EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Data exclusivity, market protection and paediatric rewards

Workshop for Micro, Small and Medium Sized Enterprises
EMA
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Evolving regulatory framework and introduction of different types of incentives

In 1990's	2000	Revision 2004-5	2006
Data exclusivity • MRP/NAP: 6 or 10 yrs • CAP: 10 yrs	**Orphans** Market exclusivity (ME)	**Data exclusivity / market protection** • 8+2/(+1) yr ME (new indication) • +1 yr data exclusivity for well established substance (new indication) • +1 yr data exclusivity legal status switch	**Paediatrics** • Supplementary Protection Certificate extension • 10+2 yrs ME (orphans)

Data exclusivity and market protection provisions

Rules on data exclusivity and market protection

MAA reference product submission date	**Centralised procedure**	**National, MRP, DCP**
Before 20 Nov. 2005 (CP) 30 Oct. 2005 (NP)	10 years data exlusivity	6* or 10** years data exclusivity
After 20 Nov. 2005 (CP) 30 Oct. 2005 (NP)	**8 years data exclusivity** **+2 years market protection** **(+1 year market protection)**	

*AT, DK, FI, IE, PT, ES, EL, PL, CZ, HU, LT, LV, SE, SK, MT, EE, CY, BG, RO, NO, IS, LI

** BE, DE, FR, IT, NL, SE, UK, LU

Incentives:
Data exclusivity and market protection

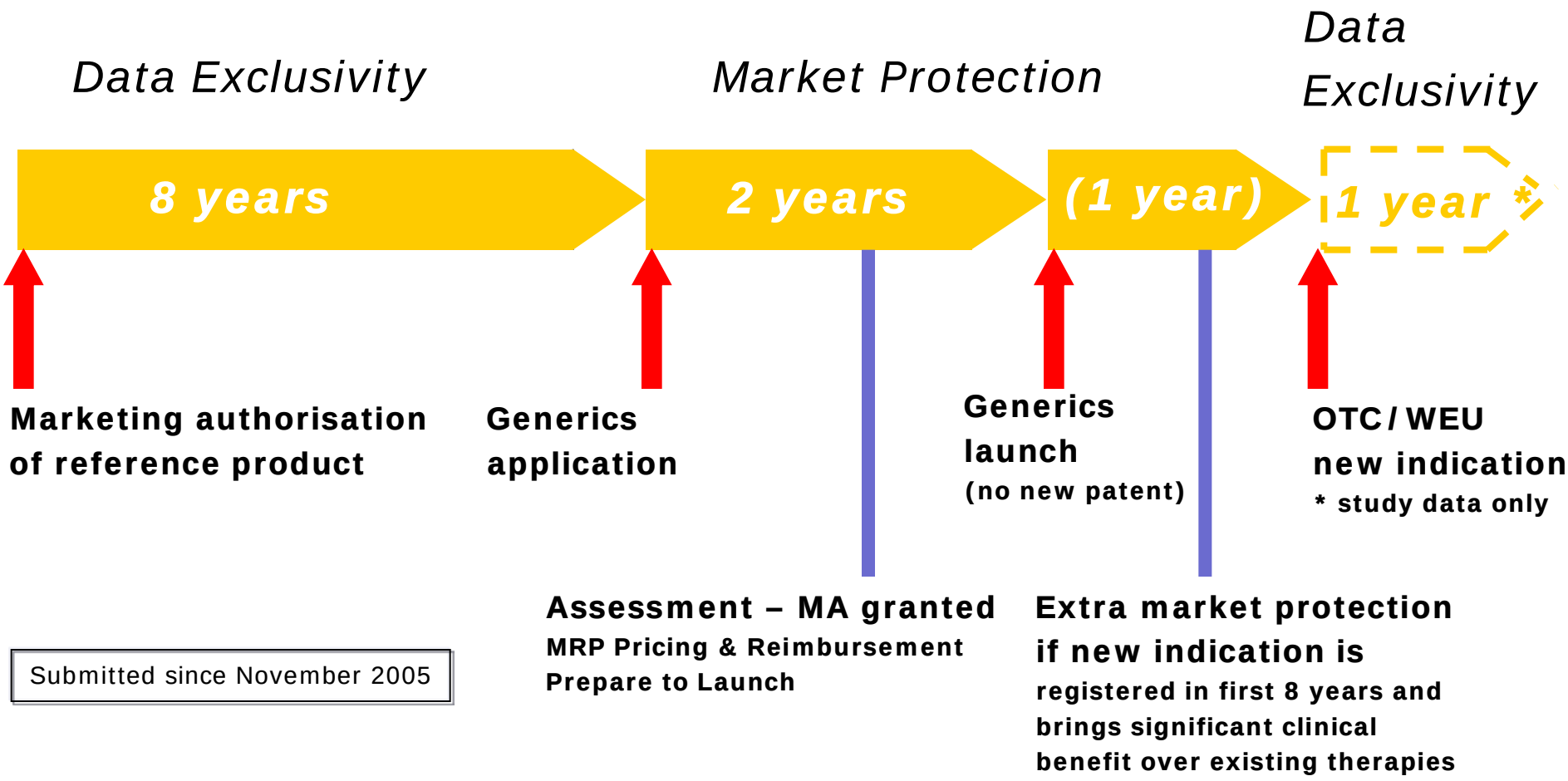
Data exclusivity

= Period of time during which a Company cannot cross-refer to the data in support of another marketing authorisation, i.e.:
generics, hybrids, biosimilars cannot be validated by the Agency

Market protection

= Period of time during which a generic, hybrid or biosimilar cannot be placed on the market, even if the medicinal product has already received a marketing authorisation

8+2(+1) exclusivity formula



Submitted since November 2005

Provisions on extended market protection and data exclusivity

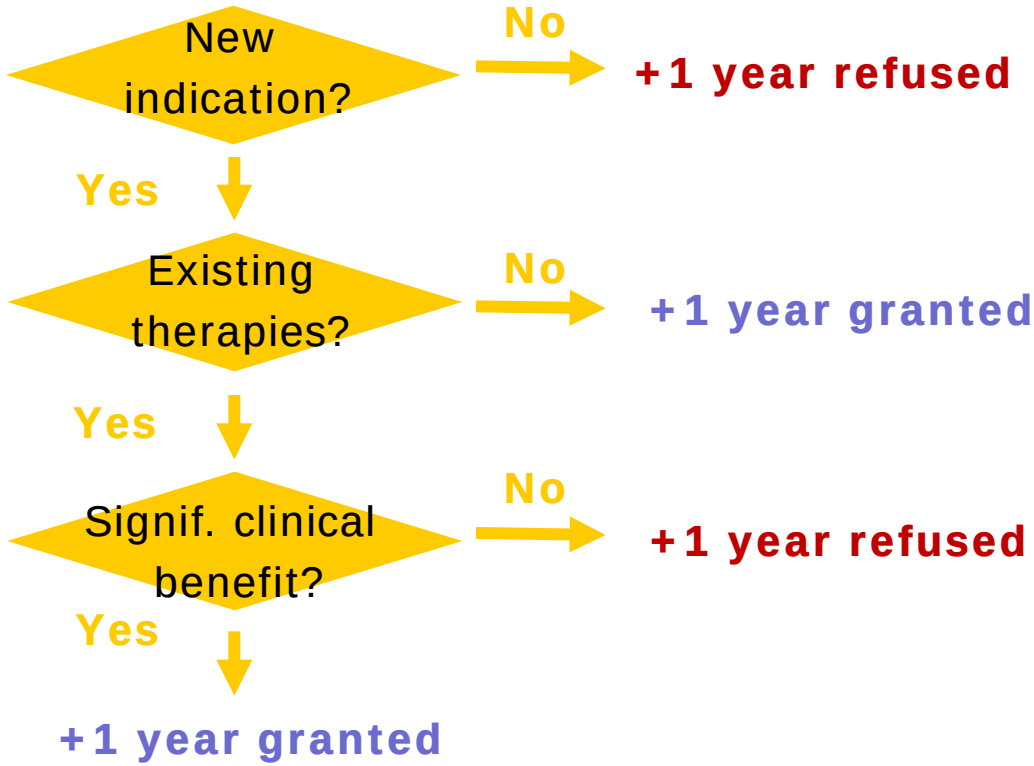
+1 year market protection for a new therapeutic indication which brings significant benefit in comparison with existing therapies *(Art. 14(11) Reg. (EC) No 726/2004) - For initial MAA submitted after 20 November 2005 and authorisation of new indication within 8 years*

