joint scientific and HTA advice Registries Initiative - "late dialogues" on real-world evidence Parallel EMA/FDA scientific advice
Accelerated Review of Marketing Application	**Priority Review** Designation • assessment within 180 days (300 days standard)	**Accelerated Assessment** (AA) • maximum 150 days (210 days standard review)
Orphan Drug Designation	• medicine intended to treat a disease affecting fewer than 200,000 people in the US • 7 years marketing exclusivity • tax credits for clinical testing and grants • common EMA/FDA application for orphan designation	• Drug addressing unmet medical need in rare disease with prevalence of not more than 5 in 10,000 • 10 years marketing exclusivity • centralised procedure • orphan specific scientific advice • reduced fees • common EMA/FDA application for orphan designation

https://www.orphastrategy.com/early-access/

Additional Resources relevant to Early Access, Rare Diseases and Orphan Drugs

- European Commission Rare Diseases Policy and Links Page
- European Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP")
- European Commission expert group on rare diseases
- European Commission Supporting rare diseases registries and providing a European Platform for rare diseases registration
- The Innovative Medicines Initiative (IMI) and IMI Get Real
- Advancing Evidence Generation for New Drugs - IMI GetReal's Recommendations on Real-World Evidence
- Real-world evidence (RWE) Navigator by IMI Get Real - education, guidance, directory of RWE resources
- EMIF - European Medical Information Framework. One platform for data discovery, assessment and (re)use: EMIF Data Catalogue
- BD4BO - Big Data for Better Outcomes is a comprehensive European research programme aiming to develop key enablers to support health care system transformation through the use of big data (includes ROADMAP and HARMONY)
- HARMONY (IMI) - Healthcare alliance for resourceful medicines offensive against neoplasms in hematology. The HARMONY project aims to use 'big data' to deliver information that will help to improve the care of patients with these diseases.
- The European Patients' Academy (EUPATI) is a pan-European project implemented by a multi-stakeholder consortium from the pharmaceutical industry, academia, not-for-profit, and patient organisations.
- ADAPT SMART platform for the coordination of Medicines Adaptive Pathways to Patients (MAPPs) activities
- EUnetHTA European Network for Health Technology Assessment
- PARENT (PAtient REgistries iNiTiative) and PARENT Registry of Registries (RoR)
- COMET (Core Outcome Measures in Effectiveness Trials) Initiative
- Europe PMC is a repository, providing access to worldwide life sciences articles, books, patents and clinical guidelines
- Orphanet, the reference portal for information on rare diseases and orphan drugs
- OrphaNews, electronic newsletter presenting an overview of scientific and political news about rare diseases and orphan drugs
- Orphanet Reports Series, texts covering topics relevant to all rare diseases, new reports are regularly put online and periodically updated
- Orphanet Rare Disease Registries in Europe Report (PDF), updated May 2017
- RD-ACTION Data and Policies for Rare Diseases - an integrated, European approach to the challenges faced by the rare diseases community
- Post-authorisation efficacy studies (PAES), EMA scientific guidance
- EURORDIS is a patient-driven alliance of patient organisations representing 733 rare disease patient organizations in 64 countries
- EPF - European Patients Forum: an umbrella organisation that works with patients' groups in public health and health advocacy across Europe.
- European networks of reference for rare diseases
- FasterCures, a US based think-tank that works to speed and improve the medical research system with a focused on patient centricity. 10,000 diseases. 500 treatments. We have work to do.
- FasterCures' 21st Century Cures Act Tracker, regularly updated to keep track of the implementation of the 100+ sections in Division A, which include the key provisions relevant to biomedical research and innovation.
- Patients Count Network - A searchable digital directory of patient foundations (US based)

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
https://www.orphastrategy.com/news-ispor-issue-panel/

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Show of Hands
Interactive Case Study Selection

① RWD Collection in EAPs and CUPs:
Interactive Development of Pros and Cons

② Managed Entry Agreements for Medicines with CMA

③ Biopharmaceutical Portfolio Offerings – Emphasising Value over Volume

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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

Issues	Pros	Cons
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/validated 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 • Deceased 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

Real-World Data Collection
In Early Access / Compassionate Use

- 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

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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)
- disease burden
- unmet need
- net clinical benefit
- response rate
- patient views
- healthcare system
- societal preferences
- innovation

- Pricing agreement
- Based on early promise and the degree of uncertainty
- % of drug payment to manufacturer
- % in escrow (e.g. OMP/rare disease fund)

- Post-authorisation studies with due diligence
- Full evidence spectrum: RCTs, pragmatic trials, RWE, PASS

- Re-assessment at set milestone with consistent value framework
- Economic and budget impact analysis
- Benefit/risk and value confirmed full payment to manufacturer
- Early promise not (fully) confirmed partial or no payment

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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

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Go Round #3
What are you taking away?

Goal: summarise our learnings as a group

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

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Thank you for the active participation!

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Consulting

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"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