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CBG MEB
COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Novel regulatory tools & drug development support mechanisms

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Vice-chair EMA Scientific Advice Working Party
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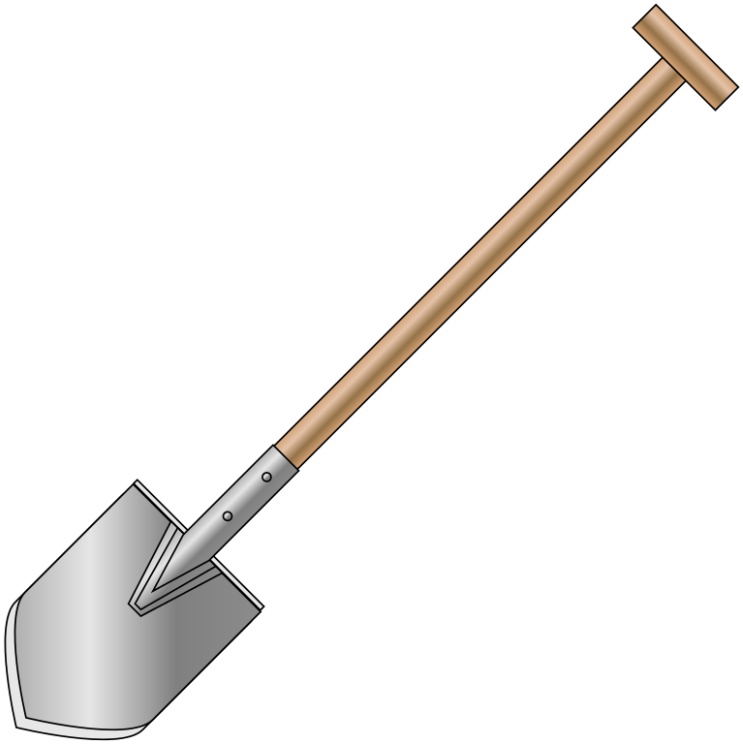
Today's program

09:00-09:40	Introduction to Day 3. How regulators work and think: the basics (Peter Mol)
09:40-09:45	Q&A
09:45-10:05	Novel regulatory tools & drug development support mechanisms (Peter Mol)
10:05-10:10	Q&A
10:10-10:25	Coffee break
10:25-10:50	Scientific advice (European & national) (Marjon Pasmooij)
10:50-10:55	Q&A
10:55-11:20	Case example – ATMP scientific advice (Viktoriia Starokozhko)
11:20-11:25	Q&A
11:25-11:40	Coffee break
11:40-12:10	Novel methodologies and Real World Evidence supporting drug regulatory decision-making
12:10-12:30	Final Q&A round (Moderator: Marjon Pasmooij)

Novel regulatory tools



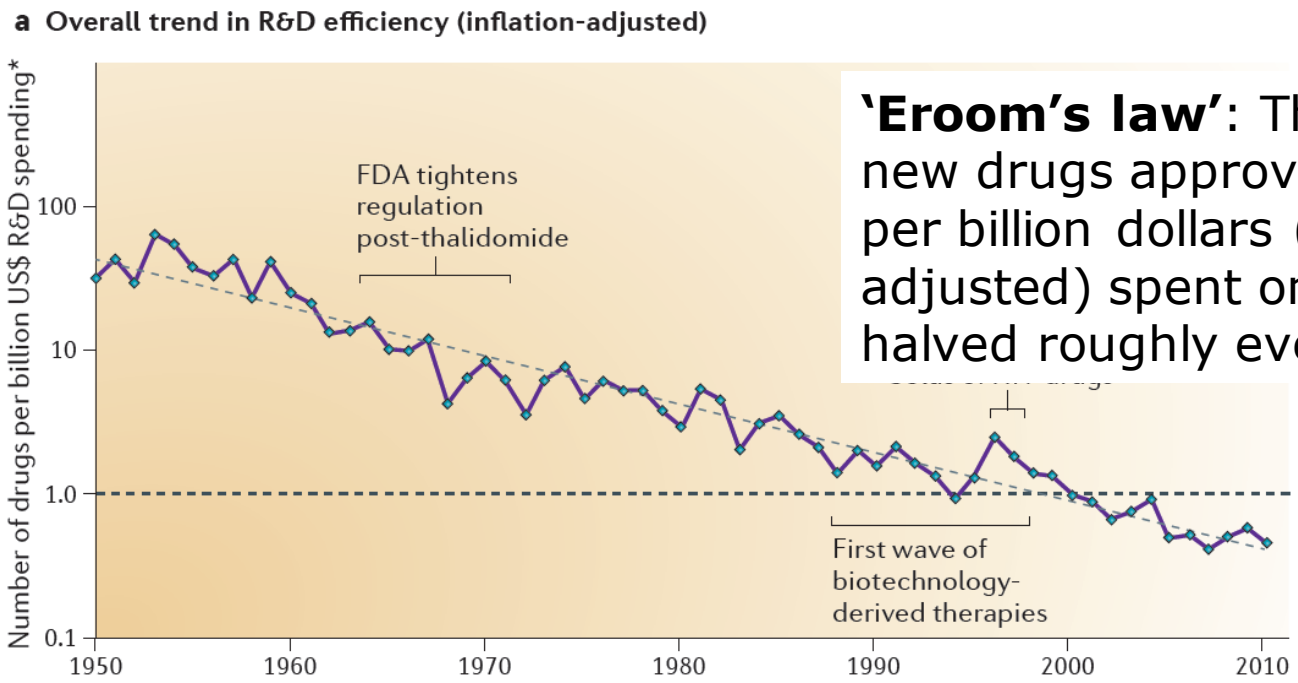
PRIME

Adaptive Pathways
& Conditional Approval

New Drug approval - difficulties

"The needed **development of new therapies**, however, is **hindered by** reliance on study methodology and **regulatory frameworks that are not conducive to new**."

