



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Adaptive Pathways – Regulators' learnings

Francesca Cerreta
EMA – Scientific Advice





Development support and early access at EMA

Legislative tools

- Conditional MA
- Accelerated assessment
- Scientific advice
- Orphan designation
- ATMP classification, certification
- CHMP opinion on compassionate use
- SME office

Development support tool *to optimise use of existing legislative tools*

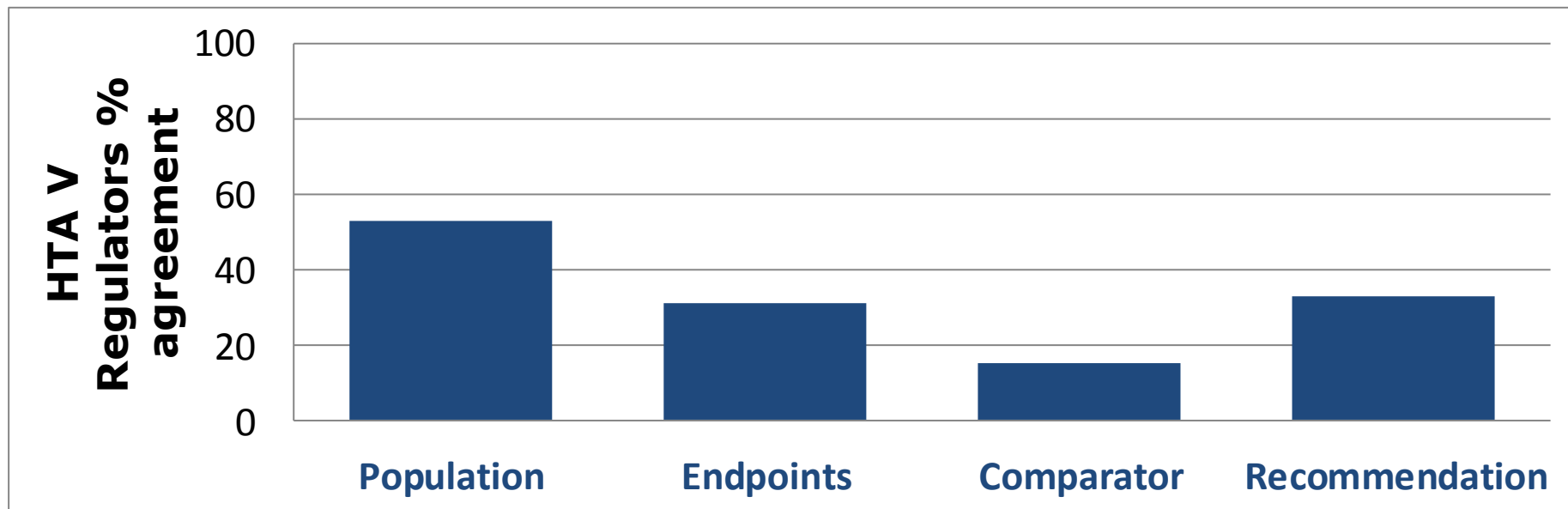
- PRIME
- ITF

Content concept : Adaptive Pathways *To define the product development pathway*

- Expansion/confirmation
- Involvement of stakeholders
- Use of Real World Data

The status quo: HTA/regulators agreement on RCT design

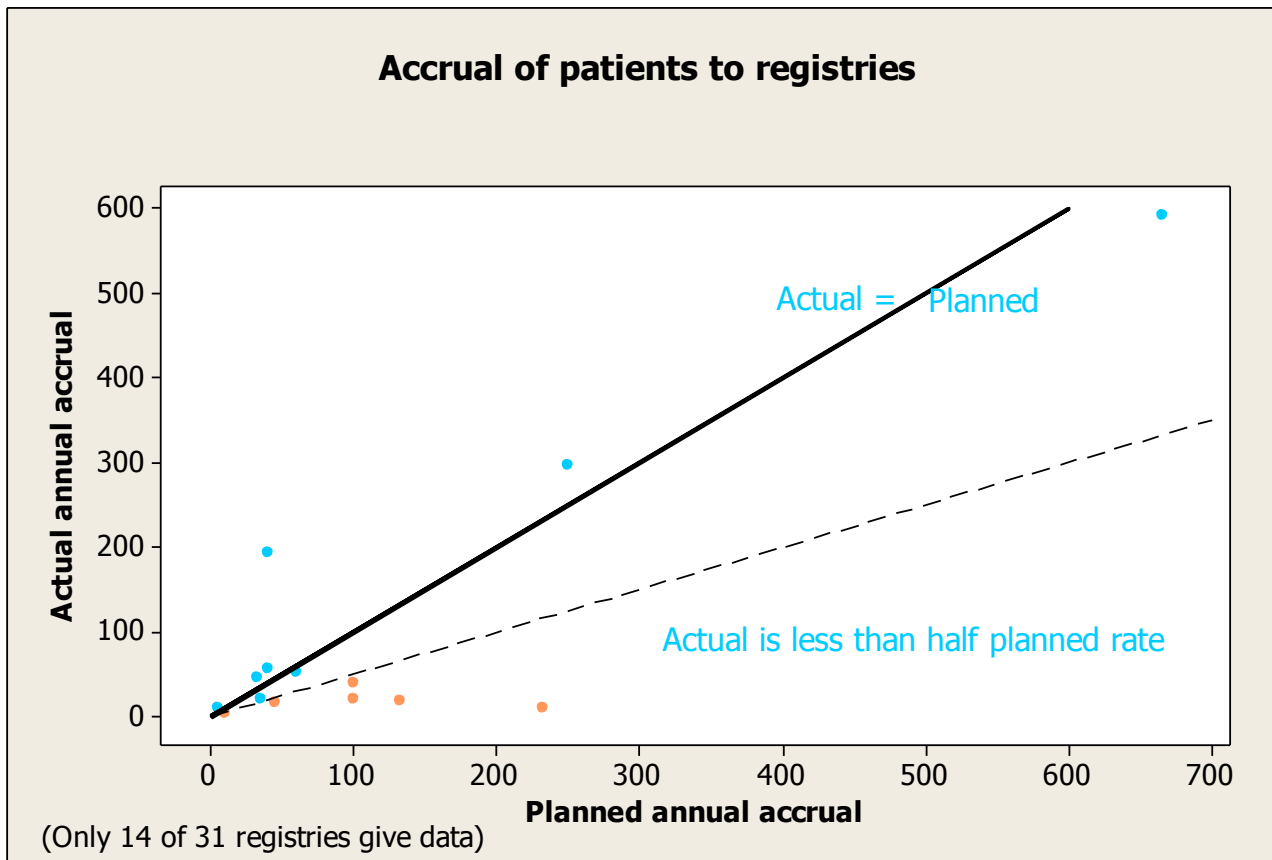
EFPIA analysis on 56 products



<http://www.efpia.eu/documents/189/61/HTA-Accelerator-In-Depth-Analysis-Final-report>



The status quo: planned vs actual number of patients in registries





Did we really need adaptive pathways?



Adaptive Pathways

Objective: provide early access to beneficial medicines that address an unmet need

Access delay issues addressed in Adaptive Pathways:

- Conditionally approved medicines face challenges and delays in HTA assessment
- Difficulties to acquire data in a traditional RCT setting (e.g. long studies for disease modifying or gene therapy drugs, complex trial logistics for antiinfectives)
- New reimbursement models may need to be considered in certain cases (e.g. pay per performance)

How AP addresses these delaying issues:

Early dialogue with the relevant stakeholders to design a smart development program that acquires the relevant evidence base, using all data sources, for a seamless decision making transition.



