EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Optimising Regulatory Strategy

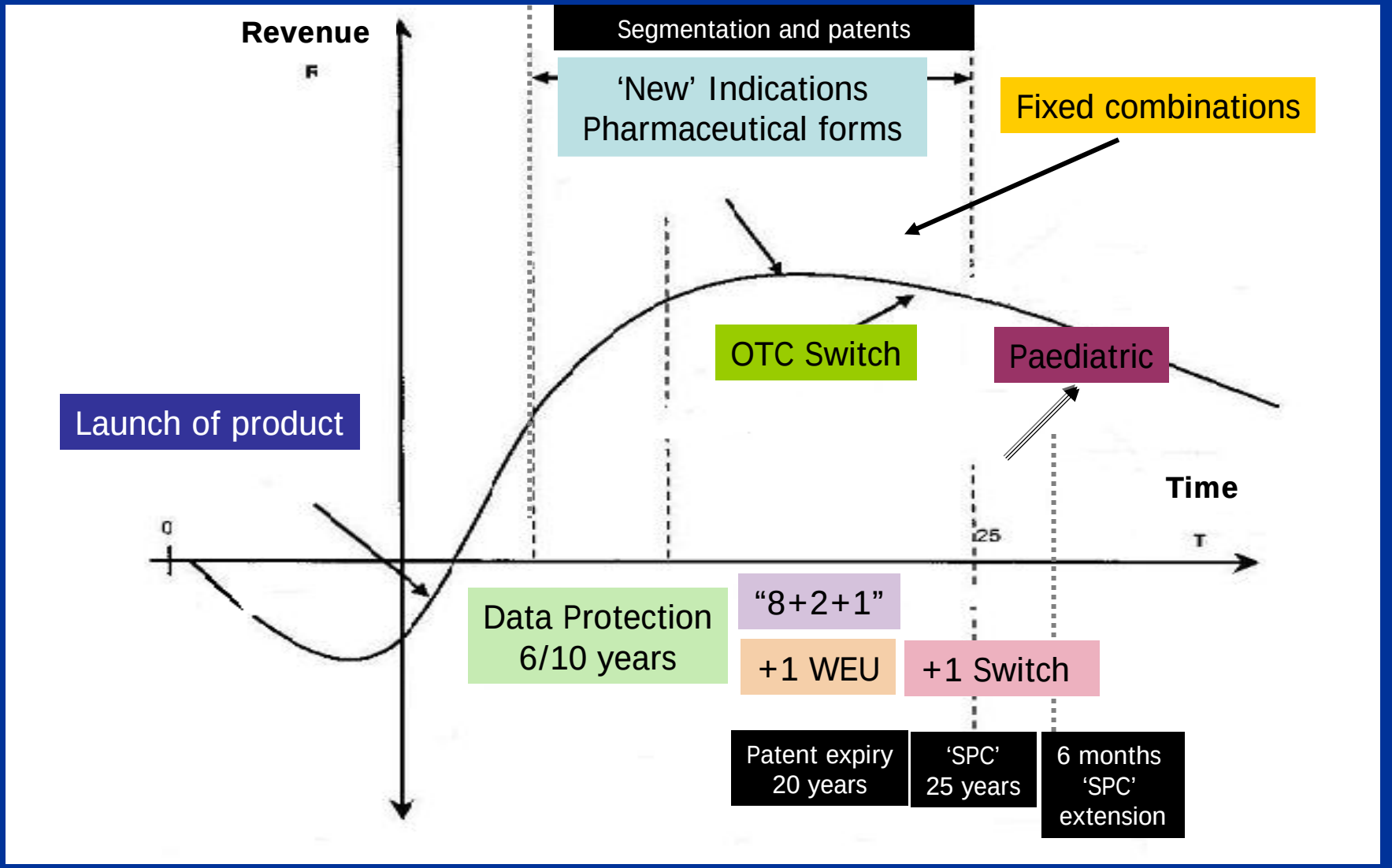
Workshop for Micro, Small and Medium Sized Enterprises,
EMA
26 May 2011