ESC CV round table, Brussels March 13-14, 2014

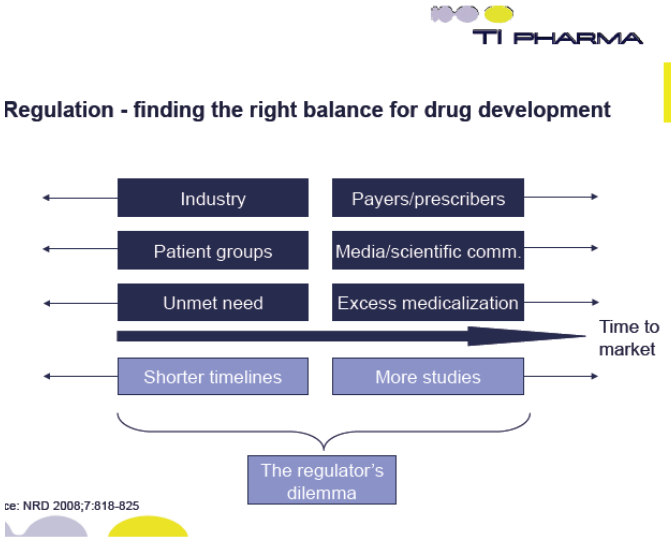


'Eroom's law': The number of new drugs approved by the FDA per billion dollars (inflation-adjusted) spent on R&D has halved roughly every 9 years

Scannell 2012 Nat Rev Drug Disc

Different Needs

my life, my choice,
mytomorrows.com



Dutch Health Minister to Parliament:

“If drugs could be brought safer and faster to the market, patients would not have to call as often upon organisations like My Tomorrows.”

Adaptive Pathways

Adaptive pathways*

- Scientific concept of development and data generation
- Iterative development with use of **real-life** data
- Engagement with other healthcare-decision makers

PRIME

- Dedicated and reinforced procedural support for promising medicines
- Enable accelerated assessment
- Better use of existing regulatory & procedural tools

*Pilot project was concluded in 2016

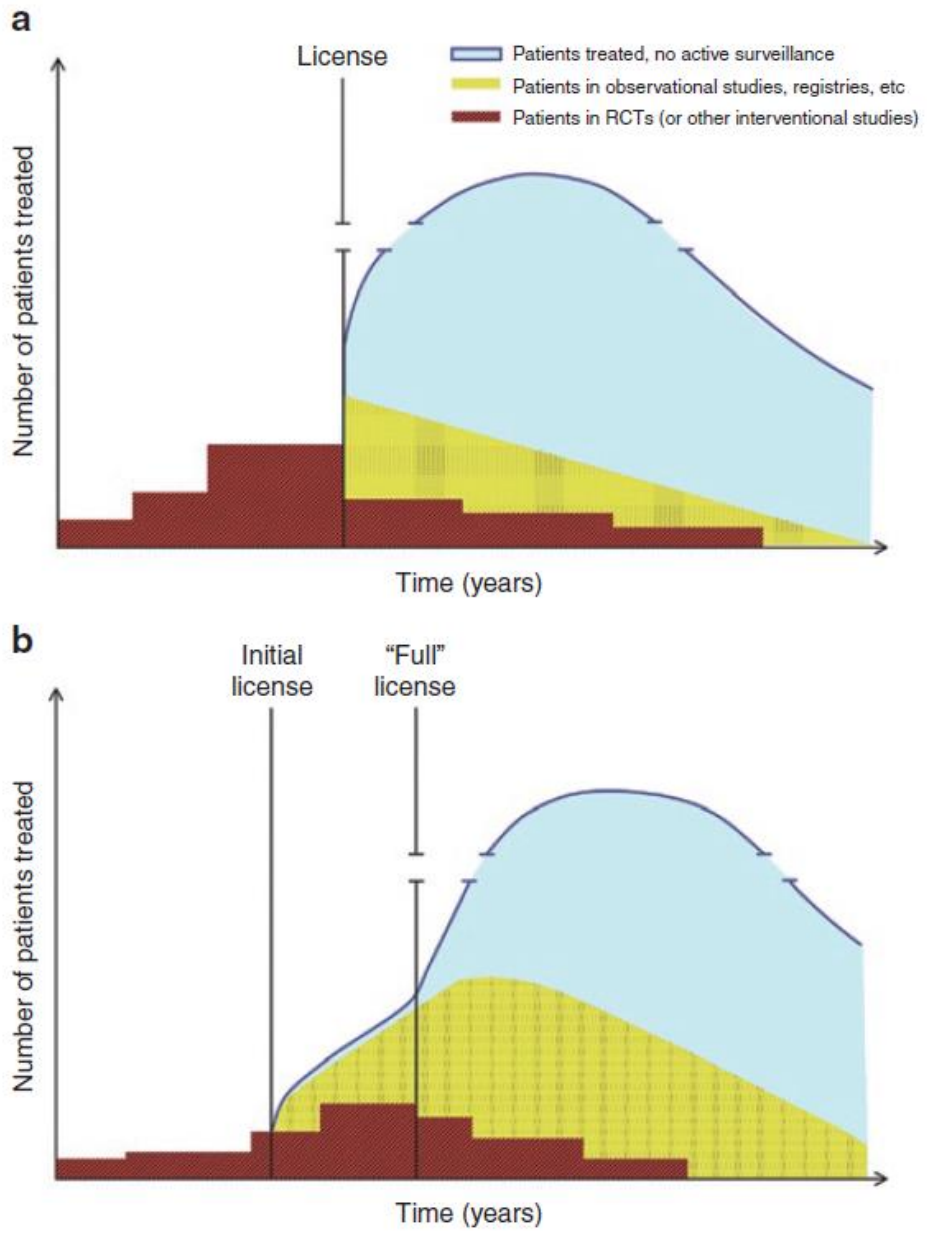


Figure 1 Time course of evidence generation and accrual rates of patients treated with a new drug under the current and adaptive licensing (AL) scenarios. The schematic representation is modeled on example 1 (weight-

