EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

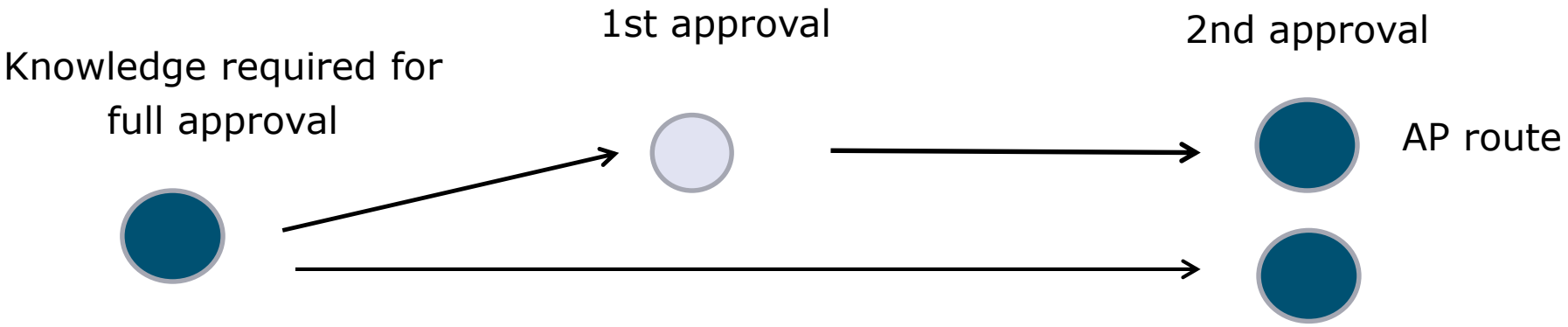
EMA Adaptive Pathways Pilot Report to STAMP

20 October 2015
Francesca Cerreta – Scientific Advice, EMA

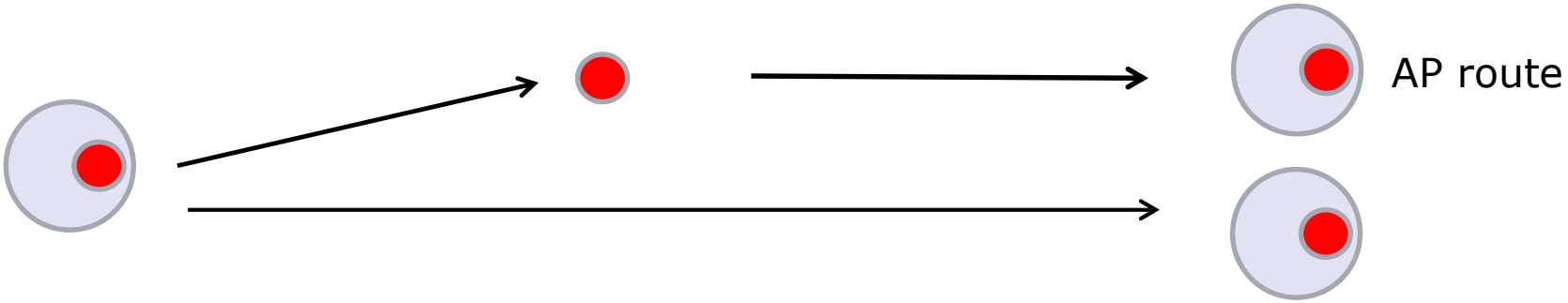
1995 2015 EMA

The Adaptive Pathways concept

1) Conditional approval scenario



2) Expansion of indication scenario



Criteria for AP candidate selection

1. An iterative development plan: start in a well-defined subpopulation and expand, or have a Conditional Marketing Authorisation, maybe surrogate endpoints and confirm
2. Real World Data (safety and efficacy) can be acquired to supplement Clinical Trials
3. Input of all stakeholders, particularly HTAs, is fundamental

Unmet medical need is self-fulfilling.

..a product lifecycle outlook

If we look at these criteria….AP is already here even if we do not call it so.

Lemtrada (Multiple sclerosis)

Expensive ($160K) drug with difficult safety profile. 2 courses of treatment at month 0 and 12.

5-yr open label follow up results: 60-68% of patients did not require retreatment (remission, relapse, disability, MRI..)

Follow-up may continue to 10-15 yr. Biomarkers?

Would these results have been obtainable in an RCT?

How will these findings affect the B/R and value proposition?

