EURORDIS
Rare Diseases Europe

EURORDIS Proposals to Develop more Rare Diseases Therapies and Improve Patients' Access

Yann Le Cam, Chief Executive Officer, EURORDIS

8 May 2014, Berlin

EURORDIS OBJECTIVES

To achieve the quickest access to
as many safe, efficient
and affordable medicines
with a real therapeutic added value,
for all rare disease patients
in the European Union

The European Regulation for Orphan Drugs: a corner stone

Strong advocacy movement from the patients through EURORDIS

16 December 1999: Adoption of the European Regulation on orphan medicinal products

- 2000: Creation of the COMP - Committee for Orphan Medicinal Products at the EMA: 3 patients' representatives for the first time
- Market exclusivity for 10 years after MA
- Fee waivers for orphan designation and reduced fees are granted by the European Medicines Agency (EMA)
- EMA provides protocol assistance to companies
- Pharmaceutical companies developing orphan drugs may be eligible for specific grants from EU and Member State programmes as well as initiatives supporting research and development.

This includes the EU Community framework programmes

The European Regulation for Orphan Drugs: a corner stone

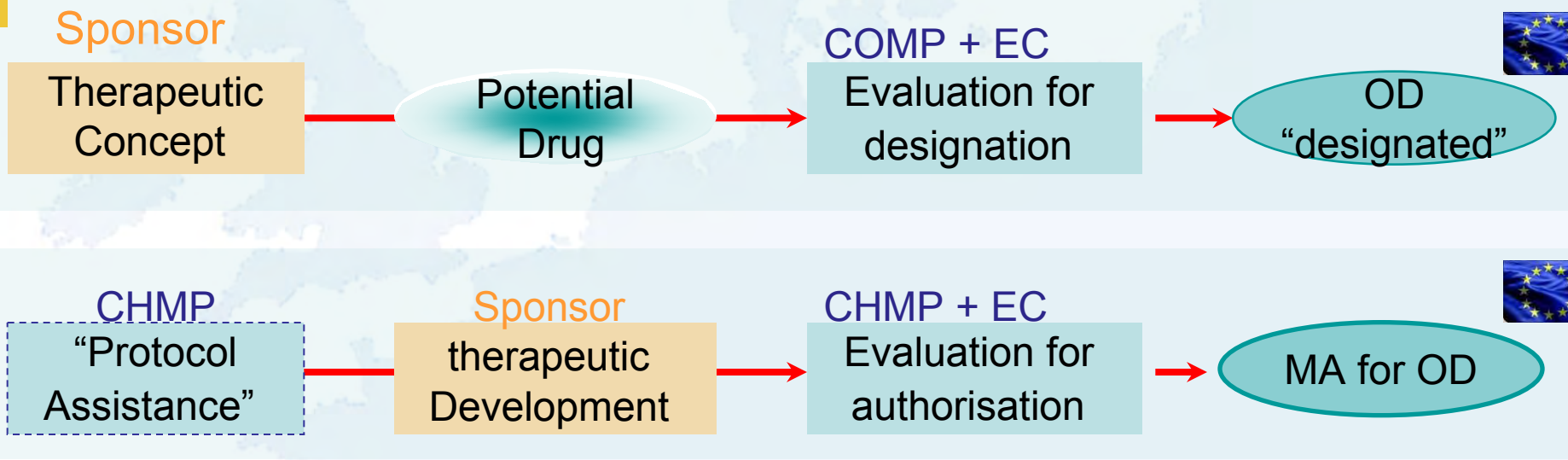
- Development of Orphan Drugs
- Development of biotech SMEs