+ 1 year data exclusivity for a new therapeutic indication for a well-established substance, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication *(Art. 10(5) Dir. 2001/83/EC) (=+1 WEU)*

+1 year data exclusivity for a change in classification of a medicinal product on the basis of significant pre-clinical tests or clinical trials *(Art. 74(a) Dir. 2001/83/EC) (=+1 OTC switch)*

Decision tree for +1 year market protection

EC Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new indication in order to benefit from an extended (11-year) marketing protection period [November 2007]



Is it a new indication?

SmPC guideline [Sep 2009], Section 4.1 Therapeutic indications

*'The indication(s) … should define the **target disease** or **condition** distinguishing between treatment (…), prevention (…) and diagnostic indication. When appropriate it should define the **target population** ….'*

- New target disease
- Different stages or severity of a disease
- Extended target population for the same disease
- Change from the 2nd line to 1st line treatment
- Change from combination therapy to monotherapy, or from one combination therapy to another
- Change from treatment to prevention or diagnosis of a disease
- Change from treatment to prevention of progression or to prevention of relapses of a disease
- Change from short-term treatment to long-term maintenance therapy in chronic disease

What are the existing therapies?

Satisfactory methods of diagnosis, prevention or treatment of the disease. These include:

- **Authorised medicinal products** in 1 or > MSs in the proposed indication
- **Non-pharmacological** approaches (e.g. psychotherapy)
- Other 'state-of-the art' **therapeutic methods** for the indication

Off-label use of medicinal products not considered existing therapies!

How does it compare to existing therapies?

Justification of significant clinical benefit

Improved efficacy

Same level of evidence needed to support a comparative efficacy claim for two different medicinal products. Direct comparative clinical trials preferred

Improved safety

The relative safety profile will have to be globally assessed compared to existing therapy(ies), preferable through comparative trial(s).
No important reduction in benefit should be seen

Major contribution to patient care

- *New mode / route of administration*
- *Treatment alternative*
- *Response different from other treatments in a substantial part of the target population*