Aim of AP pilot is to support development, not institute new procedures or a "qualification"

If we look at these criteria….AP is already here even if we do not call it so.

Entresto (sacubitril + valsartan; heart failure; composite endpoint of CV death or HF hospitalization.) Expensive drug with benefits realised in a long timespan.

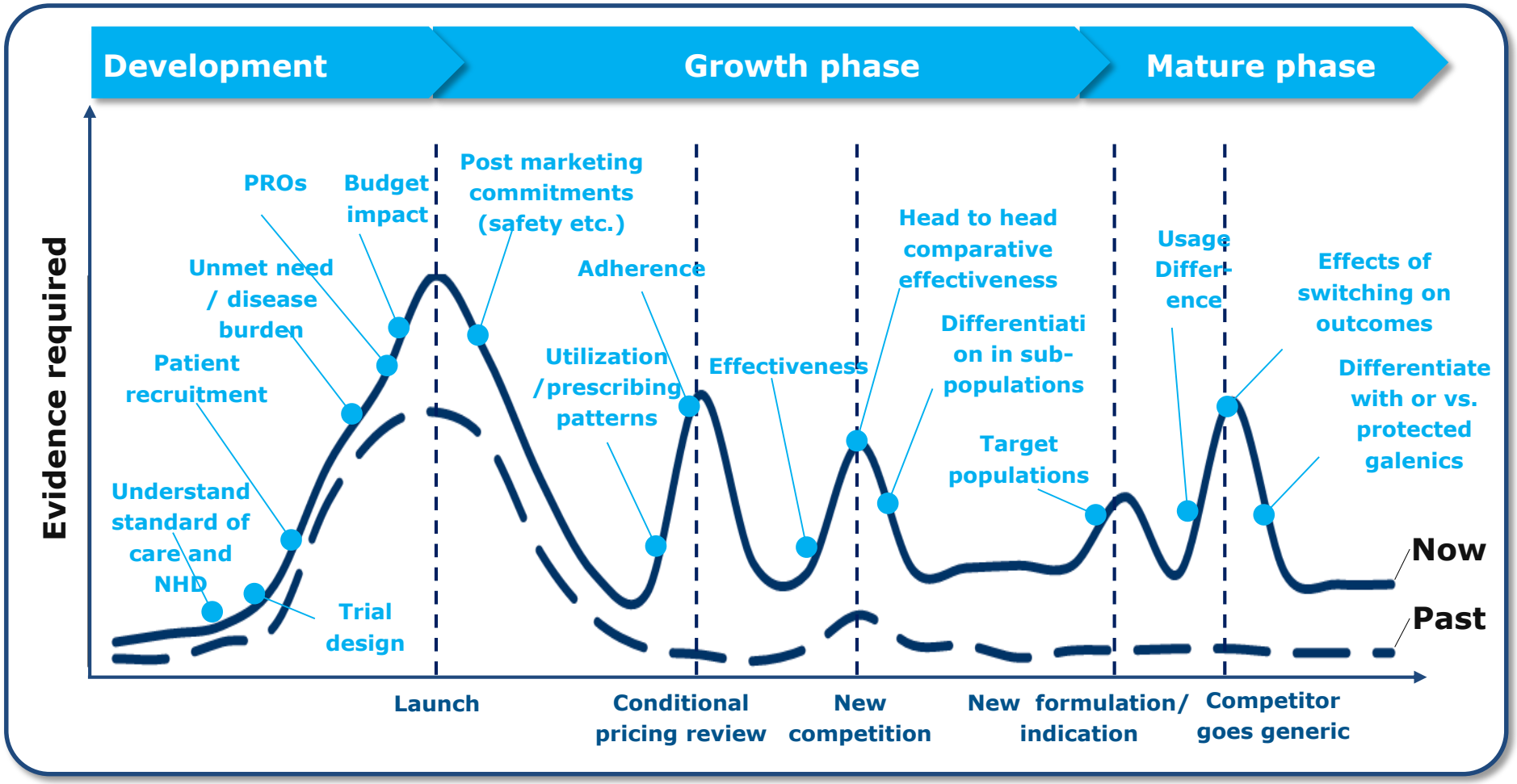
Olysio (Sovaldi's competitor, Genotype I) Pay-per-performance agreements reached with some payers.

