EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The Regulator as Gatekeeper and Enabler for Drug Development – a CHMP perspective

New Developments in Drug Regulation

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Outline of presentation

- introduction – the role of a regulator
- "traditional" tools in the tool-box
  - guidelines
  - scientific advice
  - procedures – eg Conditional Approval
- newer tools
  - SME office, ITF
  - product specific BE guidance
  - use of "Real World Data"
- transparency
- interaction with other stakeholders
- discussion & conclusions

Health warning: I have shamelessly used abbreviations through the presentation


The Regulator
Tough environment
Working hard for the government
Representing the society
Gatekeeper and Enabler
Paving the way!

The EMA Mission...

is to foster scientific excellence, for the benefit of public and animal health.

We are strongly committed to public and animal health.

We support research and innovation to stimulate the development of better medicines.

Gatekeeper and Enabler

Current challenges…

- Drug development increasingly costly and time consuming, insurmountable barrier for smaller players
  - High (and growing?) attrition rate
  - Cost / duration of (late) clinical phase keeps rising
- Change in the marketplace, drug development no longer such profitable business as it used to be
- Risk of active dis-investment from pharma R&D
- Increased complexity – many stakeholders

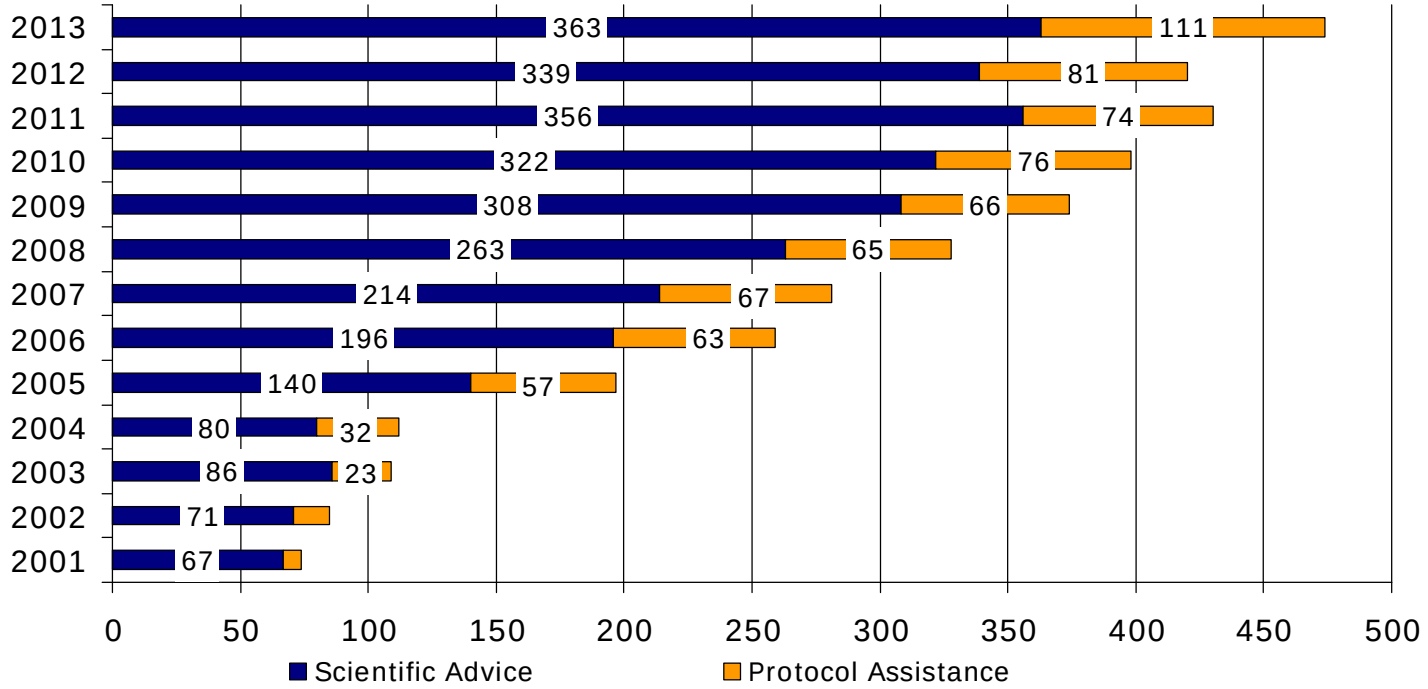
"traditional" tools in the tool-box

- Guidelines
  - Q, S, E & PhV
  - EU and ICH
  - science should drive guidelines…
  - not only for industry
  - Filip gave a good example yesterday