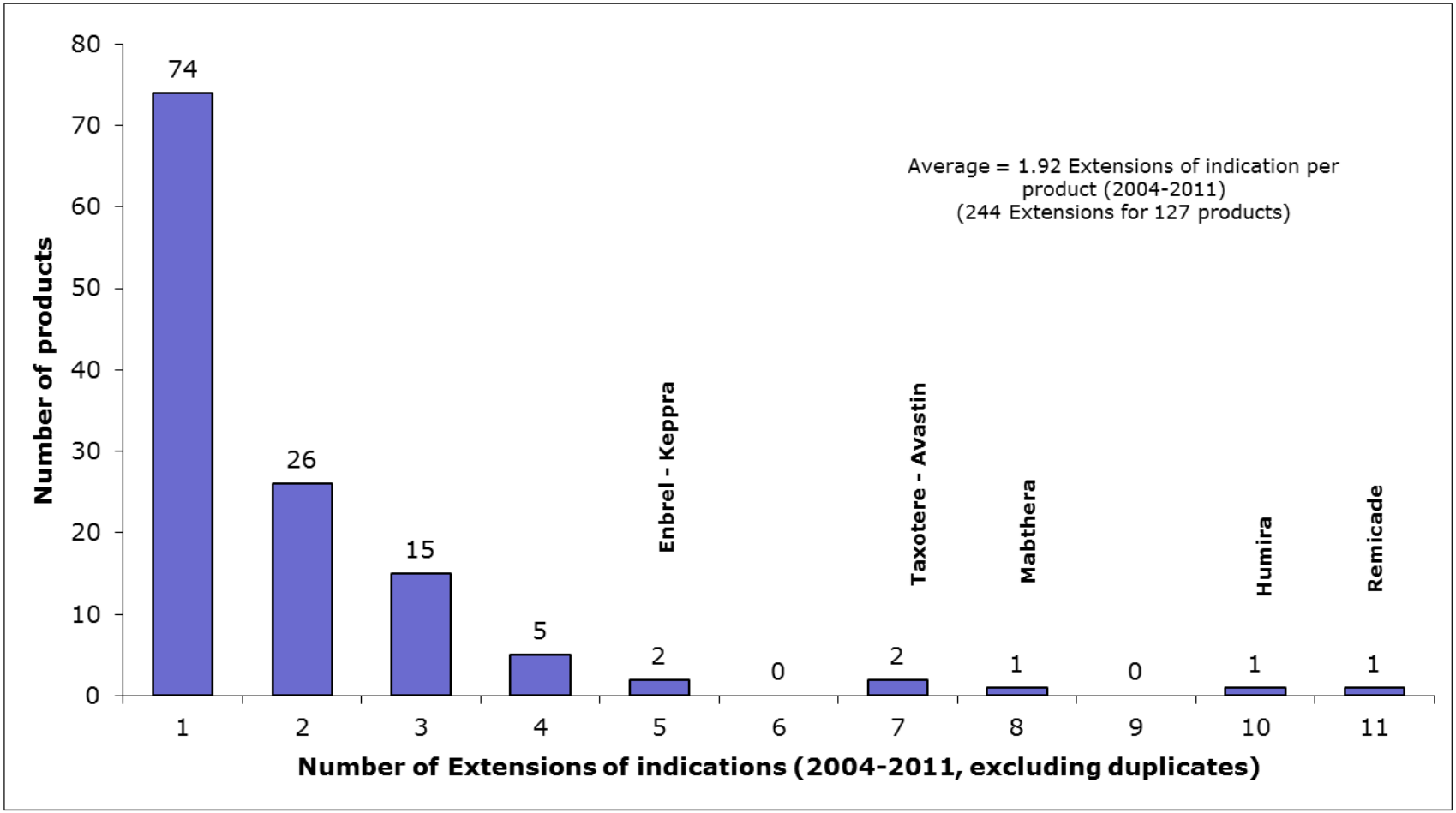
Examples
8+2(+1) year market protection

Medicinal product	Therapeutic indication	Grounds for acceptance / refusal
TORISEL (temsirolimus) **+1 year granted**	*Treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL)* **New target disease**	In the EU there are no approved treatments for relapsed MCL.
ZYTIGA (abiraterone) **+1 year granted**	*Treatment of men with mCRPC after failure of androgen deprivation therapy.* **Different stages or severity of a disease**	There are no available treatment options in the EU for patients with mCRPC who are asymptomatic or midly symptomatic.