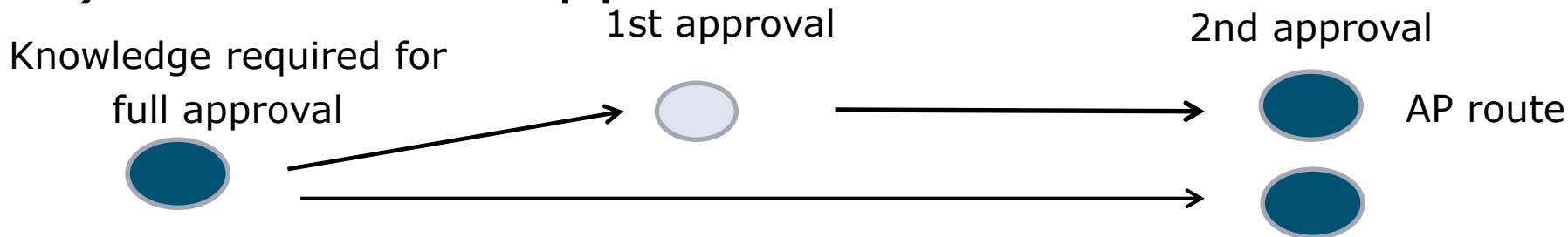
Criteria for a good candidate product

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

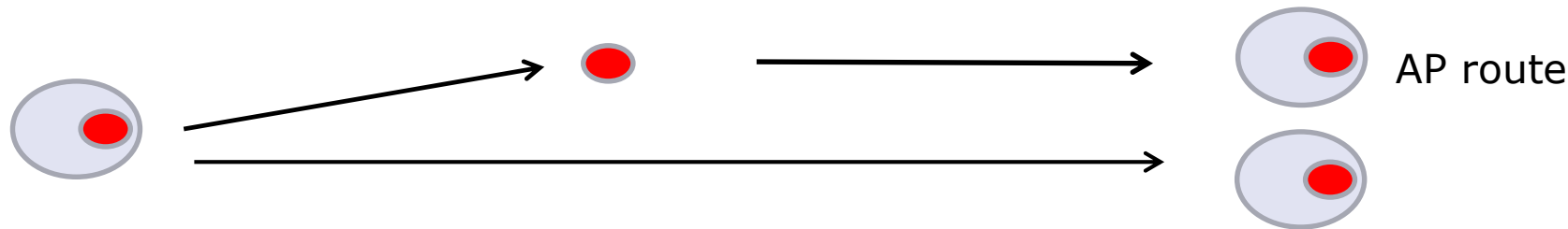
If these are not present, other support schemes are more suitable

The Adaptive Pathways concept

1) Conditional approval scenario



2) Expansion of indication scenario



Prescription control to initially licensed population

Influenced by: frequency of disease, precision of diagnosis, availability of therapeutic alternatives, price and reimbursement, point of dispensing (hospital, specialised doctor), societal pressure and expectations.

Achievable?

- Not for private prescription,
- facilitated by single IT prescription system which includes diagnosis
- balance resources required to achieve the control and cost of the drugs

How?

- all treated patients in registries (cost, plausibility, feasibility of registry).
- model on the traceability schedules in place for medicinal blood products?



Some RWE examples in AP applications

- Registries: natural history of the disease, SoC, resource utilisation, adherence to treatment, effectiveness, long-term outcomes, drug utilisation, PROs, time to treatment failure..
- Single arm studies for rare diseases vs outcomes in disease registries;
- Open label salvage studies to obtain expansion of the indication;
- Efficacy and safety data from early access/compassionate use to supplement RCTs in small populations;
- Linking drug registries to risk-sharing schemes for reimbursement (pay per performance, annuity payments...)
- Investigation of non-serological outcomes for vaccines

RWE acquisition should be designed to **address justified uncertainties** emerging during the evaluation process.

A RWD plan to address downstream stakeholders needs

A managed entry approach is essential to the AP paradigm

Value may change both upwards and downwards with further data acquisition

resource investment – minimum impact on clinical practice

Must be designed to be useful to patient and prescriber, correctly communicated

clear-cut ACTIONABLE performance measures should be chosen (eg Sustained Virologic Response, survival rates) for re-assessment of B/R value and P&R

Risk-sharing price reductions are simpler to implement and easier to negotiate solution for drugs with marginal benefit :not affect practice of treatment and low burden of additional data collection, but miss the opportunity of RWD collection and B/R refinement.