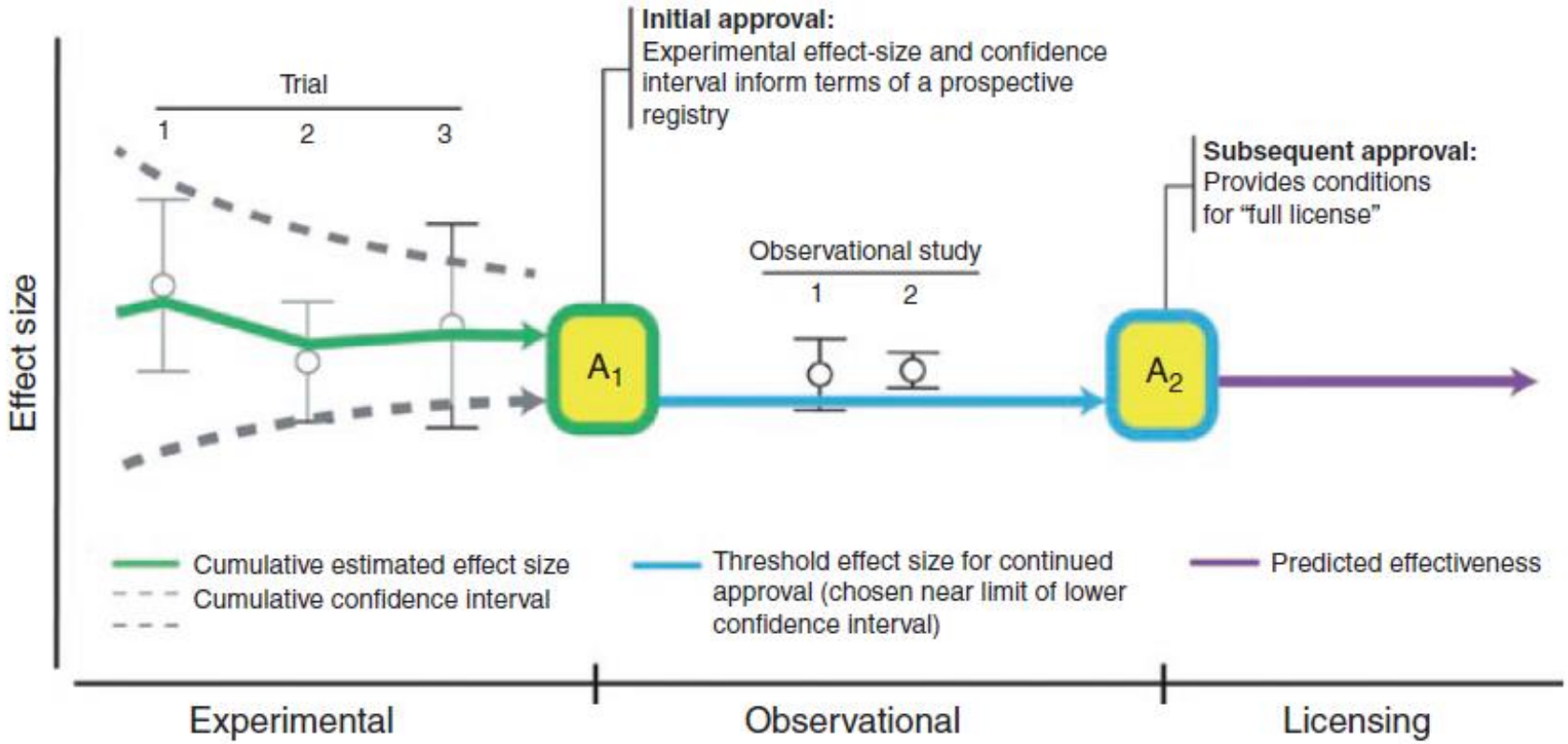
Evidence generation & Adaptive licensing

a)Current: patients treated pre-approval in RCTs; once approved population treated expands rapidly, but little information (e.g registries or observational studies)

b)Adaptive: fewer patients pre-approval, post licensing slower uptake due to ***prescribing restrictions***, most patients in **observational** (comparative effectiveness) studies or RCTs, after full approval less active surveillance over time

Eichler et al. 2012 CPT

Evidence Generation in 'Adaptive Pathways'



Eichler et al. 2012 CPT

Adaptive Pathways

Conditional Approval*

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Adaptive Pathways ~ Conditional Approval

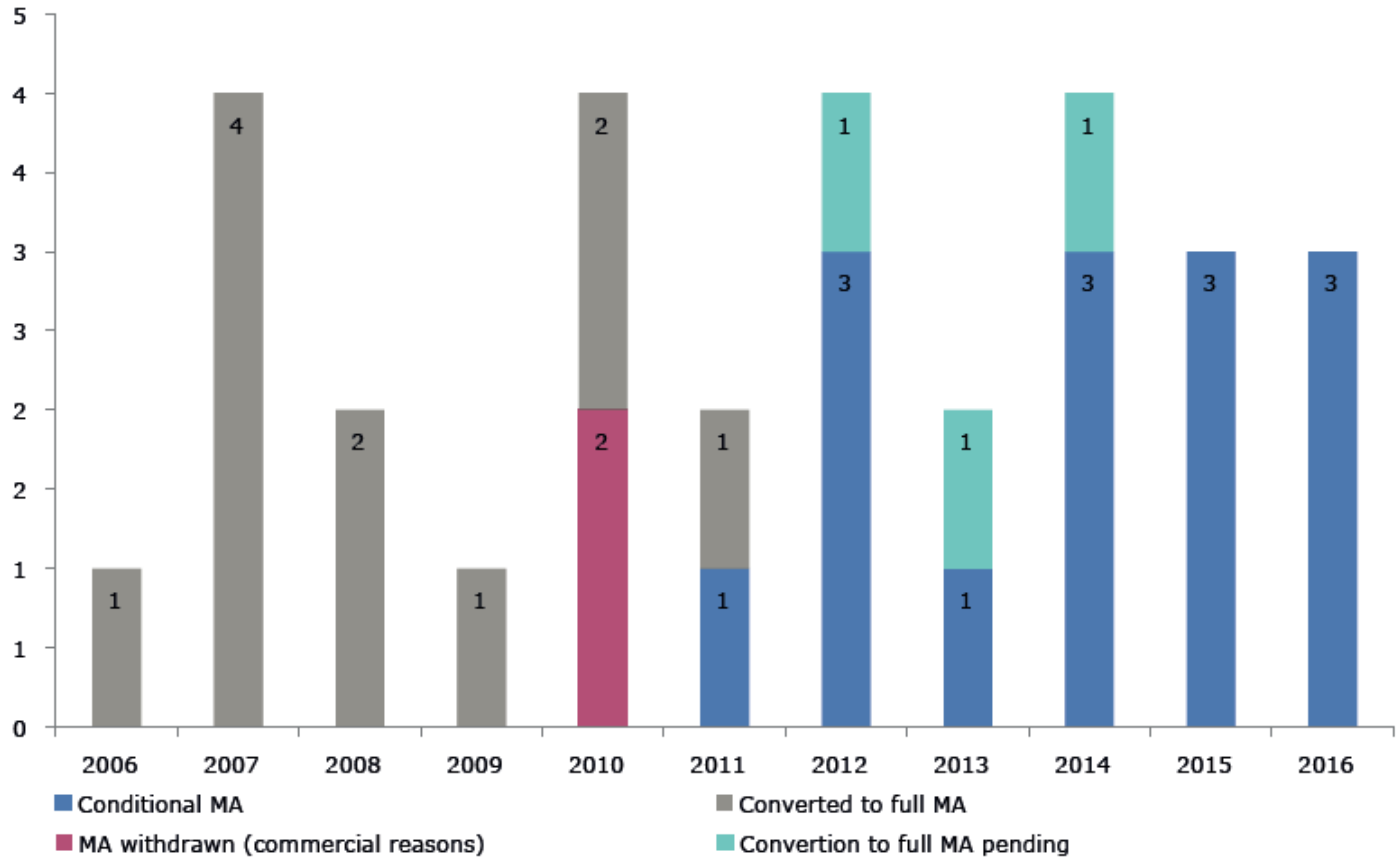
Conditional Approval & Exceptional Circumstances