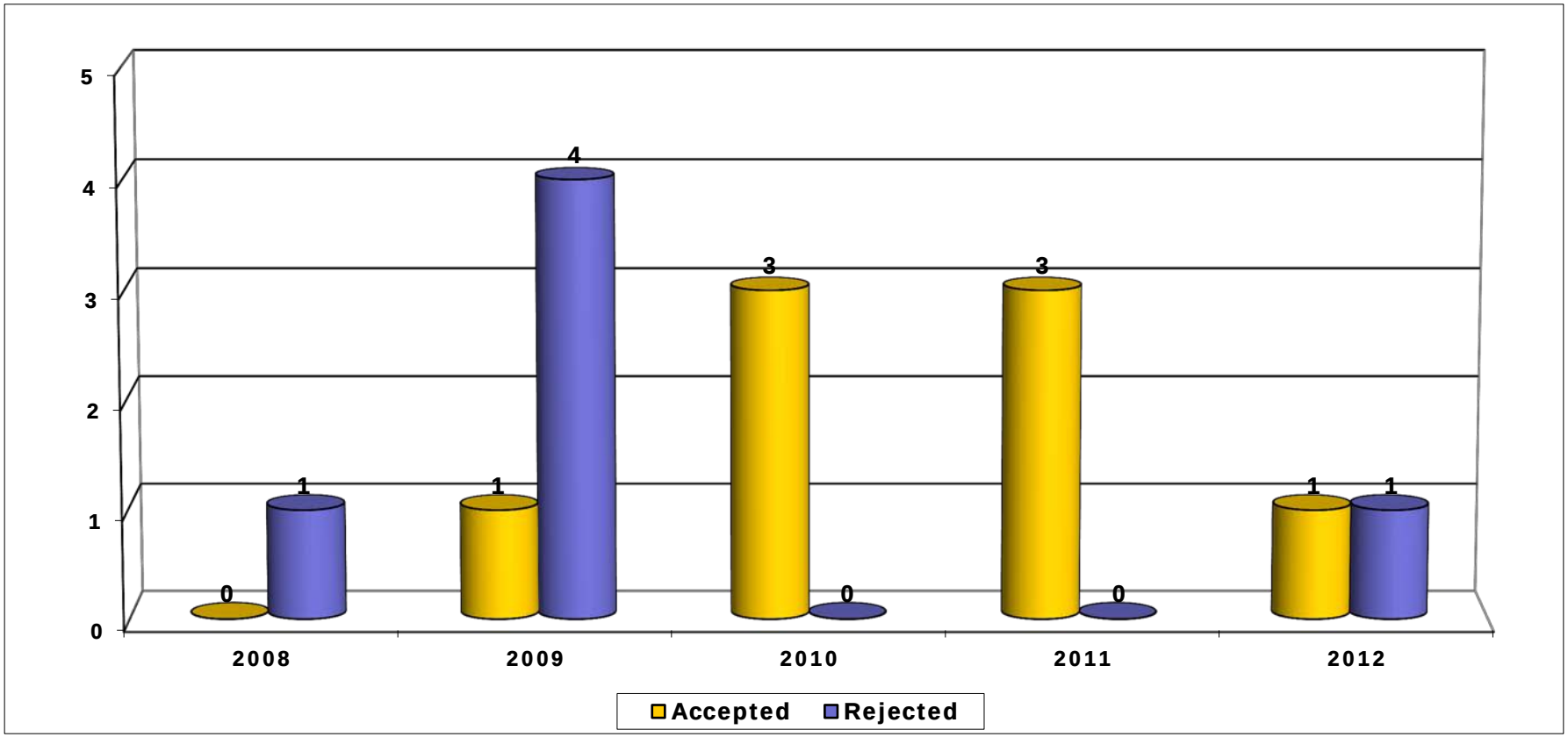
Examples
8+2(+1) year market protection

Medicinal product	Therapeutic indication	Grounds for acceptance / refusal
ISENTRESS (raltegravir) **+1 year refused**	*ART-naïve patients*	Lack of proof of superior efficacy results and safety profile.
PREZISTA (darunavir) **+1 year refused**	*Co-administered with low-dose ritonavir in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in ARV treatment-naïve adults.*	Lack of proof of superior efficacy and safety profile not significantly better.
YONDELIS (trabectedin) **+1 year refused**	*Treatment of patients with relapsed platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin (PLD)*	Lack of head-to-head comparison of trabectedin + PLD with platinum based regimens

Extensions of indications – 2004-2011



Overview of extensions of exclusivity 2008-2012



Orphan medicinal products

New =
market exclusivity!

Development of orphan medicines

"Patients affected by rare diseases have the same rights as fellow citizens."

Orphan designation criteria

- Rarity of condition (< 5 in 10,000) or insufficient return on investment
- Seriousness of condition (Life threatening/chronically debilitating)
- Existence of satisfactory methods

http://www.ema.europa.eu/htms/human/orphans/intro.htm

Incentive: Market exclusivity

Market exclusivity (=Orphan)

= Period of time during which a medicinal product which is similar* to an orphan medicinal product cannot be validated by the Agency, even if based on a full, complete dossier

* Similar means similar principal molecular structure and same mode of action and same indication

Extend Market exclusivity to 12 years (=Paediatric orphan)

= for orphan indication(s) covered by a condition benefiting of 10 years of market exclusivity and for which the paediatric investigation plan (PIP) is completed

Market exclusivity for orphans

Data Exclusivity

Market Protection

Submitted since November 2005

Marketing authorisation of reference product

Generics application

Generics application

OTC / WEU

*** study data only**

Market Exclusivity (Orphan)

for indication(s) for a separate orphan designation for which the PIP is completed