"traditional" tools in the tool-box

- Guidelines
  - Q, S, E & PhV
  - EU and ICH
  - science should drive guidelines…
  - not only for industry
- Scientific advice (Qualification Advice/Opinion)
  - national and EU

Scientific Advice and Protocol Assistance



...a few additional thoughts on Scientific advice

- educational aspects
- "binding" for regulators, advice to companies
- avoid wish lists
- context
  - written vs f-2-f
  - formal vs informal
  - background material – company presentations

"traditional" tools in the tool-box

- Guidelines
  - Q, S, E & PhV
  - EU and ICH
  - science should drive guidelines…
  - not only for industry
- Scientific advice
  - national and EU
  - informal and formal
- Procedures
  - Conditional MA, Approval under exceptional circumstances (EBOLA?)
  - Accelerated assessment

Newer tools (mixed bag)

- SME office (EMA and national)
- Innovation Task Force (ITF) – "safe harbor"
- Product specific BE guidance
  - SD vd MD, strengths, NTI, analytical aspects etc
- Use of "Real World Data" (RWD)
  - efficacy: more talk than action
  - randomized registry studies?

Transparency

- EPAR, publications
- Workshops (eg MS 2013, AD 2014)
- increased interaction with patients
- focus on the B/R section – Effects Tables

ET example – Caprelsa for thyroid cancer

	Effect	Description	Unit	Placebo	Vandetanib	Uncertainties / Strength of evidence	References
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46 95% CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
	PFS (median)	Weibull model	Months	19.3	30.5	Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?	Single-arm study in RET negative patients post-approval.
	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13	45	No clear effect on PRO/QoL (missing data)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; Life-threatening	%	2.0	10.8	Duration of follow up in the pivotal study is short *vs.* the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4)
	QTc related events Grade 3-4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4	Risk of developing further major cardiac SAEs including Torsades de pointe?	Restrict to symptomatic and aggressive disease (see SmPC 4.1).
	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4	49.8		Explore lower dose (see See Table 20. Summary of the RMP)

Interactions with other stakeholders – how to make the chain strong…

Approval – Reimbursement - Adequate use

EU National/Regional National/regional/local

Ongoing activities.....

- Joint Scientific advice: Regulators & Heath Technology Assessment
- Increased interaction with patients and patient representatives
- Interaction with the health care providers

Adaptive Licensing/Medicines Adaptive Pathways

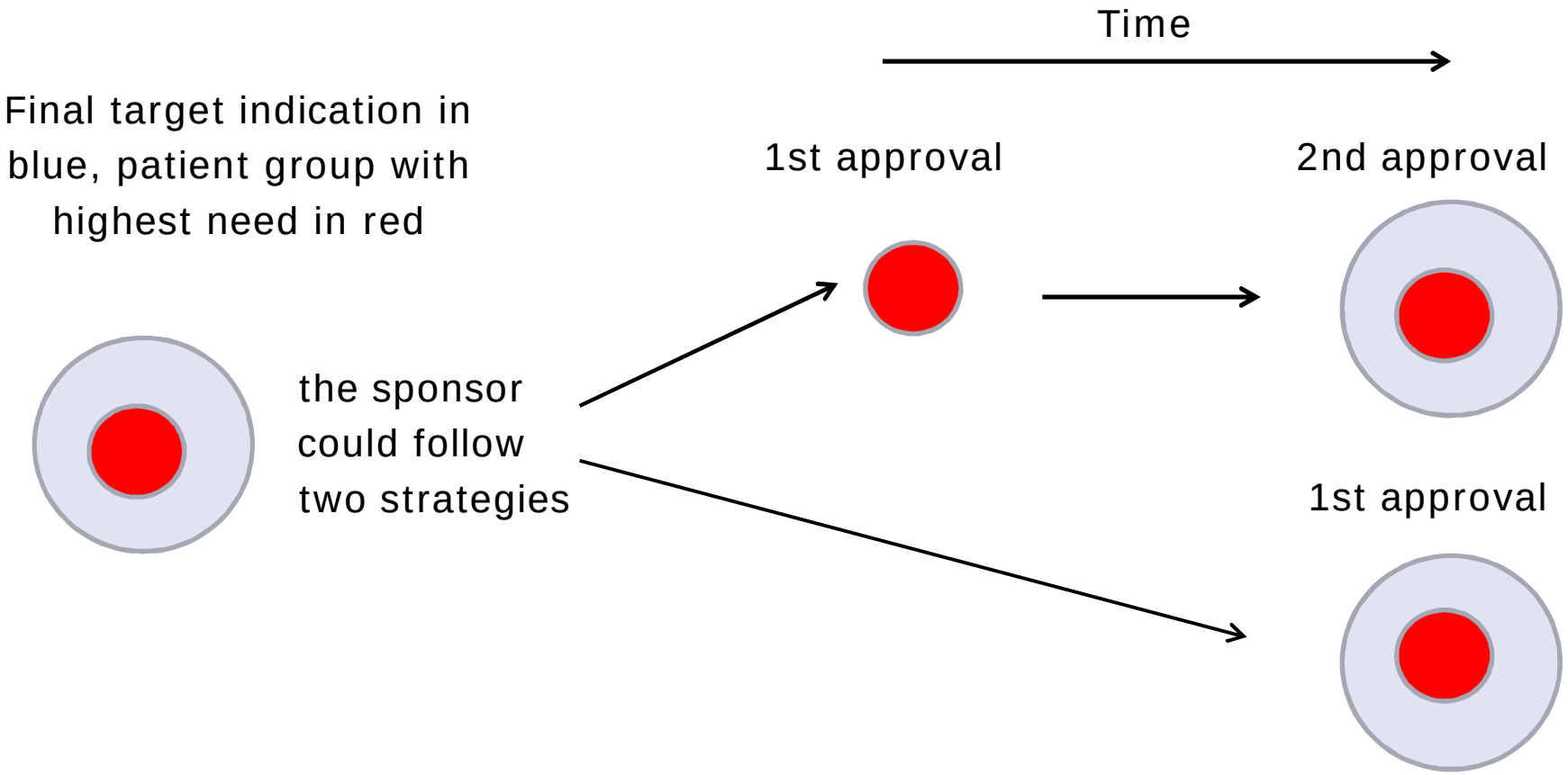
(MAP, MAPP, MAP2P)