Conditional Marketing Authorisation (Regulation EC No 726/2004, article 14(7))

- A renewable MA valid for one year and subject to specific obligations
- For the following medicinal products:
  - for treatment, prevention or medical diagnosis of seriously debilitating diseases or life-threating diseases
  - To be used in emergency situations, in response to public health threat
  - Designated as orphan products
- And fulfilling the following criteria:
  - **positive** benefit-risk balance
  - Applicant able to provide comprehensive clinical data **IF NOT Exceptional Circumstances**
  - 'the benefit to public health of the immediate availability on the market outweighs the risk inherent in the fact that additional data are still required.'

Conditional Approval - EMA 10 year review 2006 - 2016

Figure 4. An overview of conditional marketing authorisations granted by the year of authorisation and current status



https://www.ema.europa.eu/en/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf

Conditional Approval – for what? 2006 - 2016

Figure 5. Conditional marketing authorisati
by the therapeutic area (N=30)

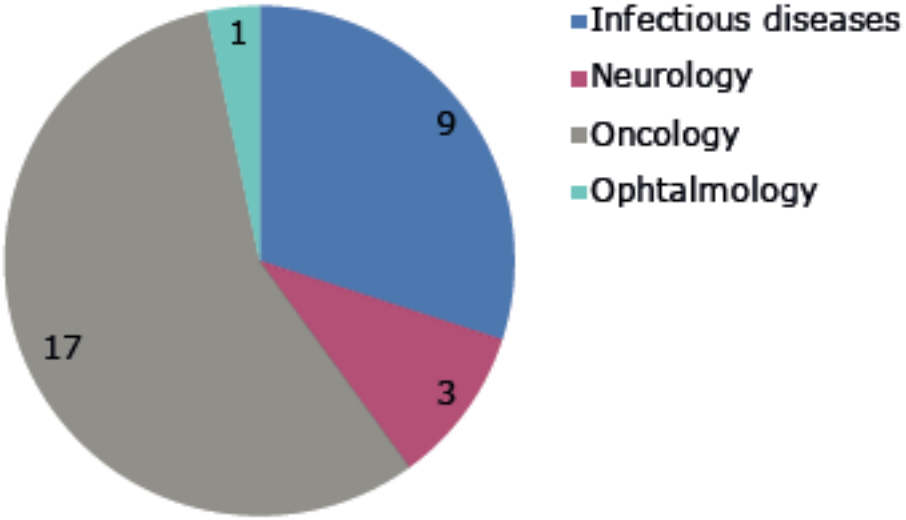
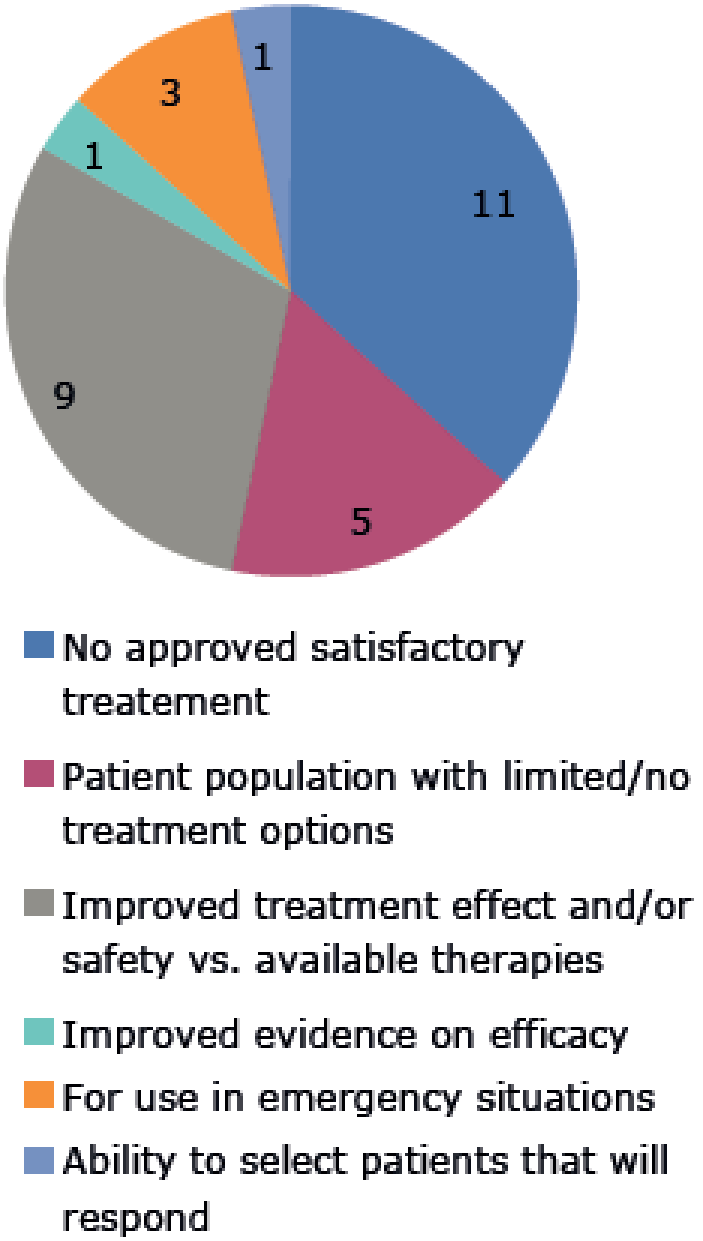