Marketing authorisation of reference product

'similar' application

Generics application

Market exclusivity principles

- Market exclusivity in Orphan Regulation runs in parallel with normal rules on data exclusivity and market protection
- Therapeutic indication for a separate orphan designation benefits from 10 years market exclusivity
- No mix of orphan and non-orphan indications in the same MA allowed

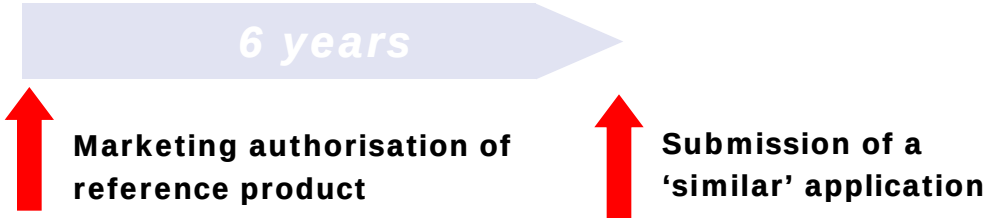
However, the MA can cover several ODD

➔ which triggers its own market exclusivity period kicking-off from start of approval of the indication (i.e. initial MA or Type II/extension)

Market exclusivity for orphans

Market Exclusivity (Orphan)

Market Exclusivity (Orphan)



Note: Only if therapeutic indications are for separate orphan designations

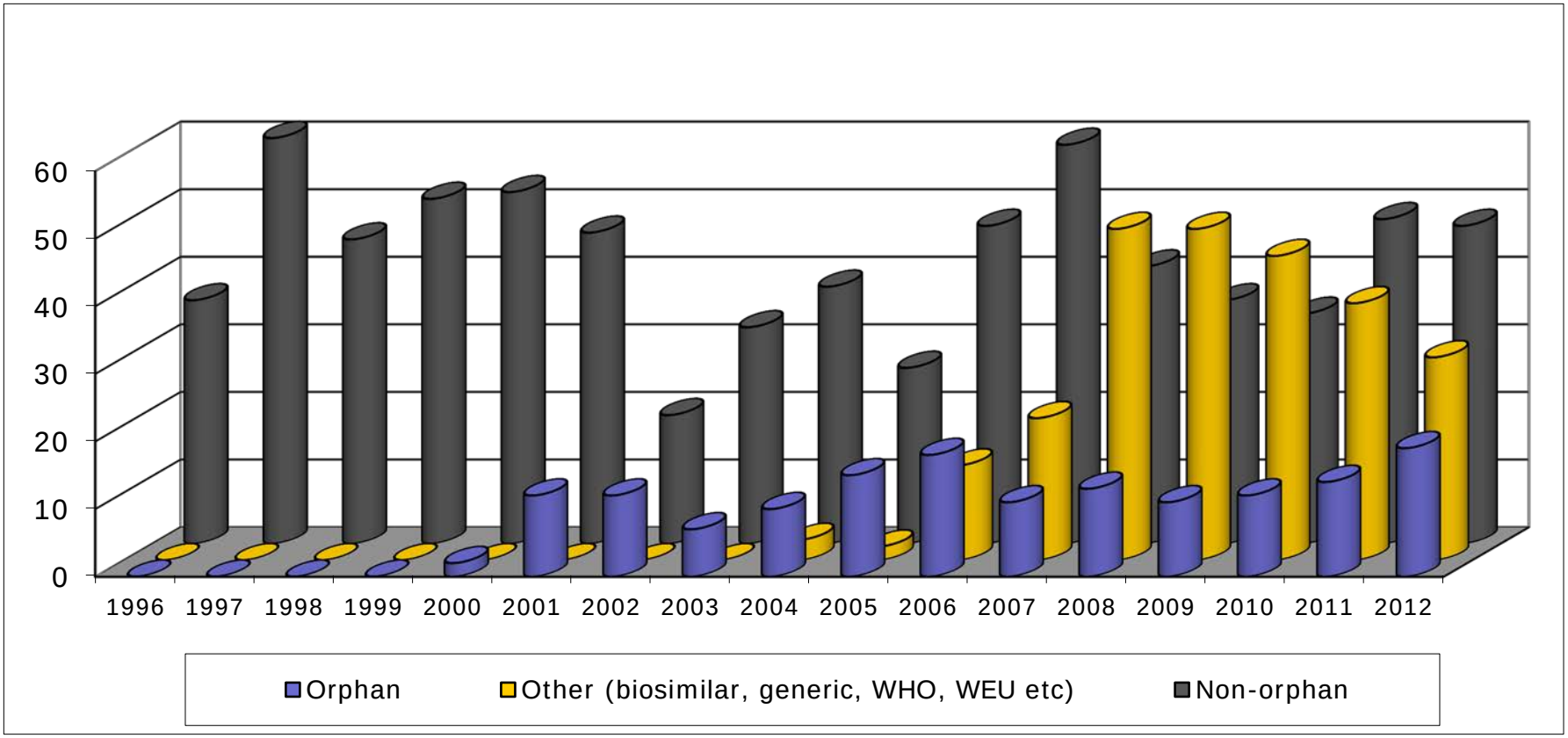
Example Nexavar orphan with several ODD and ME periods