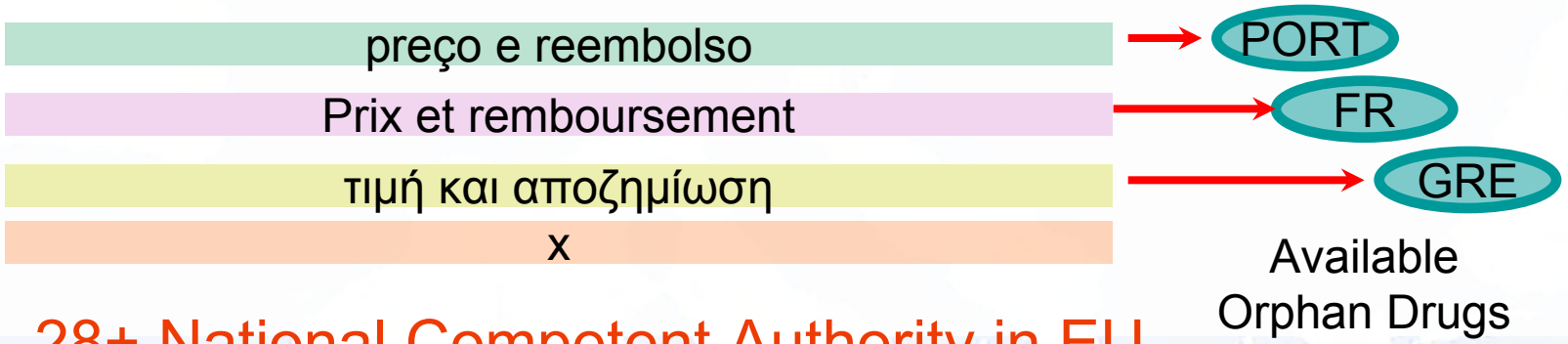
➔ **RAISE HOPE FOR THE PATIENTS & FAMILIES**

Since 2000, as of March 2014 :

- **1247 Orphan Drugs designations by EMA/EC**
- **85 Orphan Drugs received an EU Marketing Authorisation by EMA/EC**

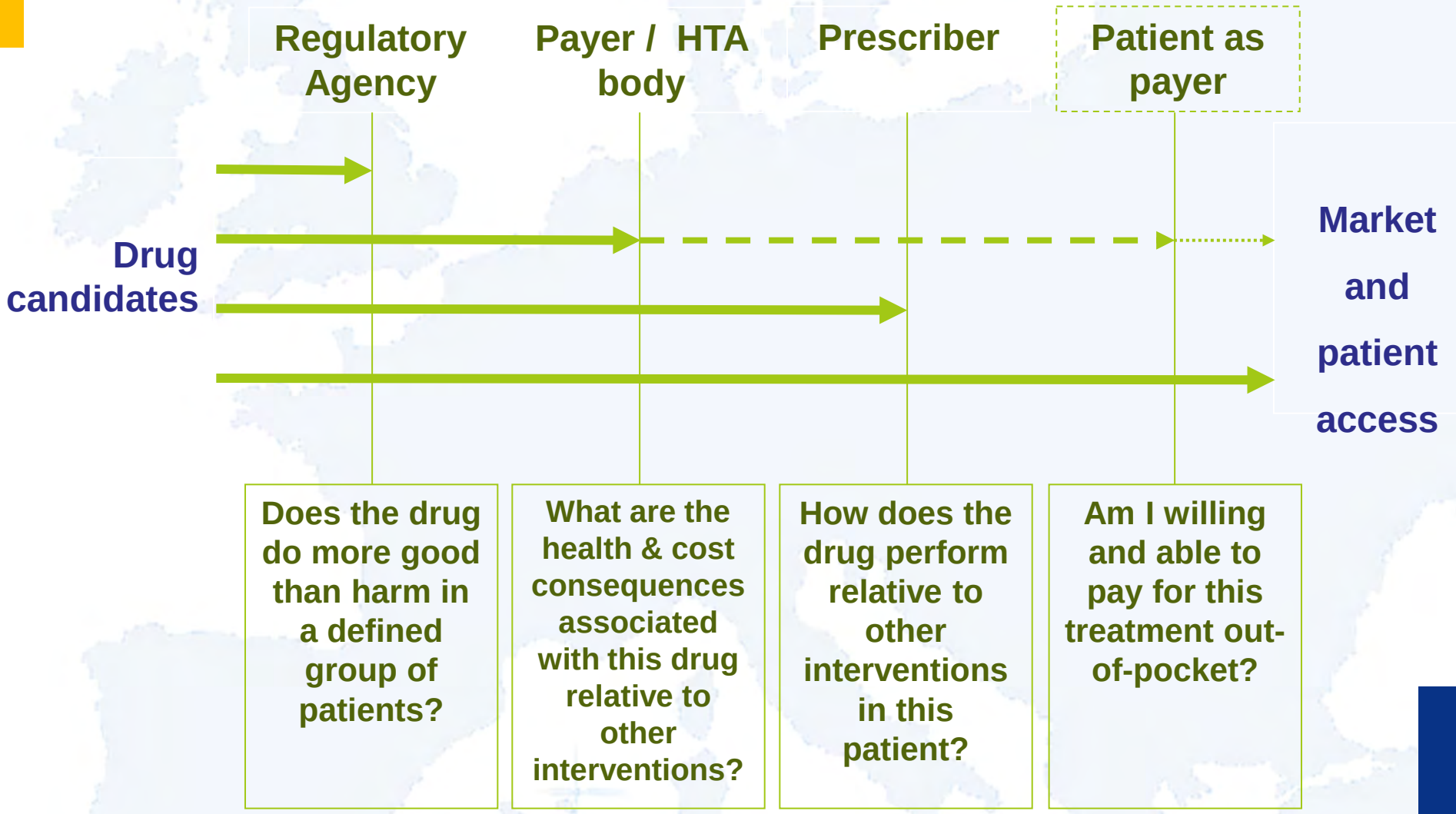
From drug development to marketing authorisation and access