Figure 7. Categories of medical need(s) addressed by the CMA products (N=30)



BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2011.03995.x

Additional safety risk to exceptionally approved drugs in Europe?

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Keywords
conditional approval, drug safety, exceptional circumstances, licensing of drugs, regulatory affairs

Europe
1999-2009
289 NAS central approval
-46 EC/CA procedure
-243 'standard'

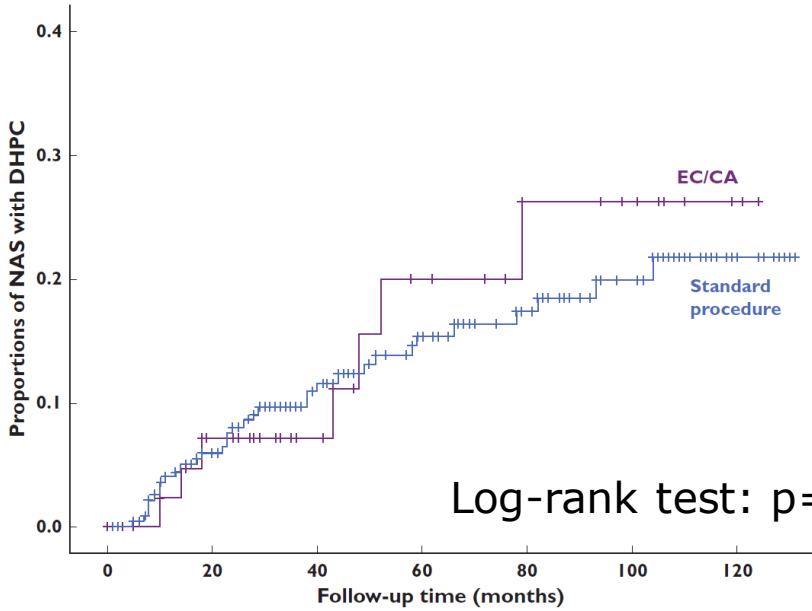


Figure 1
Proportion of new active substances (NAS) that obtained a marketing authorization between 1999 and 2009 under exceptional circumstances/conditional approval (EC/CA) or standard marketing authorizations with or without a Direct Healthcare Provider Communication (DHPC)