Orphan condition	Nexavar indication	EC approval
Hepatocellular carcinoma (treatment) (EU/3/06/364)	• *Treatment of hepatocellular carcinoma*	29/10/2007
Renal cell carcinoma (treatment) (EU/3/04/207)	*For the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.*	19/07/2006

Example Tracleer
orphan with several ODD and ME periods

Orphan condition	Tracleer indication	EC approval
Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (treatment) (EU/3/01/019)	• *Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in:* - *Primary (idiopathic and familial) PAH;* - *PAH secondary to scleroderma without significant interstitial pulmonary disease;* - *PAH associated with congenital systemic to pulmonary shunts and Eisenmenger's physiology;* - *Some improvements have also been shown in patients with PAH WHO functional class II*	15/05/2002
Systemic sclerosis (scleroderma) (treatment) (EU/3/01/019)	*Indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.*	07/06/2007

Trends in EU marketing authorisation applications 1995-2012



Paediatric medicines

New =
SPC extension

Development of paediatic medicines

Obligation

To study drugs in children for new products or authorised products with new indication, pharmaceutical form and route of administration

Agree Paediatric Investigation Plan by Paediatric Committee (PDCO)

- PIP outlines timing & measures to be undertaken
- Deferral or Waiver, if applicable
- Compliance check at time of marketing authorisation application

http://www.ema.europa.eu/htms/human/paediatrics/introduction.htm

EU Paediatric REG: obligations vs incentives

	Obligation	Incentive	Type of MP
New# Medicinal product	Paediatric Investigation Plan or Waiver	6 months extension of SPC*	Necessary for **validation** of application
On Patent and authorised Medicine	Paediatric Investigation Plan or Waiver	6 months extension of SPC*	When new indication or new route or new pharmaceutical form: necessary for **validation**
Orphan Medicine	Paediatric Investigation Plan or Waiver	2 additional years of market exclusivity*	In addition to 10 years
Off patent Medicine	None (voluntary PIP possible for PUMA)	8+2 years of data protection	Research funds Paed. Use MA (PUMA)

**if compliance with PIP, information, approval EU-wide*

#according to GMA concept

Incentive: SPC extension

- '*Sui generis*' intellectual property right
- Provide additional monopoly to compensate the time to get a MA
- SPC application to be lodged within 6 months of the grant of the MA
- SPC extension to be lodged 2 years before the SPC expiry
- Enter into force after the expiry of the 'basic patent'
- Duration: negative *(Merck v Deutsches Patent Case C-125/10)* up to 5 years

Rewards conditions

- Development is compliant with agreed PIP
- Results of studies included in Product information
- Product is authorised in all MSs (except for PUMA)
- Compliance statement in MA