28+ National Competent Authority in EU

Decision makers on the road to market access



Toward a new sustainable business model for innovative rare disease therapies

- **Times are changing**: Economic pressure & Demographic pressure on healthcare budgets / RD scientific opportunities from translational research & Stratified therapies / Growing investors expectations / Society sustainability & values
- **The current business model of ODs is not sustainable**
- An evolution not a revolution + risks of not acting now
- **Look at essential & long term common interest at stake** across patients, across companies, across competent authorities, rather than antagonising the short term & short take diverging interest
- **Corporate responsibility & leadership & policy innovation**

KEY CONCEPTS

- RD Treatments Evidence Generation is a Continuum
- Flexibility of Regulators should become an Official Policy
- Focus on Effectiveness beyond Quality, Safety and Efficacy
- Bridging the Gap Between EU Centralised Regulatory Decision and National Decisions on Pricing & Reimbursement
- Enhancing the Dialogue Between all Stakeholders all Along the Product Development & Life Cycle

Rare Disease Treatments Evidence Generation is a Continuum !

- **Marketing Authorisation is not anymore an on/off switch**
- **Better and broader collection of relevant data is needed**

Data collected all along the life cycle of the medicine on risks as well as on benefits:

- Clinical trials
- Compassionate use
- Real life studies (actual heterogeneous population and real life constraints beyond clinical trials)
- Off label use

Flexibility of Regulators Should Become an Official Policy

- **Regulators are flexible (based on EMA and FDA experience) but need to say it clearly → in order for the process to be more visible, predictable, attractive and with more consistent scientific opinions**
- **Regulators need to have a supportive approach: Being a Gate Keeper is not good enough + Regulators should be Partners for successful developments**
  - Conditional Approval
  - Need for an intense roll-over process of Scientific Advice & Protocol Assistance before and after MA
  - Adaptive clinical trial design
  - Next: Patients Progressive Access / Adaptive Licencing

Focus on Effectiveness Beyond Quality, Safety and Efficacy

- **Dialogue between regulators (EMA), HTA (EUnetHTA),** sponsors, medical experts, patient representatives to adapt Clinical Trial designs, **as early as possible** (ex: methodology in small population, de-link efficacy trials and safety trials, historical control)
- **Anticipate more the therapeutic value demonstration during the Pre-MA Research Activities** (ex: registries, natural history, Good Clinical Practice Guideline on Diagnostic & Care) through Protocol Assistance (EMA)
- Early dialogue between regulators (EMA) and HTA (EUnetHTA) is also important to **anticipate and adapt Post MA Data Generation**

Bridging the Gap Between EU Centralised Regulatory Decision and National Decisions on Pricing & Reimbursement

- One way or another, **HTA and Payers need to be involved in all procedural aspects at the EMA** to be well informed about the reality of medical needs, the potential and reality of the product, the uncertainties and the pathway to generate additional evidence for well targeted patients and good medical practices