Priority Medicines : PRIME scheme

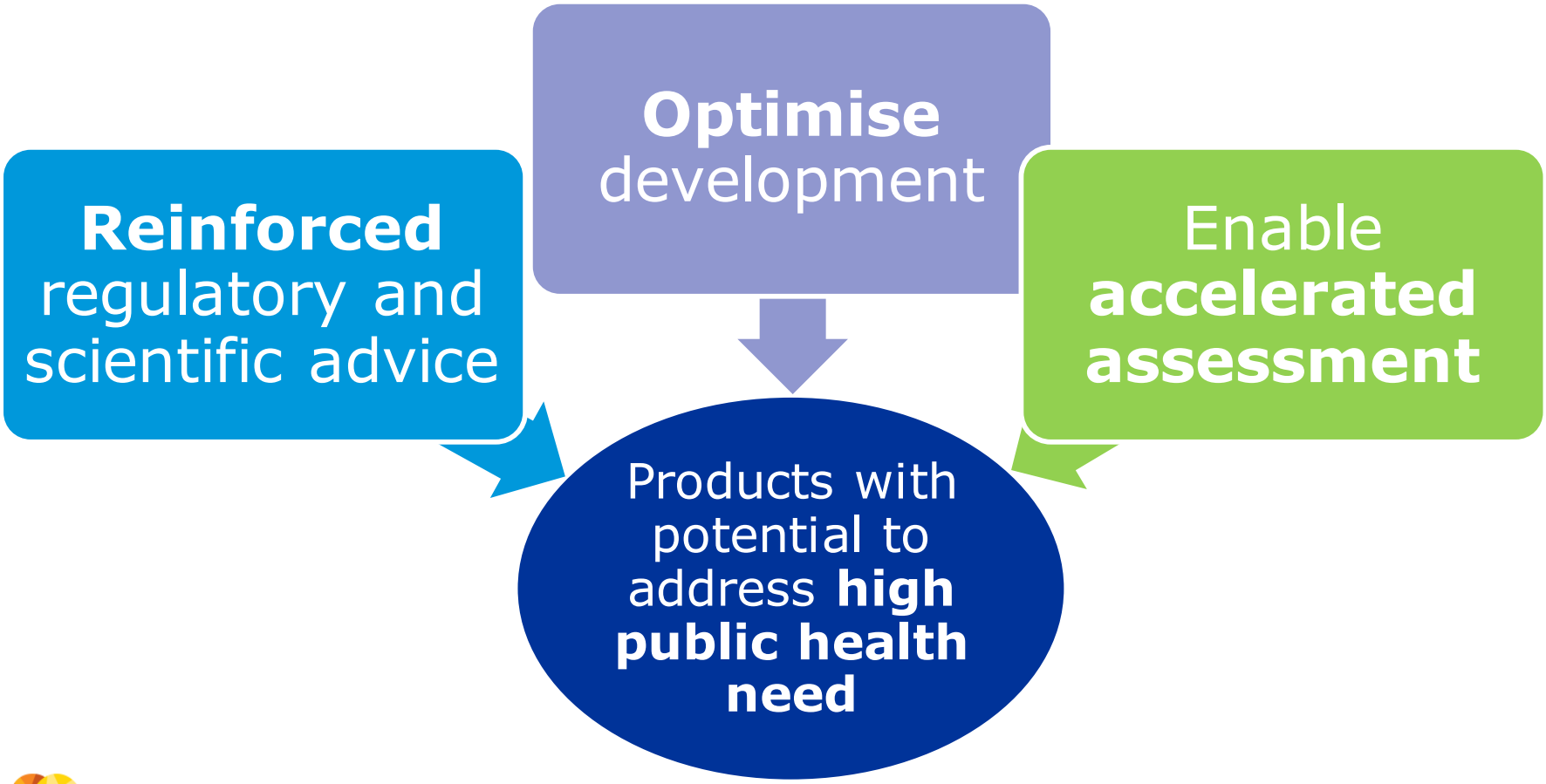
EUROPEAN MEDICINES AGENCY

Why?

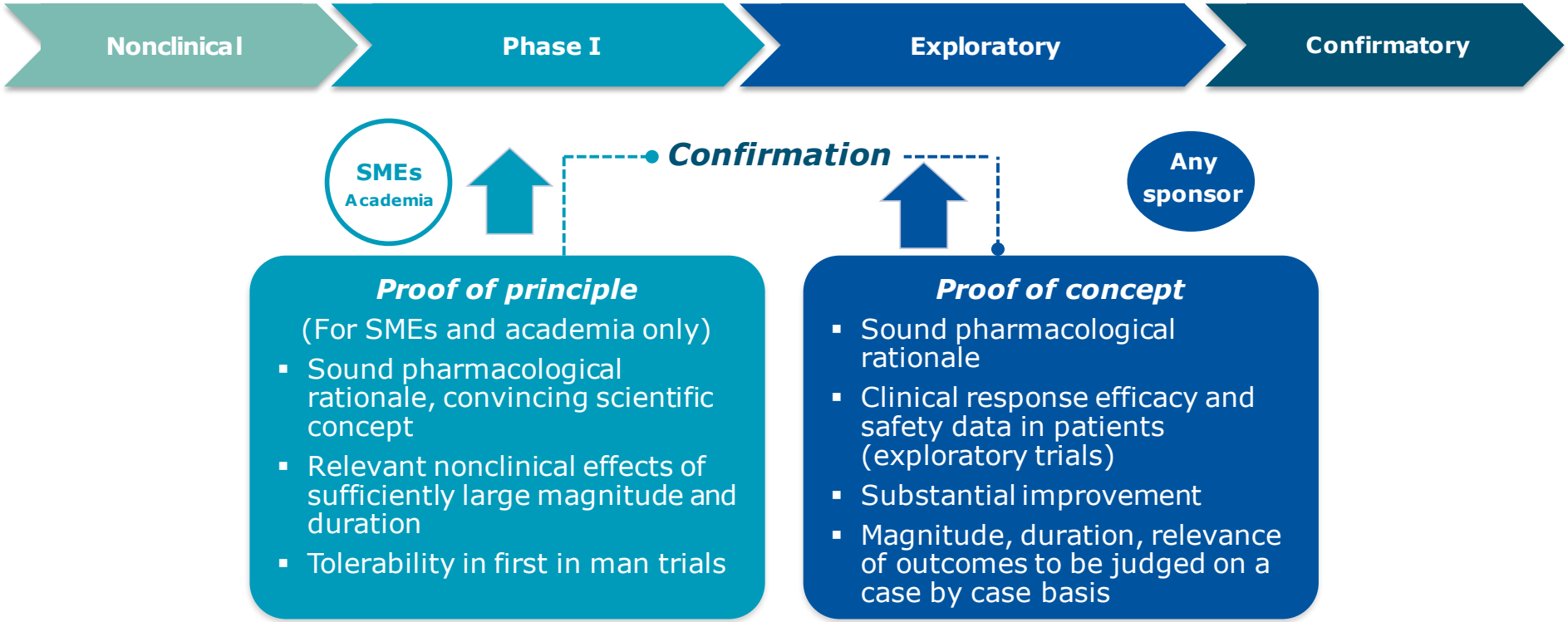
Patient access to important medicines	• Areas of unmet need • EU Medicines Agencies Network Strategy to 2020 • Opportunity for better use of the existing regulatory tools
R&D	• Scientific and regulatory challenges • Importance of early dialogue with regulators and scientific advice • Difficulty in obtaining capital investments for academic sponsors & SMEs
EU competitiveness	• FDA Breakthrough Therapy programme (2012) • Japanese Sakigake (2014) • Opportunity to complement National initiatives to stimulate innovations