Presented by: Zaide Frias
Head of Regulatory Affairs, EMA

Evolving regulatory framework and introduction of new incentives

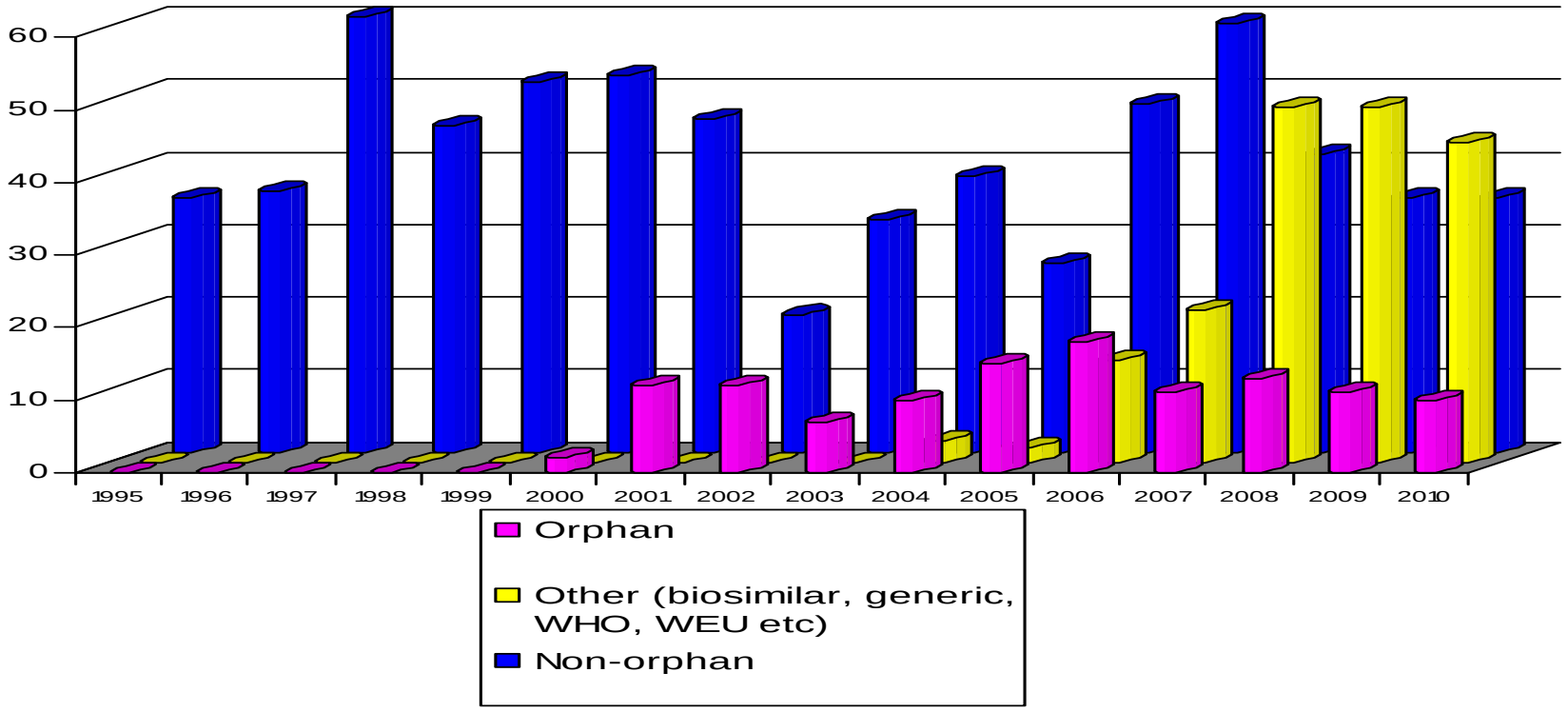
In 1990's	2000	Revision 2004-5	2006	2007
Data protection MRP/NAP 6 or 10 yrs CAP 10 yrs	**Orphans** Market exclusivity (ME)	**"Early Access" tools** Conditional MA Accelerated assessment **Data / market exclusivity** 8+2/(+1) yr ME (new indication) +1 yr data exclusivity for well established substance (new indication) +1 yr data exclusivity legal status switch **SME status**	**Paediatrics** Supplementary Protection Certificate extension 10+2 yrs ME (orphans) Scientific Advice free	**ATMPs** Fee reduction Certification of quality and non clinical data (SME)

