A paradigm shift for orphan and specialty products in Europe - accelerating patient access with patient-centred real-world evidence

David Schwicker

Content

1. The EU, a dramatically shifting playing field for speciality and orphan drugs → the advent of accelerated access (AA)
2. A new paradigm for the approval and market access of orphan and speciality drugs in Europe → exceptions the new norm
3. The role of real-world evidence and patient-centred research in the new paradigm
4. Generating evidence for accelerated access
   → is Phase II the new Phase III?
   → will Phase III and Phase IV merge?
   → the dawn of the PROMs (patient-relevant outcome measures)
5. Observational research trends and challenges in Europe
   → new laws, guidelines and initiatives
   → why you should invest time in research sites
6. Q & A
   → optional: case study Acromegaly

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Background

- Europe lags significantly behind (Hall AK, Carlson MR, 2014):
  - United States: 448 approvals of orphan products in over 30 years since the ODA
  - 78 approvals in 14 years of European orphan drug regulation
- Access to innovative medicines and orphan drugs varies substantially between EU member states, mainly due to funding:
  - Several national HTA authorities view the cost-effectiveness of orphan and speciality drugs critically (Gammie T et al., 2015)
- Mounting political pressure to accelerate access:
  European Parliament Committee on the Environment, Public Health and Food Safety (ENVI) draft report (Oct. 2016):
  - EU legislation for harmonized pricing and reimbursement criteria
  - Overhaul of orphan drug regulation
- Rising influence of patients and patient organisations in the European regulatory bodies leads to a growing demand for timely access to innovative therapies

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Reality Check 2016 for Orphan Drugs: the same dossier can lead to different appraisals

Product / Indication	Key Clinical Evidence	HTA Assessment Outcome (status early 2016)
Teysuno (tegafur, gimeracil, oteracil) advanced gastric cancer (in comb. with cisplatin)	• Phase III RCT (n = 527) • Multicentre, open label • Active comparator arm • Non-inferior to comparator (first endpoint)	• Reimbursement: Sweden, Italy • Conditional reimbursement: UK, Scotland • Rejection: Germany (in review) and France
Inlyta (axitinib) advanced renal cancer	• Phase III RCT (n = 723) • Multicentre, open label • Active comparator arm • Statistically significant benefit (first endpoint)	• Reimbursement: Sweden, Italy, UK, Scotland, France • Conditional reimbursement: Germany
Kalydeco (Ivacaftor) cystic fibrosis	• Two Phase III RCTs (n = 213) • Placebo controlled • Statistically significant benefit (first endpoint)	• Reimbursement: France, Italy, Germany • Conditional reimbursement: UK, Sweden • Rejection: Scotland

Source: adapted from Kilburg, A, 2015

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Non-Consensus between European HTA Agencies

Consensus Issues	Non-Consensus Issues
• Time horizon of analysis • Presentation of results • Use of decision models	• Choice of comparators and outcome measures • Perspective of analysis (health care or societal) • Inclusion of costs (direct / indirect) • Discounting rates for costs and effects • HRQoL methodology • Weights for calculating QUALYs • Uncertainty (deterministic or probabilistic sensitivity analysis)

Summarized from: EUnetHTA Methods for health economic evaluations - A guideline based on current practices in Europe (May 2015)

- Compiled with feedback from 33 member countries (25 have published guidelines)
- Complete overview of current methodological guidelines used in Europe
- Source: http://www.eunethta.eu/outputs/eunethta-methodological-guideline-methods-health-economic-evaluations

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What is being done?

- Greater understanding that benefit-risk and value judgements in rare diseases require unique and innovative approaches
- Establishment of rare disease policies and initiatives
  - Accelerated market approval (MA) → conditional market approvals (CMA)
  - Accelerated market access → conditional reimbursement
  - Early – i.e. before MA – managed and alternate funding (MEAs)
- Emphasis on
  - Early joint scientific and HTA advice
  - Iterative product development and generation of further evidence
  - Early inclusion of patient views and preferences
- Adapted HTA criteria for rare diseases
  - Level of innovation → addressing unmet medical needs
  - Significant contribution to patient care
  - Lower thresholds on efficacy and safety / lower significance levels
  - Economic data less considered, lower cost-effectiveness thresholds
  - Involvement of patient groups