EUROPEAN MEDICINES AGENCY

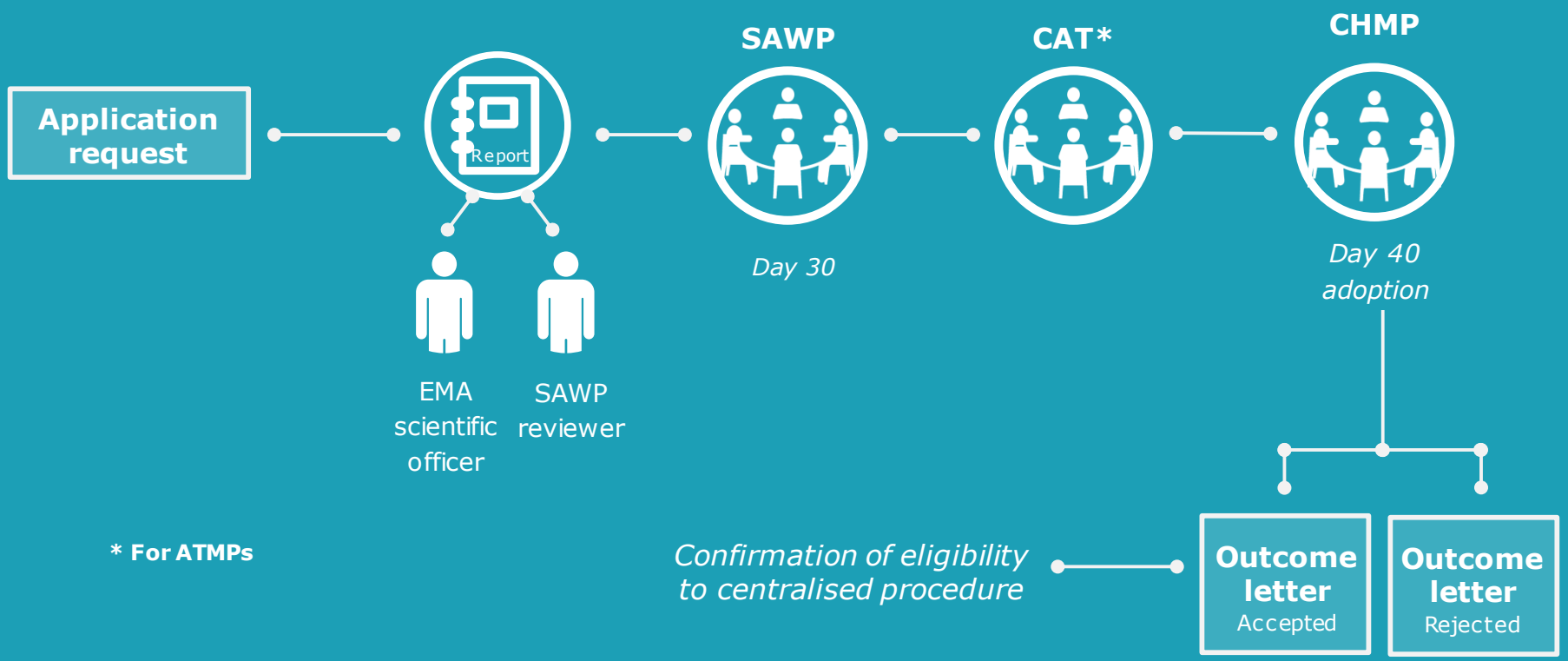
Fostering development of medicines with high public health potential



Entry points PRIME eligibility and required evidence



Assessment of Eligibility: 40-day procedure



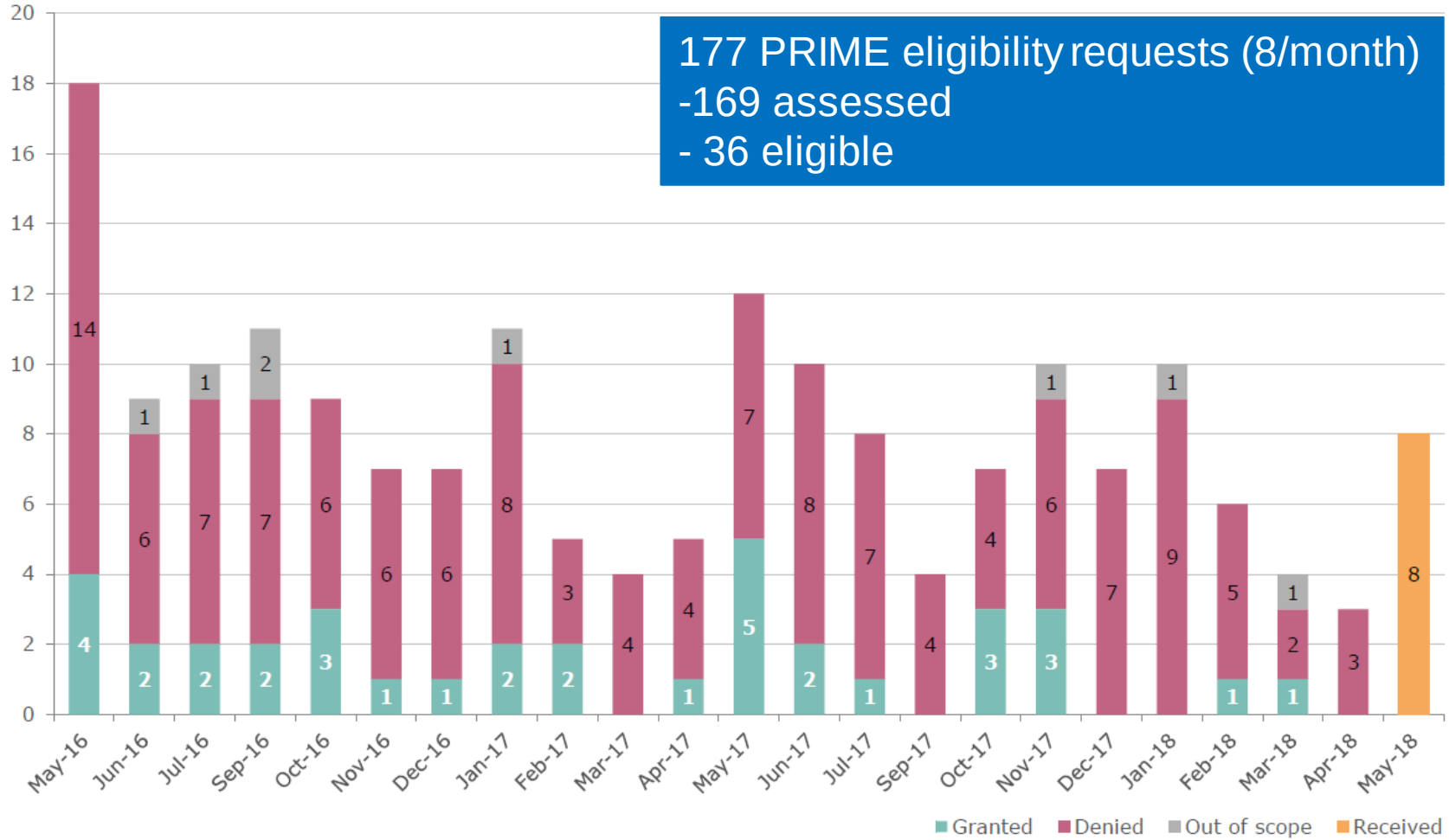
Features of the PRIME scheme

Early access tool, supporting patient access to innovative medicines.