Aim of AP is to bring together stakeholders who can advise prospectively on development

What have we learned on

Real World Evidence and Registries

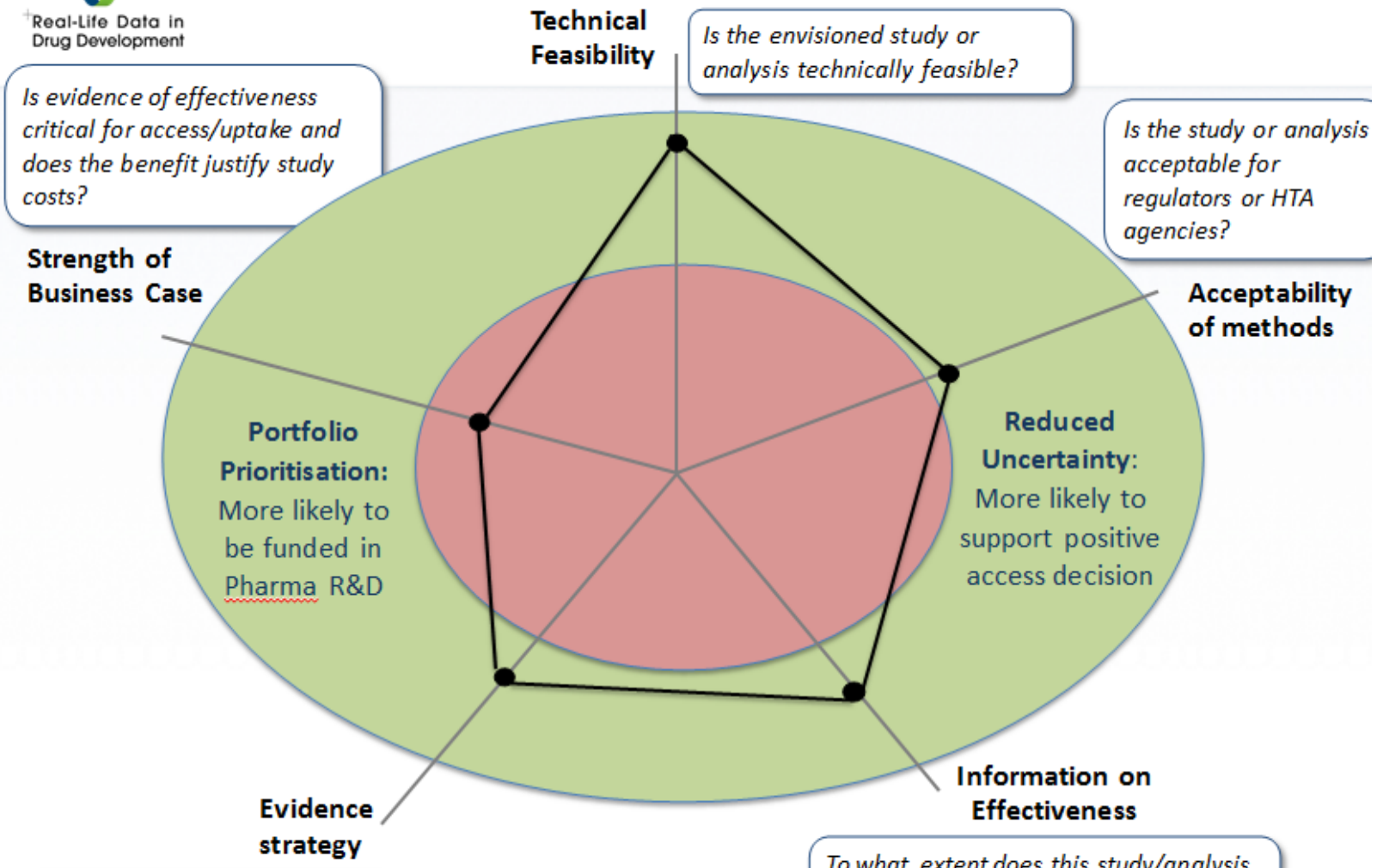
RWE can support access throughout the lifecycle



Source: IMI GetReal

RWE DECISION MAKING: 5 KEY ATTRIBUTES

Get Real
Real-Life Data in Drug Development



The research leading to these results has received support
agreement no [115303], resources of which are composed
Programme (FP7/2007-2013) and EFPIA companies' in kind
www.imi.europa.eu

RWE examples in AP applications (1)