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EMA Accelerated Access Initiatives

- Adaptive Pathways (**AP**)
  - Aim: provide real-life case studies for timely access to medicines
  - Conditional approval and/or reimbursement during further evidence generation
  - Current status: ~60 products submitted; 20 selected and in process
  - CMA: 8 Phase II/early Phase III drugs approved, reimbursement: Germany 7 of 8, France 7 of 8, UK NICE none, UK SMC 3 under PAS (Stindt J, 2016)
- PRIority MEdicines (**PRIME**):
  - Aim: offer early, proactive and enhanced scientific, regulatory and HTA support at key milestones in development
  - Early identification of eligible products at proof of principle (prior to Phase II)
- "**Late Dialogues**" and patient registries pilot programs
  - Aim: post-launch data generation with one (set of) studies for regulators and HTA bodies, including real-world evidence
  - Generation of refined real-world based benefit-risk and value assessments
  - Parallel regulatory/HTA scientific advice on post-authorisation studies

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EU Accelerated Access Initiatives

- European Commission Expert Group on Safe and Timely Access to Medicines for Patients (**STAMP**)
- **ADAPT SMART –** Accelerated Development of Appropriate Patient Therapies (IMI funded)
  - Joint enabling platform: 22 companies, EMA, HTAs, EU patient orgs, academics
- **EUnetHTA –** European Network of Health Technology Assessment
  - Aim: reduce time lag between regulatory and reimbursement decisions, reduce divergences across HTA bodies (slow progress since 2004)
  - 6 pilot projects on rapid relative effectiveness assessment (REA) of pharmaceuticals
  - Development of an HTA core model, guidelines synthesizing national criteria
  - National uptake of REA limited to date – Austria leading user
  - Pros: at the table on the ground level, potential influence, close interaction with national HTA bodies
  - Cons: negative REAs risk spreading to 33 member countries, significant additional resources

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National Accelerated Access Initiatives

- Mainly focussed on funding of orphan and speciality medicines before market authorisation
  - UK:
    - Early Access to Medicines Scheme (**EAMS**)
    - Patient Access Scheme (**PAS**)
    - UK Cancer Drugs Fund (**CDF**) (£340m)
  - France: Authorization for Temporary Use (**ATU**)
  - Italy: **Fondo AIFA 5%** (5% of promotional expenditure, €45m).
  - **Compassionate use**: myriad of further programs across EU member states leading to marked differences in access to innovative medicines
- Represent an increasingly interesting potential opportunity for early revenue generation