- **Written confirmation of PRIME eligibility** and potential for accelerated assessment;
- **Early CHMP Rapporteur appointment** during development;
- **Kick off meeting** with multidisciplinary expertise from EU network;
- **Enhanced scientific advice** at key development milestones/decision points;
- **EMA dedicated contact point**;
- **Fee incentives** for SMEs and academics on Scientific Advice requests.

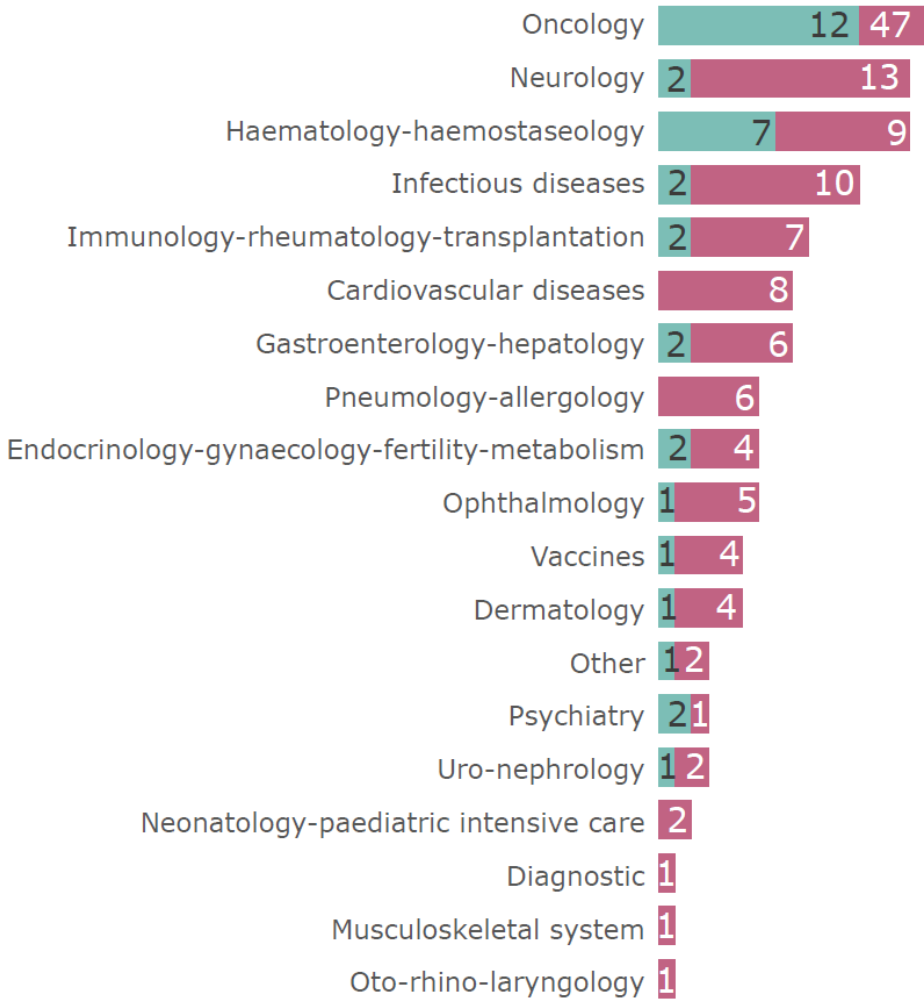
PRIME – 2 years of experience

Figure 1. Overview of PRIME eligibility requests received



PRIME - eligibility

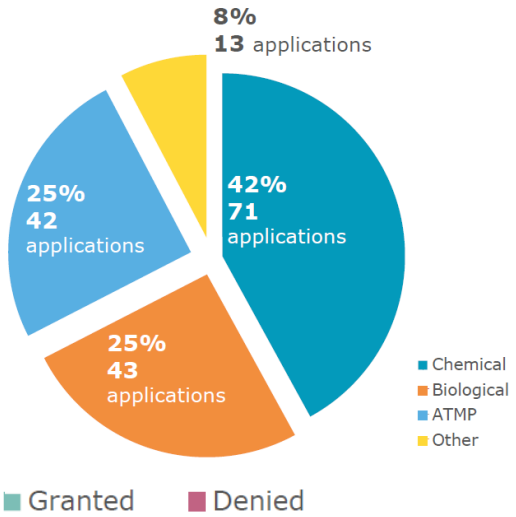
Figure 2. Overview of PRIME eligibility requests granted and denied by therapeutic area



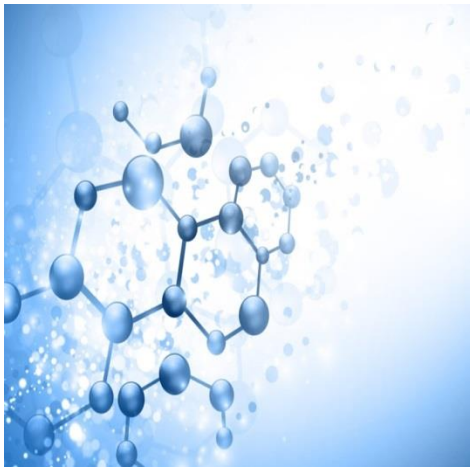
36 products eligible
-30 rare diseases (onco, haematology)
-16 paediatric

-25% requests ATMPs ->
15 (42%)granted!

Figure 3. PRIME eligibility requests by type of product



In summary,



Eligibility review: robust, short time, in writing

Quality of applications received is generally high

Kick-off meeting: excellent opportunity to initiate interaction and flag issues

Rapporteur appointment enables early identification of potential issues

Excellent collaboration across committees

Iterative scientific advices with opportunity for multi-stakeholders involvement

Scheme triggers discussions across product type / class

Take home

New challenges

- ATMPs, targeted therapies, agnostic indications, personalized medicine, pandemic

Novel regulatory tools

- Adaptive Pathways
  - iterative data generation
- Conditional Approval, Exceptional Circumstances
- PRIME
- *Rolling review (the basics)*
- *Scientific Advice & Innovation Task Force (Marjon Pasmooij)*

Positive B/R balance at time of Marketing Authorisation Application!

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Questions?

GOEDE MEDICIJNEN GOED GEBRUIKT