- An approach on pricing based on **Value**, means a common understanding of what is Value and earlier marketing authorisation also means an understanding of this value as well as what the uncertainties are

MAIN PROPOSALS

1. **Early Dialogue / scoping / de-risking : EMA + HTA + Payers + PO + Experts**
2. **RD Data Collection & Registries & Natural History Studies**
3. **Clinical Trials : EU Expert Opinion + adaptive design & statistical methodology + alternative to animal models + surrogate endpoints**
4. **Progressive Patient Access / Adaptive Licensing**
5. **Stronger FDA – EMA Collaboration : Common Guidelines**
6. **CAVOMP: EMA & HTA dialogue**
7. **MOCA: Payers dialogue / Value Framework / Price negociations**
8. **Pan-European Managed Entry Agreements**
9. **Differential Pricing**
10. **National Measures in RD National Plans/ Strategies**

Early Dialogue / Scoping / De-Risking

- **EU Pharmaceutical Forum's Guiding Principles on Orphan Drugs recommend "early dialogue"**
- **Corporate Responsibility's Mechanism of Coordinated Access to Orphan Drugs recommends "early dialogue"**

  - **Early dialogue** is a dialogue, at a very early stage of development between 1 company and all relevant stakeholders - EMA, HTA, Payers, Medical Experts, Patients -on a specific product & disease (or with several companies on a specific disease) – EMA Pilots, HTA pilots
  - Early dialogue enables to discuss a) the potential to address an unmet medical need (**scoping**) and b) the optimal research, regulatory, and health policy approach (**de-risking**)

Clinical Trials

- **Legislation**: Ongoing advocacy to improve the EU Regulation on Clinical Trials: call for a European Expert Opinion (centralised at and facilitated by the EMA, rather than national or local Expert Opinion) for clinical trials in rare diseases

- **Regulators:** Promotion of **Adaptive clinical trial design & statistical methods** (Current EMA Guideline, further research for science based policy by regulators)

- **Research**: Promotion of research on **alternative to animal models** for new validated in vivo models + Promotion of research on **biomarkers** and surrogate endpoints

Progressive / Adaptive Licensing

- **Progressive Patients Access / Adaptive Licensing**
  - For diseases which are severe, with no alternative therapies or non-satisfactory therapies
  - Within current regulatory framework:
    - Conditional Approval
    - Progressive enlargement of targeted population treated based on hospital prescription & inclusion criteria
    - Collection of data within post-MA research activities (safety, efficacy, effectiveness) including new pharmacovigilance legislation, risk management plan...