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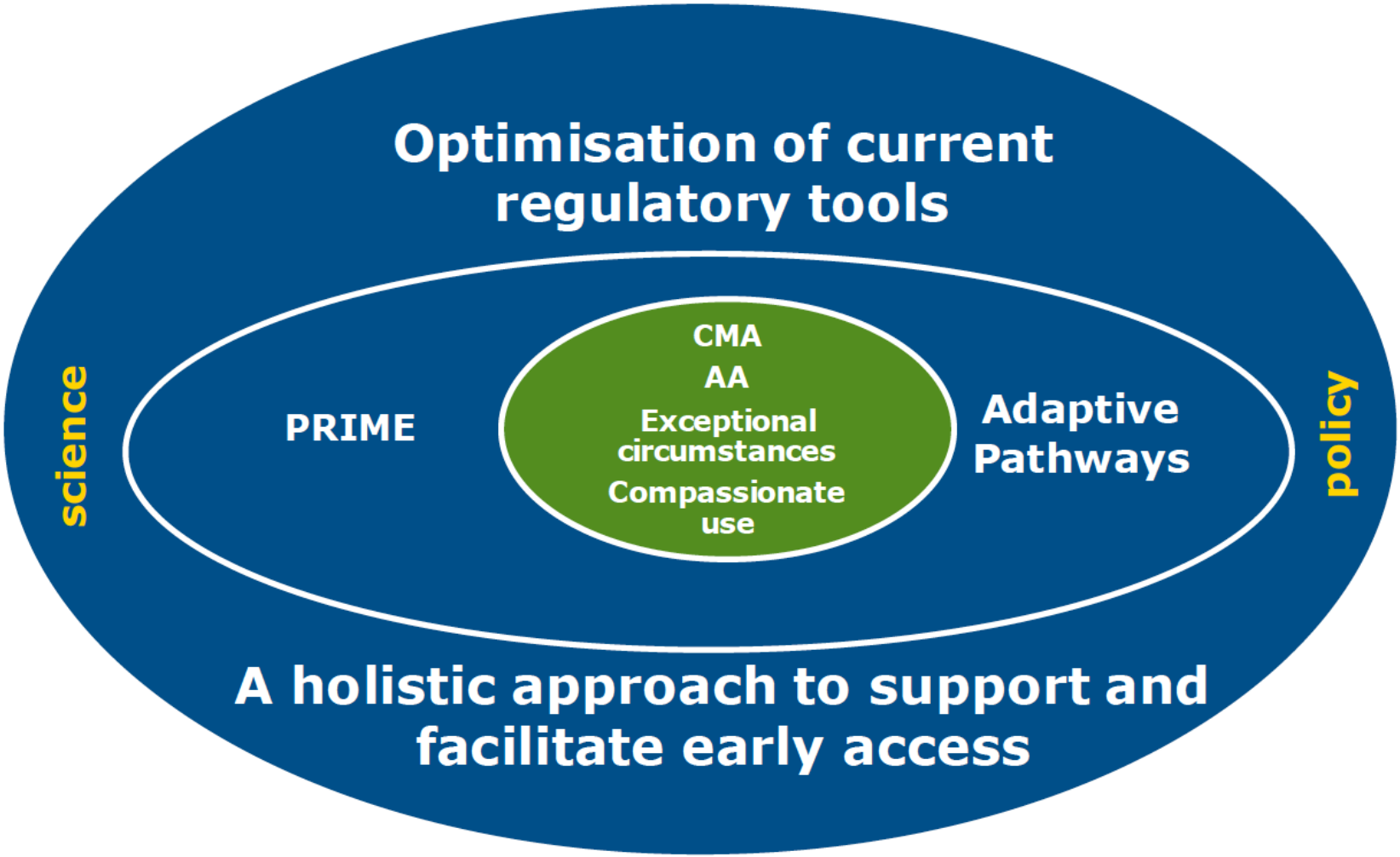
In Summary: The Bigger Picture



Source: European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) - update – Health Technology Assessment Network, May 2016

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A Proposed Paradigm Shift

- **Minimising the time** to market authorisation, access and reimbursement is now – at last – becoming a joint goal of all stakeholders in the EU
- The new **accelerated access (AA) programs** – once fully established – will create a paradigm shift in the market authorization (MA) and reimbursement of orphan and speciality products in Europe
- This shift is **happening now** and may well see **adaptive pathways become the norm** - not the exception – of MA and access in rare diseases
- **Focussed on transformative potential**: medicines that offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options or address clear unmet medical needs
- Accompanied by a **shift in perception** of conditional market authorization (CMA) and conditional reimbursement
  - FROM a “rescue solution” and a threat with added risks
  - TO a key opportunity that is proactively planned

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A Proposed Paradigm Shift

- Accelerated access programs emphasise the need for **iterative product development** and the generation of **further evidence**
- Currently two approaches for approval in stages developing:
  - Initial approval and reimbursement based on **Phase II data** in a well defined patient population with a clear unmet need, followed by extension to wider indication(s) once safety, efficacy and quality of care data is available → continued development in Phase III
  - CMA and reimbursement based on **surrogate endpoint data** (Phase II and III) combined with continued evidence generation with the **use of real-world data** → Phase IV

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Requirements to Sustain the Paradigm Shift

