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SCIENCE MEDICINES HEALTH

Adaptive Pathways – Learnings from pilot

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EMA development support and early access for medicines addressing unmet need

Development support tools

Optimise use of legislative tools

- PRIME
- ITF

Legal tools

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

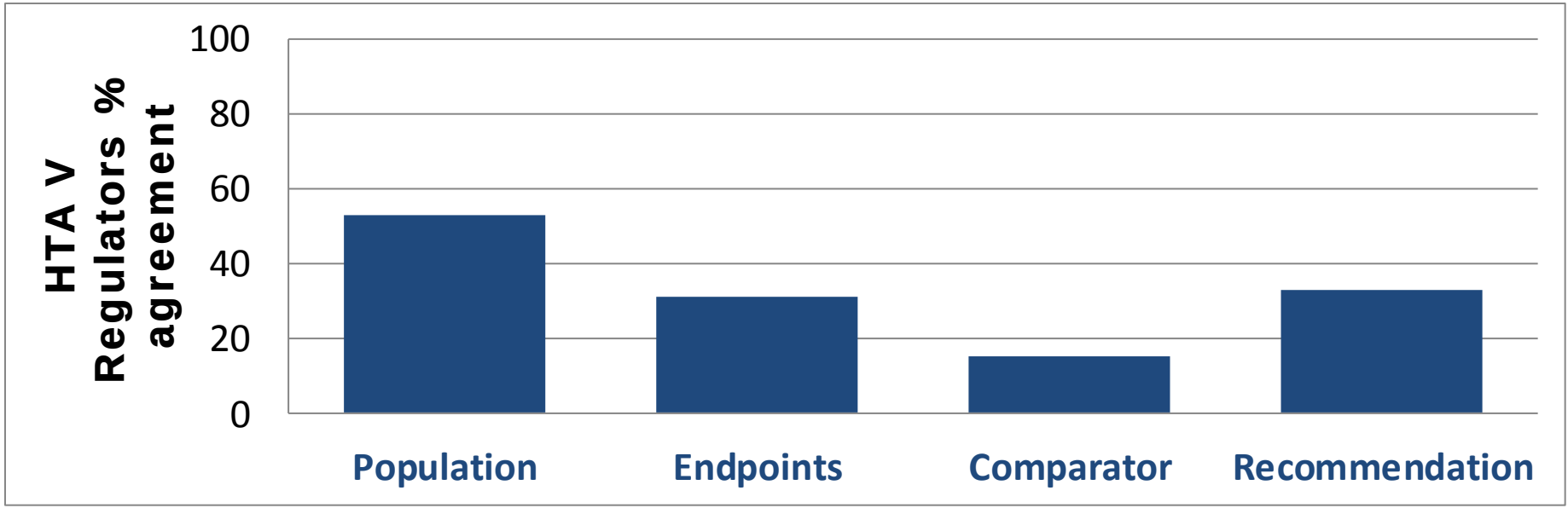
Content concept : Adaptive Pathways

Define the product development pathway

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

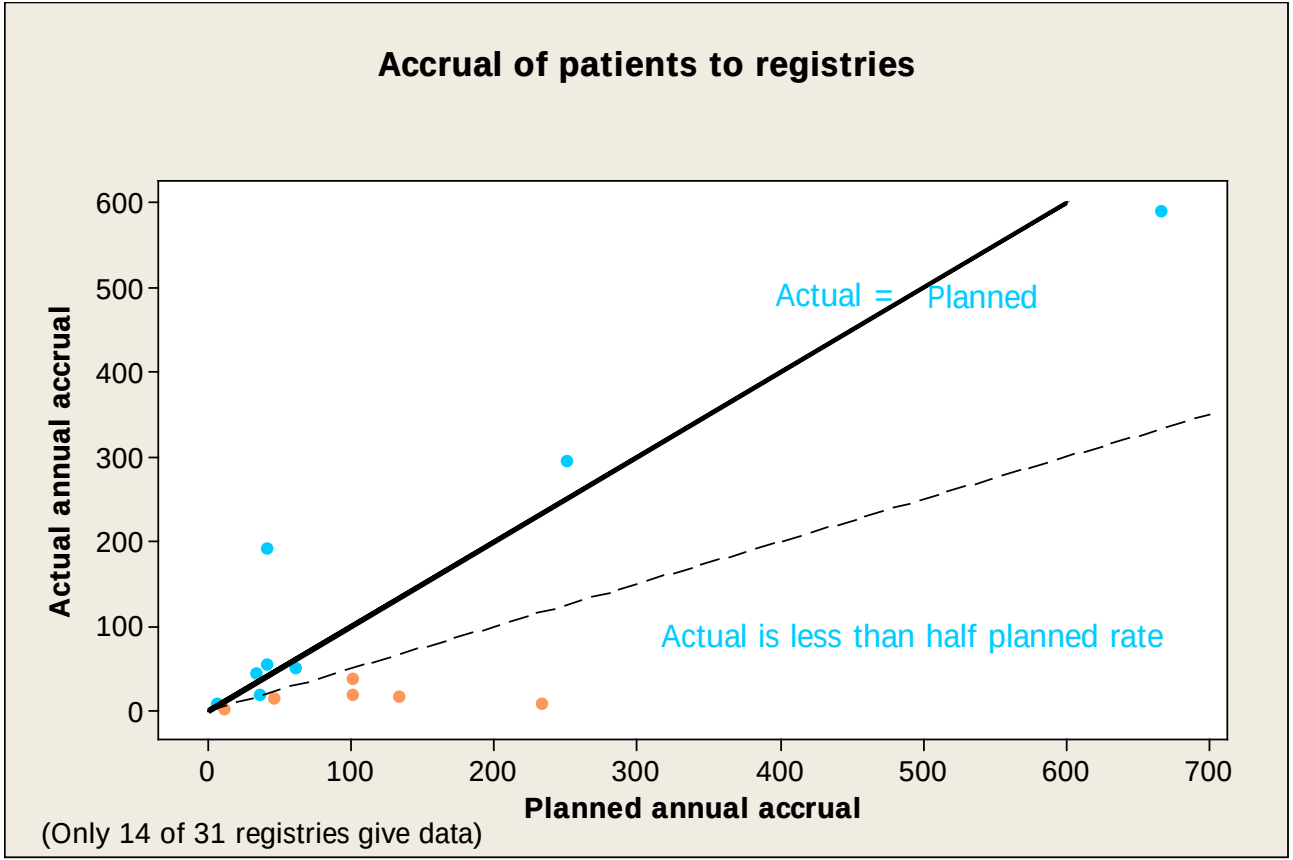
The status quo: HTA/regulators agreement on RCT design