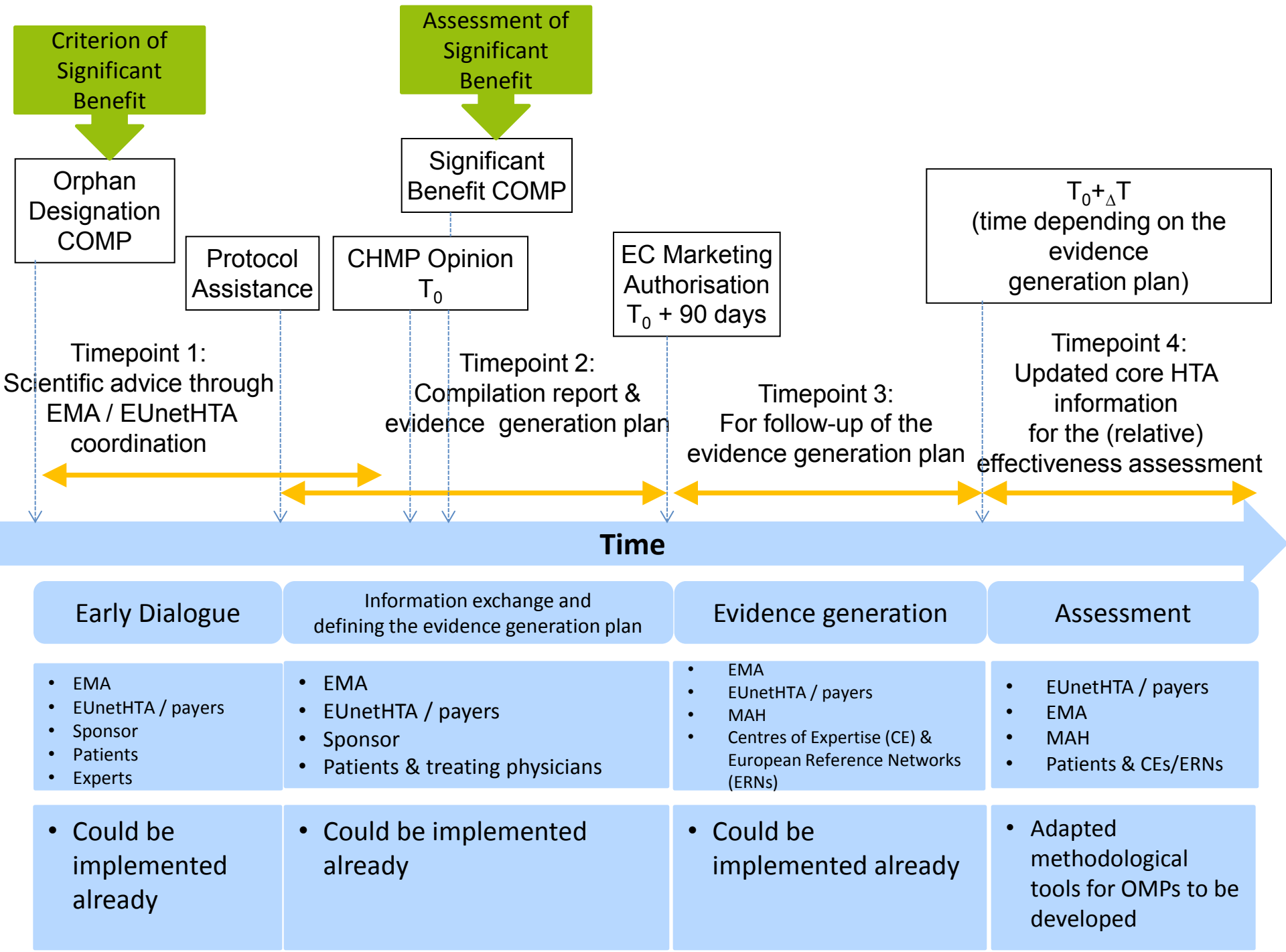
→ A current high priority for EURORDIS. Pilots in 2014?

Call for a Stronger FDA – EMA Collaboration: Beyond Orphan Drugs Designation

- **Coordinated Guidelines on the methodology of clinical trials & statistical methods per disease or relevant group of diseases**
- Parallel Scientific Advice & Protocol Assistance
- Sharing of File, Mutual acceptance of data and Mutual Consultation on Assessment at time of MA
- Coordination of Post-MA research plans

CAVOMP: Four Time Points

1. **Early dialogue / Protocol Assistance**
2. **Compilation Report & evidence definition / Evidence Generation Plan**
3. **Follow-up of the evidence generation plan**
4. **Assessment of Relative Effectiveness**


Criterion of Significant Benefit
Assessment of Significant Benefit
Orphan Designation COMP
Significant Benefit COMP
Protocol Assistance
CHMP Opinion T_0
EC Marketing Authorisation T_0 + 90 days
$T_0+_\Delta T$ (time depending on the evidence generation plan)
Timepoint 1: Scientific advice through EMA / EUnetHTA coordination
Timepoint 2: Compilation report & evidence generation plan
Timepoint 3: For follow-up of the evidence generation plan
Timepoint 4: Updated core HTA information for the (relative) effectiveness assessment
Time
Early Dialogue
Information exchange and defining the evidence generation plan
Evidence generation
Assessment
• EMA
• EUnetHTA / payers
• Sponsor
• Patients
• Experts
• EMA
• EUnetHTA / payers
• Sponsor
• Patients & treating physicians
• EMA
• EUnetHTA / payers
• MAH
• Centres of Expertise (CE) & European Reference Networks (ERNs)
• EUnetHTA / payers
• EMA
• MAH
• Patients & CEs/ERNs
• Could be implemented already
• Could be implemented already
• Could be implemented already
• Adapted methodological tools for OMPs to be developed