- **Constructive dialogue** and alignment of **all** relevant stakeholders: industry, EMA, HTA bodies, and patients
- Early **joint scientific and HTA advice** → one set of studies that satisfy all regulatory hurdles for AA
- Early inclusion of **patient views** for benefit–risk and HTA appraisals
  - Training of patient representatives to participate in decision making
- **Mitigation of risks** for the pharmaceutical industry
  - Balancing of increased costs and risks in Phase II R&D with the reward of several years of earlier market access
  - Conditional reimbursement at a premium price
  - Early revenue stream potentially crucial for small and mid-cap biotechnology firms
- **Regulatory reassurance** for the post-authorisation phase (STAMP):
  - Feasibility of specific obligations for the generation of additional evidence
  - Clarity in regulatory processes and actions to be taken in the case of delays and negative outcomes – i.e. a clear exit strategy
  - Streamlining of annual renewal and extension processes and reports

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The Role of Patient-Centered Real-World Evidence

- From both the EMA and HTA perspective, real-world data is an **integral component** of accelerated access programs
- “Real world data is a still **underutilized resource**” EMA and STAMP
- AA programs generally include the real-world monitoring of patients (e.g. in registries), including pharmacovigilance
- **Real-world data is essential** to confirming the market approval, to broadening the indication, and to justifying the premium reimbursement of innovative products in rare diseases
- **Patient-preferences**
  - are increasingly integrated into benefit-risk and value judgements of medicines
  - this will include active patient participation in decision making both on an EMA and HTA level (Mühlbacher AC et al., 2016)
  - unmet medical need – ultimately the patients’ perspective – is a central AA element

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The Role of Patient-Centered Real-World Evidence

- EMA **COMP** defines a **significant benefit** of a product for orphan designation in three equal categories
  - an assumption of improved **efficacy**
  - an assumption of improved **safety**
  - an assumption of a **major contribution to patient care**:
    - ✓ more convenient modes of administration
    - ✓ improving patient compliance
    - ✓ improved availability of the product
    - ✓ improved quality of life of the patients
  - Expected that **most** of the data to demonstrate significant benefit will be generated during the clinical development and available prior to market authorization
- **Patient-relevant outcomes measures (PROMs)** and **HRQoL** are an integral and crucial component of the development and appraisal of medicines in rare diseases

Source: Committee for Orphan Medicinal Products (COMP) Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation, EMA, 2012

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Phase II – the new Phase III?

- Not really, **surrogate parameters as the primary endpoint** likely to remain the best option for statistical significance
- **Early joint EMA/HTA consultation** to develop consensus on surrogate endpoints and on what constitutes significant effect sizes
- Consideration of HTA relevant and/or patient-centred parameters as secondary endpoints for **supportive data**, if feasible
- Patient-Relevant Outcome Measures (**PROMs**) - early patient-relevant research, including patient preferences, satisfaction and unmet medical needs, potential major contributions to patient care (based on the current standard of care)
- **Proliferation** of validated disease-specific instruments → development in Phase II, application in Phases III and IV
- **Objective**: CMA and market access at the conclusion of Phase II
- Increase of **risk** and cost in R&D balanced with potential benefits

Source: adapted and summarised from Stindt J, 2016

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Phase III – merging into Phase IV?

- Quite possibly, the rationale for large, conventional and purely experimental Phase III studies is being **increasingly questioned**
- Pressure to **include real-world and patient-relevant** populations, comparators and outcomes as primary endpoints → pragmatic trials
  - Potential need to include multiple comparator arms (HTA perspective)
  - Broad yet clearly defined eligible population and potential sub-population analysis
  - Integration of generic and disease-specific PRO / HRQoL
  - Consideration of PROMs: patient preferences, satisfaction, unmet needs, major contributions to patient care
- Rare diseases: sites and participants largely **overlap** between Phases
  - Fully integrated post-launch study planning with joint EMA/HTA advice
  - Phase III protocols with long-term follow-up in Phase IV
  - Protocol extensions, rollover from clinical study to registry
  - Regulatory expectation that a significant proportion of treated patients are monitored in Phase IV registries and/or pharmacovigilance programs