*Product-specific or class waiver does **NOT** trigger the reward*

"Negative" PIP results do allow reward

Trends in paediatric developments within the centralised procedure 2007-2011

- New medicines authorised with a paediatric indication: 31 / 152

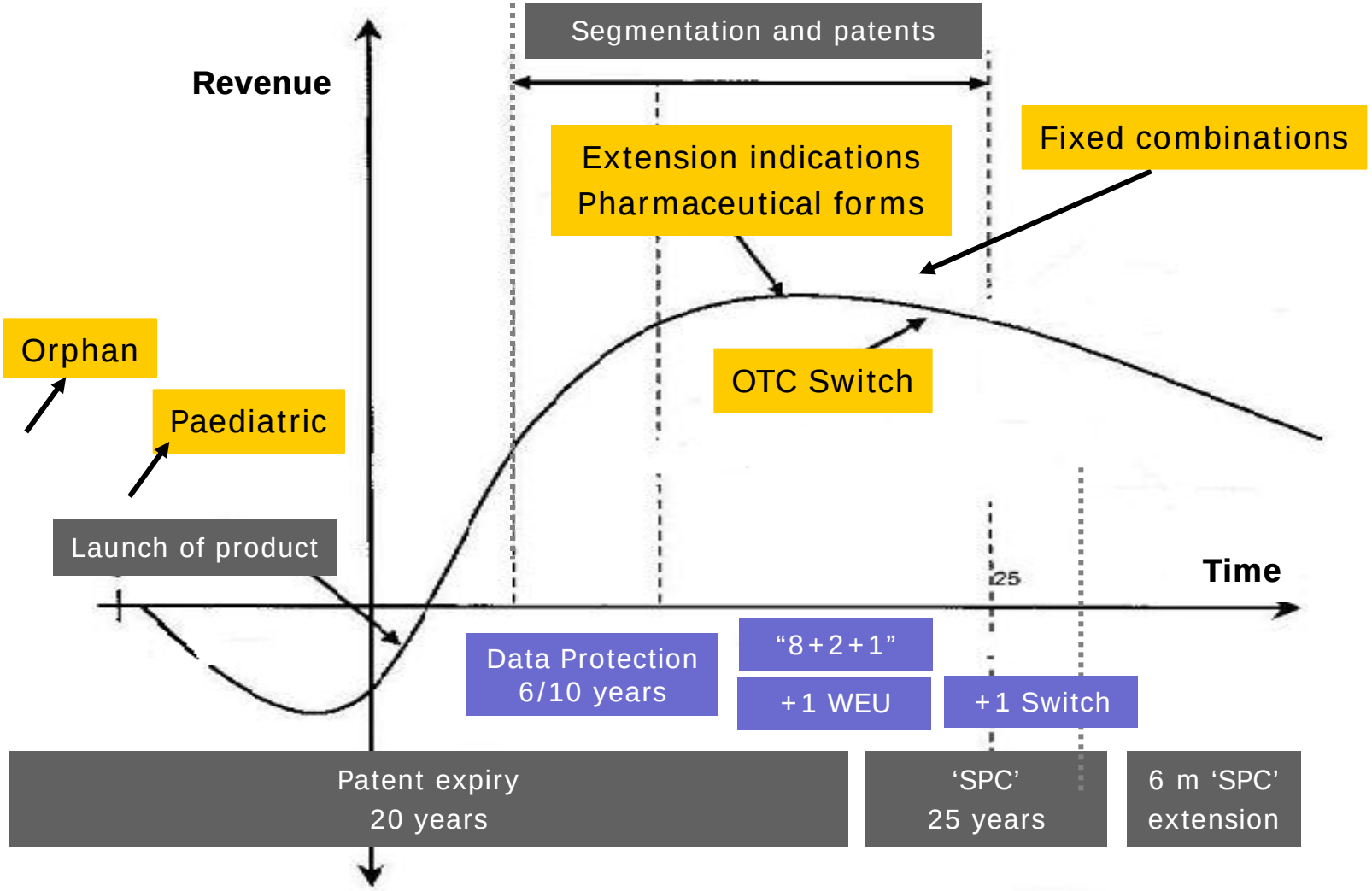
  (linked to PIP: 10)
- New paediatric uses authorised for already existing medicines: 38

  (linked to PIP: 18)
- New pharmaceutical form adapted for children: 15

  (linked to PIP: 3)

Adaptive strategies for incentive maximisation

Life cycle of innovator product



Adaptive strategies for incentive maximisation

Across the life cycle of the product:

- Explore different regulatory strategies to maximise existing legislative incentives
- Engage in early discussions of strategies with the competent authorities and with rapporteurs
- Seek regulatory and scientific advice

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