Adaptive Licencing / Adaptive pathways

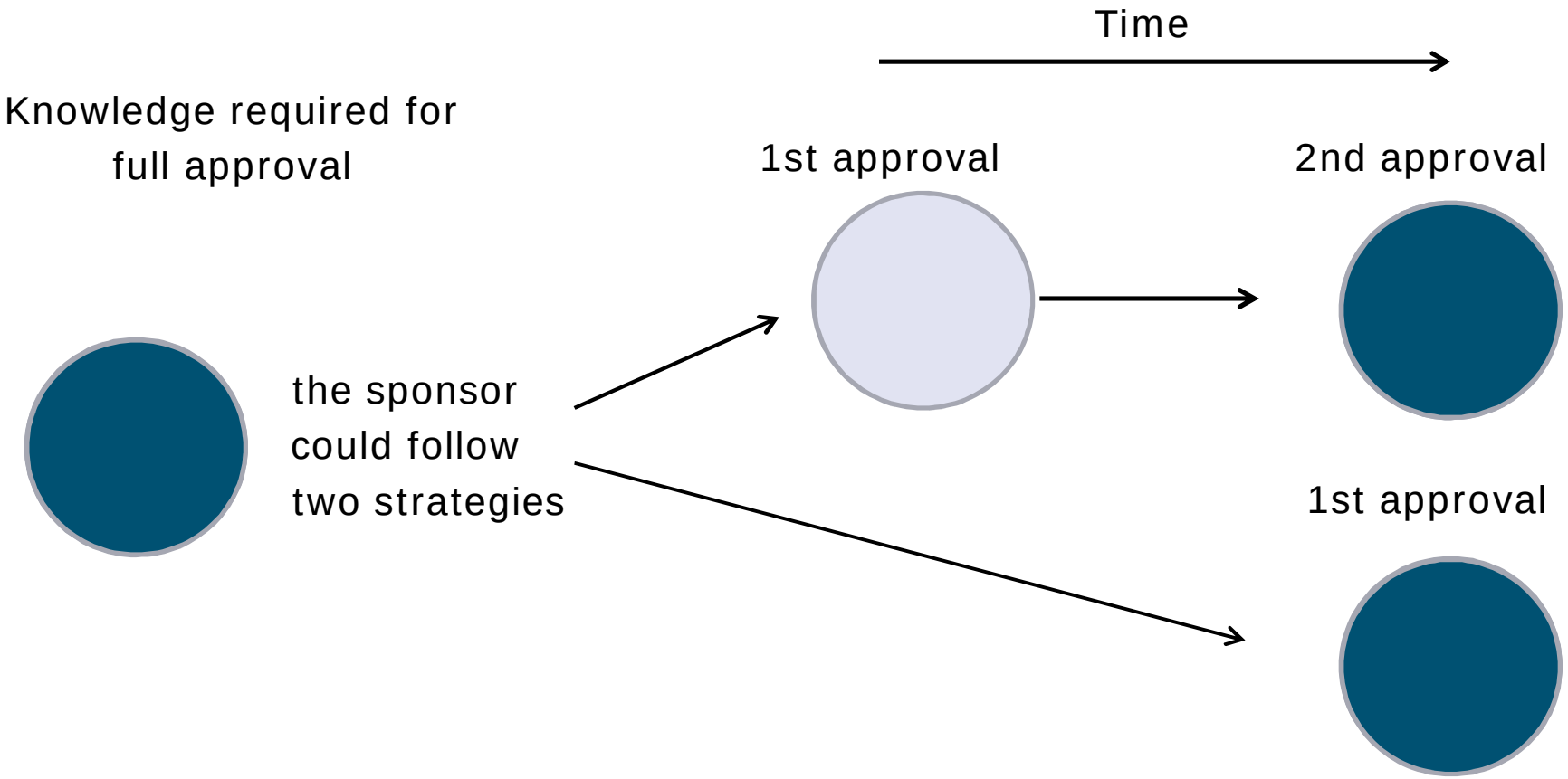
…..”The adaptive licencing process is based on a prospectively-planned process. It starts with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence-gathering and the adaptation of the marketing authorisation to allow broader patient populations to access medicine…”