Little experience on data collection from compassionate use programs. Opportunity to use better?



Clear communication in SmPC

improve sections 4.2 and 5.1 of the SmPC so that the indicated population is unequivocal:

- kind of pre-treatment,
- combination with other medicines,
- treatment duration or number of cycles,
- the investigated population
- transferability to other populations.

ATMP issues

CMC evolves continuously, pre and post-authorisation.

2 selected products wanted to discuss CMC, and both were ATMPs

Upscaling as a paradigm for adaptive licensing. Comparability considerations with manufacturing changes/extension to further sites.

Potential adaptive proposals:

1) initially license small scale production, scale up later

2) aim for restricted use in centres of excellence from the outset.

- License initially for production and use in one centre.
- Submit a variation to scale up after licensing when the investment is safer

Dedicated quality discussions are possible within AP, involving CAT and BWP



Did we really need adaptive pathways?

AP offers the opportunity to address specific product access issues by designing a development plan more **relevant** to stakeholders needs, and optimising data acquisition so as not to expose patients to unnecessary studies.

It is applicable only in a **limited** number of cases: **promise** to fulfil unmet need, clear-cut, **actionable** endpoints are required

Interaction between the “worlds” of regulators, payers, HTA

To realise the benefit and smooth the road to access, other stakeholders need to be involved, for planning and implementation.

- product prioritisation in a world of limited resources– Who should select the products?
- Selection criteria and meaning of “need” (clinical, public health, cost reduction?)
- Entry and exit schemes and pricing commensurate to performance
- Joint guideline development
- Prescription controls
- Feasibility/desirability of post-authorisation data acquisition vs other risk sharing schemes. Making the most use of available data, access to other stakeholders for their decision making
- Input in peri-approval advice, choose *actionable* endpoints for decision making
- ¹⁴Parallel assessment of RWD data (?)



Other learnings

Companies provided generally a sketchy elaboration (early stage? Risk aversion? – we need to know more!). **SMEs** so far have been more creative. **Trust** is important.

Resource intensive procedure: felt particularly by HTAs. Challenge to bring right stakeholders with right expertise into the discussion to provide good input at protocol design stage

Procedures that progressed to parallel SA/HTA had more detailed discussion....but a broader change of **mindset** may be required at all stages of evaluation.

Payers input is often needed as compared to HTA/SA (acceptability of reduced package/ risk sharing scheme unknown)



Impact on patients and public health

What positive impact do we hope to achieve?

- Support likely winners
- Support less experienced drug developers
- Support efficient, speedy development and assessment
- Support speedy decision-making post-licensing (= access/reimbursement)

**Ensure
timely
access for
patients**



Additional slides

Initial Adaptive Pathways experience

- 62 products submitted as candidates
- 21 selected for in-depth discussion with company (Stage I)
 - 4 SMEs
 - 6 are Orphan drugs
 - 5 are ATMP (Advanced Therapy Medicinal Products)
 - 5 Anticancer
- 15 Stage I discussions have taken place (stage I closed)
- 12 proposals selected for Stage II (in-depth meeting after Stage I) (1 ATMP, 5 Orphan, 3 SME; 3 anticancer)



Additional reading

- **Support for early access** (PRIME, Conditional Approval, Exceptional circumstances, accelerated assessment)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000856.jsp&mid=WC0b01ac058096f643

- **Adaptive Pathways** webpage

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce

- **PRIME guidance and table of differences with Adaptive Pathways** (EMA/191104/2015)

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/03/WC500202630.pdf

- **EMA page on patient registries** (under Human Regulatory/Pharmacovigilance tab)

• **Cross-border Patient Registries Initiative (PARENT)**. Methodological guidelines and recommendations for efficient and rational governance of patient registries – version 1.3 – <http://www.parentregistries.eu>

- **ENCePP Guide on Methodological Standards in Pharmacoepidemiology**

http://www.encepp.eu/standards_and_guidances/index.shtml