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

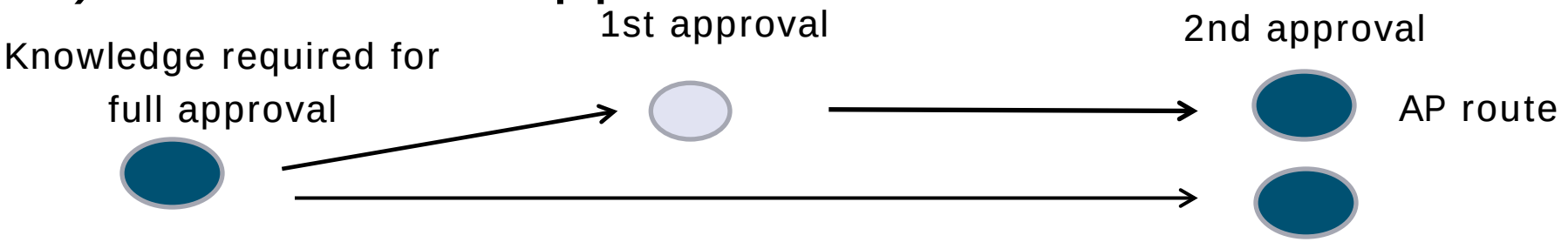
If these are not present, other support schemes are more suitable

If there is no unmet need, “normal” development should apply.

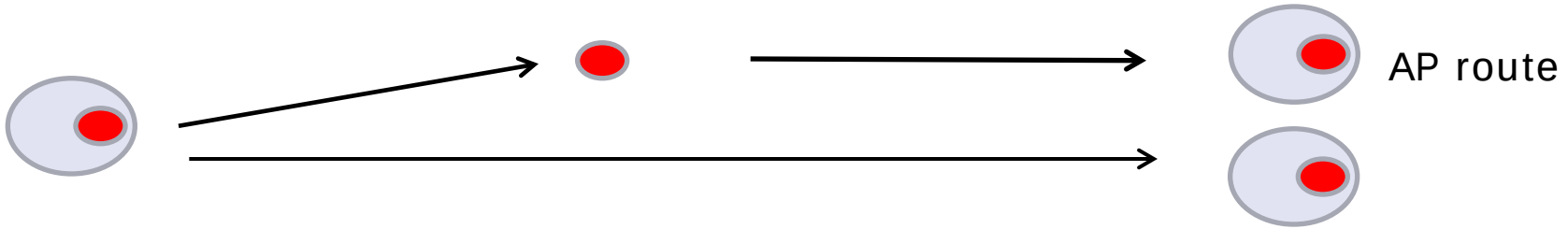
More than two thirds of candidates were redirected to other routes

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?

Real World Data – making the best use of all information sources

Case reports: a reliable source of information on safety

Well planned registry: unreliable to investigate effectiveness.

RWD acquisition should be designed to:

- **Address justified uncertainties** emerging during the evaluation process.
- **Confirm long term effects** of the medicine if initial approval is based on early or surrogate endpoints

Both already in use-could be done better! (prospectively+optimised)

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

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?

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

Learnings (1)

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To realise the benefit and smooth the road to access:

- A prospective, life-span discussion of product development with different stakeholders is possible and desirable in cases where decision making could be delayed by suboptimal planning.
- Focus product selection in a world of limited resources. Selection criteria and meaning of “need” (clinical, public health, cost reduction?).
- Increase patient participation to decide product selection, and to provide insights on risk management, feasibility, ethical aspects, and to support enrolment in trials and registries.
- Making the most use of available RWD data, feedback/access to other stakeholders for their decision making.
- Prescription controls are important

Learnings (2)

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- Discussions on entry and exit schemes and pricing commensurate to performance are possible. Payer's input on feasibility may be needed as compared to HTA/SA.
- Joint guideline development with HTAs to streamline requirements
- Input in peri-approval advice, choose *actionable* endpoints for decision making
- 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 (in safe harbour and in capability to conduct the studies).
- Confidentiality of discussions is part of the normal SA process.
- **Resource** intensive procedure: felt particularly by HTAs. Challenge to bring right stakeholders with right expertise into the discussion.

Proposed next steps (report soon finalised)

To make the process sustainable and utilise a well-tested and established framework , future submissions will be treated as parallel HTA/SA advice requests, granting an additional presubmission meeting to discuss the early draft:

- Established framework for patient participation
- More sustainable HTA input
- Publication of statistics and report annually as for other SA
- Two additional presubmissions for SMEs
- Other stakeholders (payers, FDA, WHO) may be invited if relevant

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