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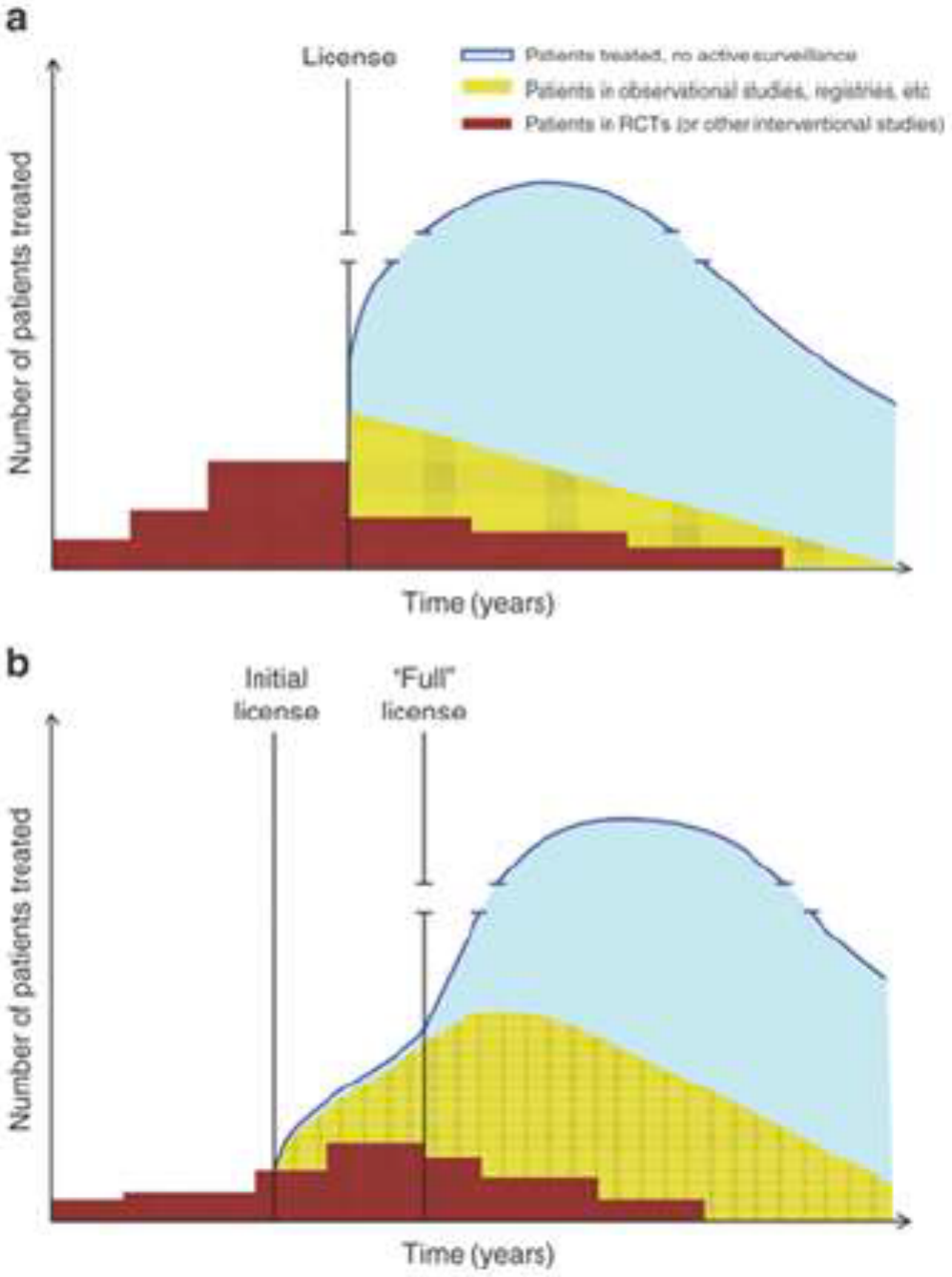
The Future Norm?



Source: Jacoline Bouvy, Scientific Adviser, NICE, taken from ADAPT-SMART, presented at ISPOR 2016, Vienna

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Observational Research Trends in Europe