…early multi-stakeholder dialogue

Adaptive pathways concept ("widening of the indication")



Adaptive pathways concept ("conditional approval")



Drivers of Adaptive pathways….

Drivers

- Patient expectations: demand for timely access and emphasis on unmet medical need
- Emerging science: fragmentation of treatment populations and early disease interception
- Healthcare systems under pressure: sustainability and rise of payer influence
- Pharma/investors under pressure: sustainability of drug development

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19 March 2014
EMA/254350/2012
Senior Medical Officer

Pilot project on adaptive licensing

There is currently much debate about adaptive pathways for new medicinal products to come to the market. The terms 'staggered approval', 'progressive licensing', and 'adaptive licensing' have been used, often interchangeably, to describe the same broad concept. More recently, the term 'Medicines Adaptive Pathways' (MAPs) or 'Medicines Adaptive Pathways to Patients' (MAPPs) is discussed as potentially more appropriate terminology. For the time being, and in the interest of internal consistency, the term 'adaptive licensing' (AL) is used throughout this document.

EMA AL pilot

Launched March 2014,

Q&A published Sept 2014.

What is it?

- A framework for informal, confidential, interactions
- Discussing ‘live’ assets
- Refine understanding of potential pathways
- Discuss how best to address potential blocking factors
- Identify additional hurdles not yet apparent

EMA AL pilot

Who? Sponsor, regulator and others as desired by the Applicant.

Which assets are prioritised?

- Iterative development pathway with iterative expansion of target population and / or progressive reduction of uncertainty around the initial decision
- Potential for real-world data collection and use
- Engagement of HTA and other stakeholders
- Unmet medical need opens to more regulatory options and acceptance of uncertainties
- Opportunity to influence clinical development
- ‘Large’ and ‘Small’ indications

Experience so far... (n=7 in the pilot)

- large interest from industry
- not an "Emergency" intake for development plans in trouble
- important for the sponsor to be able to predict obstacles
- although it is monitored and coordinated by the "AL"-group at the EMA an individual project need to be using the full capacity/competence of the system (eg SAWP)
- communication needed – eg why was a project not accepted into the pilot

EMA AL pilot

Some clarifications:

- Some mis-understanding that this is a **new** route to immediate approval
- Assets from which we can learn about AL are not always those most interesting from a public health perspective
- Non-acceptance to pilot doesn't damage chances of rapid regulatory approval

Adaptive Licencing Project: An experiment

- Advantages: Early approval and access to patients with real need, with involvement of all stakeholders and prospective planning to collect data
- Risks: Increased number of withdrawals; uncertainties may be higher in the initial licencing (?)

Discussions & conclusions

- Regulators should facilitate needed drug development
- Cost effective drug development is in the interest of the patients and the tax payer
- The Regulator should however not become drug developer
- Can we do more? – horizon scanning vs gap analysis

Thank you!

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