MOCA

- **A Mechanism for Coordinated Access to Orphan Medicinal Products – Corporate Responsibility Pharmaceuticals**
- **Consensus**: **European Transparent Value Framework**
- **Ongoing: Pilots** between volunteering EU Member States and volunteering companies to discuss the Value
- **Opportunity**: Price negotiation at European level based on **Value** (Common Assessment) + Volume (prevalence of therapeutic indication as defined in MA) + **agreed Post-MA Research Activities** – linking the 3 elements

Pan-European Managed Entry Agreements

- **Managed Entry Agreement is an area of active ongoing collaboration between EU Member States & Stakeholders – Corporate Responsibility Pharmaceuticals**
- **Consensus:** the utility of such Managed Entry Agreements for new treatments targeted at small populations – rare diseases or stratified populations
- **Ongoing**: building consensus on concept, terminology, approaches
- **Opportunity**: Managed Entry Agreements linked to Patients Progressive Access / Adaptive Licencing and to negotiations through MOCA

Differential Pricing

- **Differential pricing is already a reality in today's ODs European market** with variations of costs actually paid by MSs varying +/- 10%
- But these differences of prices have nothing to do with GDP or National Healthcare budget per capita
- Differential pricing is supported by a growing number of payers, industry, patient groups and policy makers
- Differential pricing for ODs can become a reality if associated with the negotiated / agreed price at European level - MOCA

National Measures in RD National Plans /Strategies

- **EU legislation & European Volunteering collaborative approaches** can work only if well "appropriated" by Member States and "translated" into national measures"

- **National Plans / Strategies** on Rare Diseases are an opportunity to embed these measures in Member States' policy and organisation

CONCLUSIONS

EURORDIS' Expectations

- Parallel Scientific Advice /Protocol Assistance EMA– HTA: More, Earlier, Better

- Guidelines: Anticipate, Align, Involve

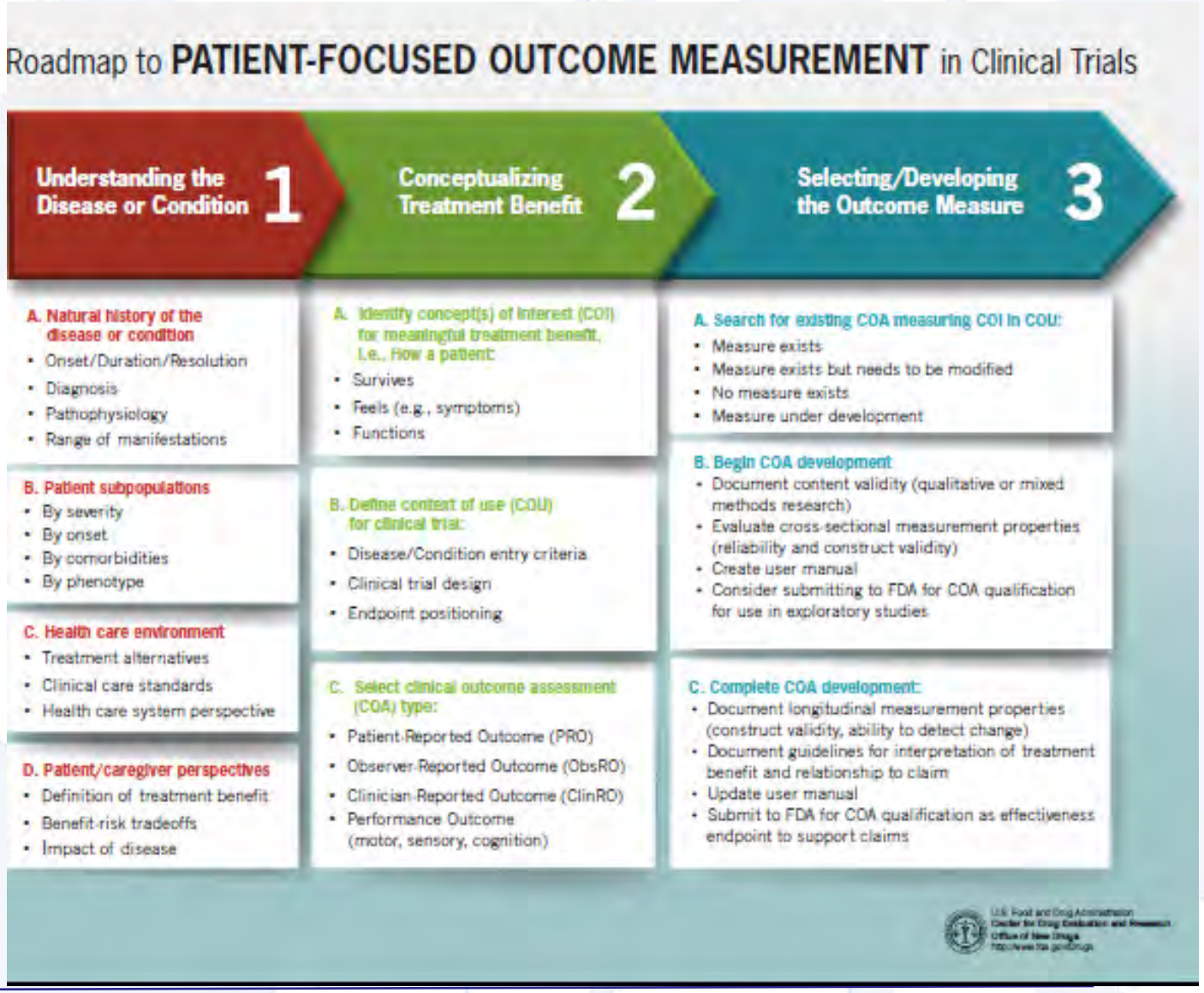
Parallel SA/PA - HTA: More, Earlier, Better