- Dynamic development and **strong interest** in real-world and patient-centred research on all levels
  - Evidenced by a multitude of new initiatives and guidelines (e.g. PARENT, COMET "Core Outcome Set" (COS), EMA pilots, EUnetHTA)
- Increased understanding of the **unique conceptual and operational challenges** and benefits of observational research, e.g.
  - Ethical committees appreciate the differences between observational designs and clinical studies and offer fast track procedures (e.g. UK NHS proportionate review)
  - Research Sites: research teams with relevant experience, specifically adapted SOPs, financial departments offer differentiated rates
  - Understanding of the limitations, the statistical methods, and the interpretation of observational data, e.g. on a regulatory level and in peer-review for publication
  - Opportunities for high-impact publications increase KOL and investigator interest
- Additional resources and **experts with relevant experience** provide opportunities for increasing the number and efficiency of studies, potentially leading to **decreased timelines and costs**

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Observational Research Trends in Europe

- Caveat: significant differences between countries and research sites remain → choosing the **right partners crucial** for success
- Long-term and excellent **relationships** with Investigators and their research teams are key success factor, particularly in rare diseases
- Sites and participants largely overlap between Phases II, III and IV
- Due to challenges in diagnosis and treatment, patients are likely to be concentrated in a limited number of teaching sites
  - "must have" sites for recruitment
- Principal Investigators are generally the leading experts in the field
  - Scientific input for study protocols and disease-specific instrument development
  - Essential to securing favourable ethical approval
  - Leading authors for peer-reviewed publications
  - Likely first adopters of the new medicine once market access is achieved

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Observational Research Trends in Europe

- Research teams have excellent and longstanding **patient relationships**
  - Intense competition between studies at leading sites
  - Observational studies often less interesting financially → creative incentives to motivate and focus the team
  - Essential to recruitment → eligible patients trust recommendations by nurses
  - Ensure quality of the research → emphasis on training (e.g. data quality and completeness, privacy and security)
  - Streamlining processes → observational research should emphasise efficiency (e.g. patient screening, inclusion and exclusion criteria, etc.)
  - Caveat: selection and reporting bias (e.g. patient satisfaction)
- Significant **investment** (mostly in **time**) in site selection and relationship building justified

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Observational Research Trends in Europe

- New **EU data protection regulation**
  - Issued May 2016, to come into effect by May 2018 (transposal to national law)
- Likely **significant impact** on observational research
  - Patient consent strengthened, always required, broad consent no longer sufficient
  - Consent must be unambiguous, need to add all eventualities on the patient consent form which patients must consent to individually (e-informed consent unclear)
  - Patient data cannot be stored indefinitely
  - Secondary research without explicit consent no longer possible (regulation for pseudonymised data unclear)
  - Data transfer out of the EU basically forbidden, in exceptions to counties which the EU has defined as having equivalent privacy laws (e.g. USA currently not included)
  - “Right to be forgotten” strengthened
- Will further increase the onus on **ethical approvals**, patient **recruitment** and **consent**, and the assurance of data **privacy** and **security** as the key operational challenges

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In Summary: Key Takeaway Points

1. Alternative pathways now represent a major potential opportunity for orphan and speciality medicines in Europe → accelerated market approval and access → early funding before approval
2. Keep a close watch on developments and, if applicable, review the planning for candidate compounds in the pipeline
   - Proactively pursue opportunities for early joint scientific and HTA advice
   - Benefit-risk evaluation of the specific opportunities offered by AA programs
   - Constructively address current practices that represent “barriers to change”
3. Implement real patient-centred research
   - Focus on the patient: research and understand unmet medical needs, preferences and satisfaction, potential significant contributions to medical care
   - Guide development decisions with patient intelligence
   - Full and early integration of real-world and patient-centred evidence generation
4. Last but not least: be nice to your investigators and research nurses
   - Invest, take the long view, build a relationship spanning from Phase II to IV

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Phase IV Programs – www.p4pro.eu

- Specialized independent HTA consultancy focused on real-world and patient-centered research in rare diseases and orphan products
- Founded in 1998 (Start-up company of the year 2000)
- Headquartered in Basel, Switzerland
- EU Office based in Austria (near Munich, Germany)
- Pan-European Registries and programs including over 10’000 sites / physicians and more than 200´000 patients
- Knowledge and experience in many therapeutic areas
- Broad coverage of outcomes, including clinical, economic, HRQoL and PROMs
- Proven scientific track record and peer-reviewed publications
- Longstanding established network of professionals and strategic collaborations across the major markets