- Use of existing disease registries to identify natural history of the disease, current SoC, resource utilisation, adherence to treatment.
- Single arm studies for rare diseases compared with outcomes inferred from disease registries
- Open label salvage studies in patients with no therapeutic options remaining, with the purpose of obtaining an expansion of the indication;
- Collection of efficacy and safety data from early access/compassionate use programs to supplement RCTs in small populations;
- Post-authorisation drug registries for effectiveness, long-term outcomes, drug utilisation, PROs, time to treatment failure, diagnosis confirmation

RWE examples in AP applications (2)

- Linking drug registries to risk-sharing schemes for reimbursement (pay per performance, annuity payments…)
- Expansion of the indication based on a mixture of disease registries and compassionate use data (for rare, severe diseases, where RCT data were available for less severe forms of the disease);
- Post authorisation studies to investigate biomarker (or other subpopulation selection criterion) status of an all-comer population;
- Investigation of non-serological outcomes for vaccines.

Learnings on RWD

Traditionally:

- Informing safety for regulators
- Important for HTAs/(relative) effectiveness

Increasing importance to supplement/inform efficacy in a real world population. Discussions within:

- EMA registries pilot
- IMI GetREAL
- Adaptive Pathways proposals

Should provide further clarity to formulate future development proposals

What have we learned on

Iteration

Proposed MA route not specified in many cases (too early, hoping to have full MA?)

Prospective CMA discussions actively encouraged after STAMP input.

Some proposals included both expansion of the indication and confirmation after CMA.

- Expansion of indication (to either less severe patients or other indications): 15/19
- Specified CMA route: 11/19 (maybe more)
- Early/surrogate endpoints proposed: 11/19

What have we learned on

HTA involvement

Who participated?

Involved in at least one procedure were HTAs from:

UK, NL, SE, DE, IT, FR, AT, NO, FI

EUNetHTA as observer

Other bodies have been involved for vaccines.

Payers participated in one case to provide high-level comments on risk sharing plan.

What were the questions asked by applicants?

- Are surrogate/early endpoints acceptable?
- How do they relate to "hard" clinical endpoints?
- What QoL/ADL data and scales are needed?
- Can existing disease registries be used for SoC, disease progression, indirect analysis of comparators and outcomes, off-label use.
- Development of co-diagnostics for subpopulation identification
- Models for risk sharing
- Design of post-approval studies for dual regulatory/HTA purpose
- Validity of data from other countries

What did we learn?

- Companies provided generally a sketchy elaboration of value proposition (early stage? Risk aversion?)
- Recognised divide in perception of risk from medical/market access division of companies (Questionnaire in ADAPT SMART)
- SMEs so far have been more creative
- Resource intensive procedure: felt particularly by HTAs
- As compared to parallel SA/HTA, payers input is missed (acceptability of reduced package)
- Challenge to bring right stakeholders with right expertise into the discussion
- Procedures that progressed to parallel SA/HTA had more detailed discussion.

Other lessons learned

- AP is a **lifecycle** approach, involve PRAC, PDCO, COMP, CAT, BWP.
- CMC poses **specific challenges for ATMPs**: discuss backup plans if CMC development does not progress as expected.
- Impossible to **quantify earlier access time**: no terms of comparison, MAA planned long time in future. Qualitative answer possible.
- Need to understand/map **which stakeholders** need to be involved
- understanding of **payers**' reaction to actual proposals or hypothetical scenarios would help.

Food for thought and for discussion

1. Is prescription control to the initially licensed population achievable?
2. Are registries linked to pay-per performance or other risk sharing schemes achievable in your Member State?
3. How to engage all critical stakeholders in a meaningful and effective way? Are all relevant decision makers involved, and if not, what are the obstacles?
4. Are there any other aspects on the feasibility of adaptive approaches that should be investigated at MS level?

Additional slides

Initial experience

- 59 products submitted as candidates
- 20 selected for in-depth discussion with company (Stage I)
- 15 Stage I discussions have taken place

Of the 20 selected products:

- 4 SMEs
- 5 are Orphan drugs
- 4 are ATMP (Advanced Therapy Medicinal Products)
- 5 Anticancer

- 11 proposals selected for Stage II (in-depth meeting after Stage I) (1 ATMP, 5 Orphan, 3 SME; 3 anticancer)
- Main reasons for rejection were:
  - Development too advanced (too late to change anything)
  - Limited learning potential for a pilot (no developed proposal for use of RWD, limited iteration)