- Continue and expand the EMA-HTA Parallel Scientific Advice
- Be more integrated – EMA-EUnetHTA
- Involve patients as experts not as observers + several patients (a “must”) + with time to be prepared

Guidelines: Anticipate, Align, Involve

- Promote more Guidelines on Clinical Trials on specific diseases or group of diseases:
  - For diseases where there are several products coming up, several designation, some market authorisation (clusters)
  - Including Patients Focused Outcome Measures (cf EMA experience on its workshops and Guidelines or Points to Consider and the new FDA approach)
  - Jointly adopted EMA and EUnetHTA
- Anticipate the development of these guidelines as early as possible as it take 12 to 18 months currently to draft, consult and adopt such guidelines

From the FDA


Roadmap to PATIENT-FOCUSED OUTCOME MEASUREMENT in Clinical Trials
Understanding the Disease or Condition 1
Conceptualizing Treatment Benefit 2
Selecting/Developing the Outcome Measure 3
A. Natural history of the disease or condition
• Onset/Duration/Resolution
• Diagnosis
• Pathophysiology
• Range of manifestations
B. Patient subpopulations
• By severity
• By onset
• By comorbidities
• By phenotype
C. Health care environment
• Treatment alternatives
• Clinical care standards
• Health care system perspective
D. Patient/caregiver perspectives
• Definition of treatment benefit
• Benefit-risk tradeoffs
• Impact of disease
A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:
• Survives
• Feels (e.g., symptoms)
• Functions
B. Define context of use (COU) for clinical trial:
• Disease/Condition entry criteria
• Clinical trial design
• Endpoint positioning
C. Select clinical outcome assessment (COA) type:
• Patient-Reported Outcome (PRO)
• Observer-Reported Outcome (ObsRO)
• Clinician-Reported Outcome (ClinRO)
• Performance Outcome (motor, sensory, cognition)
A. Search for existing COA measuring COI in COU:
• Measure exists
• Measure exists but needs to be modified
• No measure exists
• Measure under development
B. Begin COA development
• Document content validity (qualitative or mixed methods research)
• Evaluate cross-sectional measurement properties (reliability and construct validity)
• Create user manual
• Consider submitting to FDA for COA qualification for use in exploratory studies
C. Complete COA development:
• Document longitudinal measurement properties (construct validity, ability to detect change)
• Document guidelines for interpretation of treatment benefit and relationship to claim
• Update user manual
• Submit to FDA for COA qualification as effectiveness endpoint to support claims

THANK YOU