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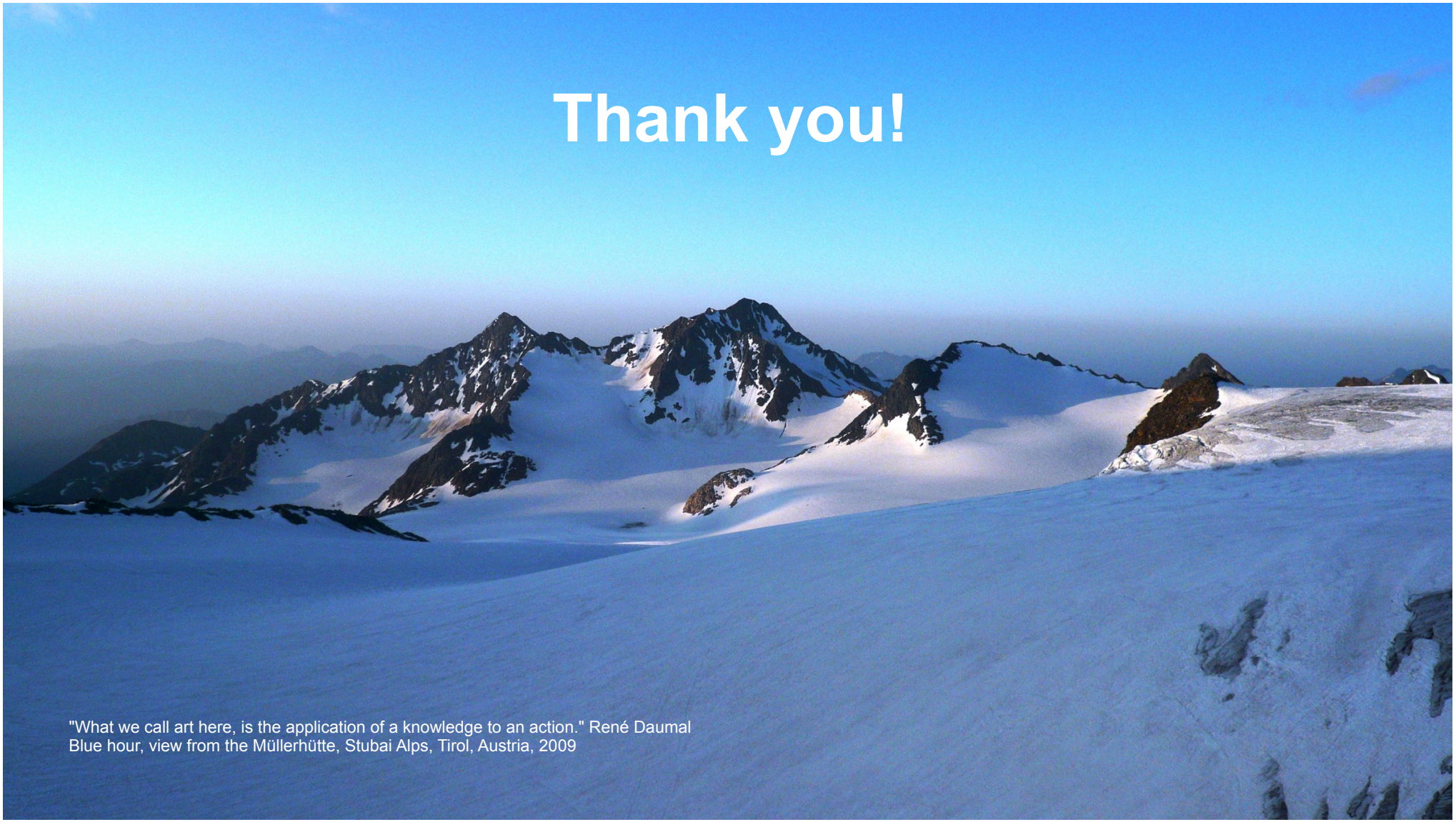
Thank you!



"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, 2009

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David Schwicker
Centralbahnstrasse 7
4010 Basle, Switzerland

EU Office:
Krössbach 4
6167 Neustift, Austria

Tel: +43 664 7345 2514
Email: david@p4pro.eu
Web: www.p4pro.eu