Lifecycle of innovator product



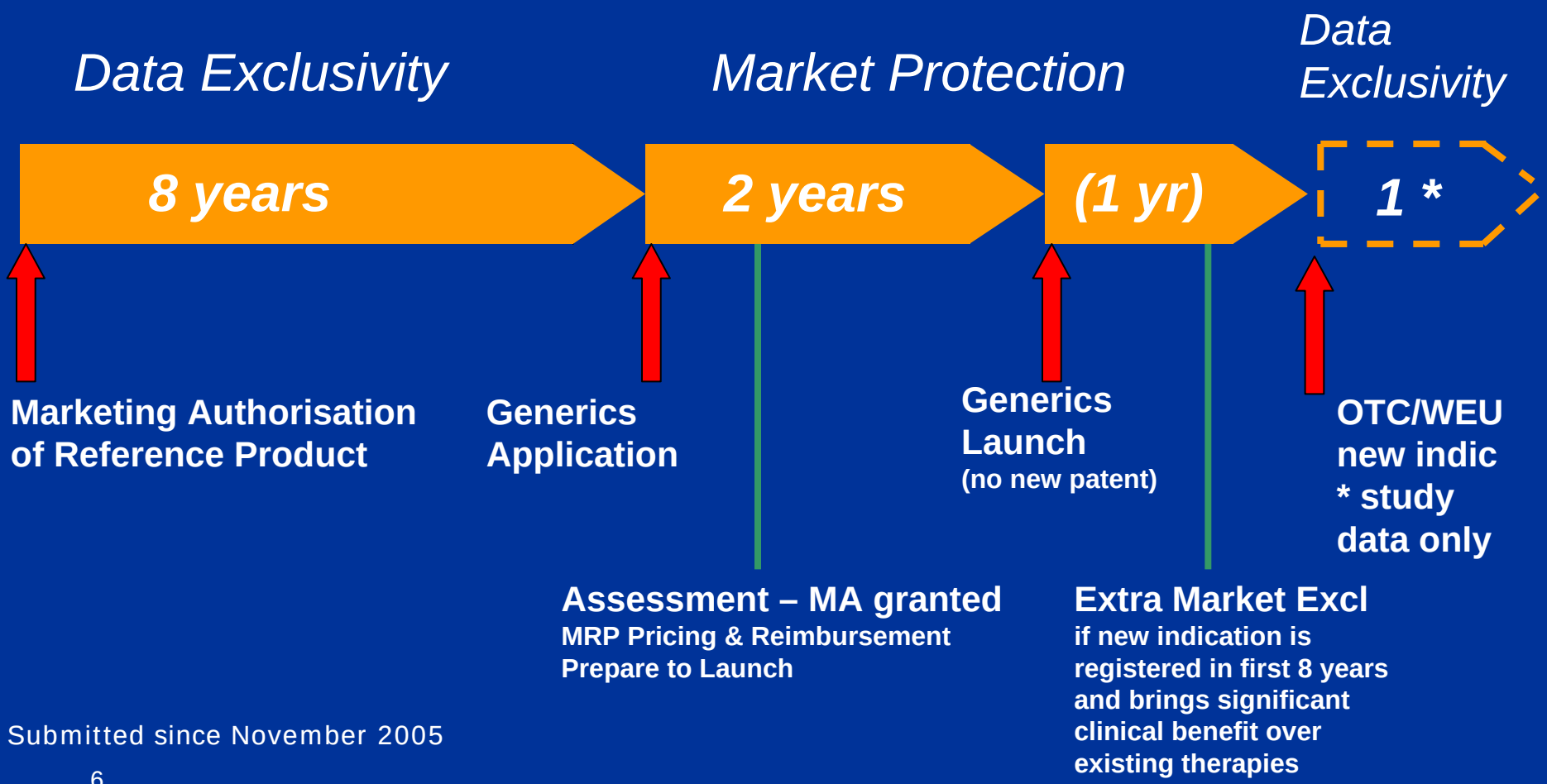
Data and market exclusivity provisions

Trends in EU Marketing Authorisation Applications 1995-2010



Data Exclusivity

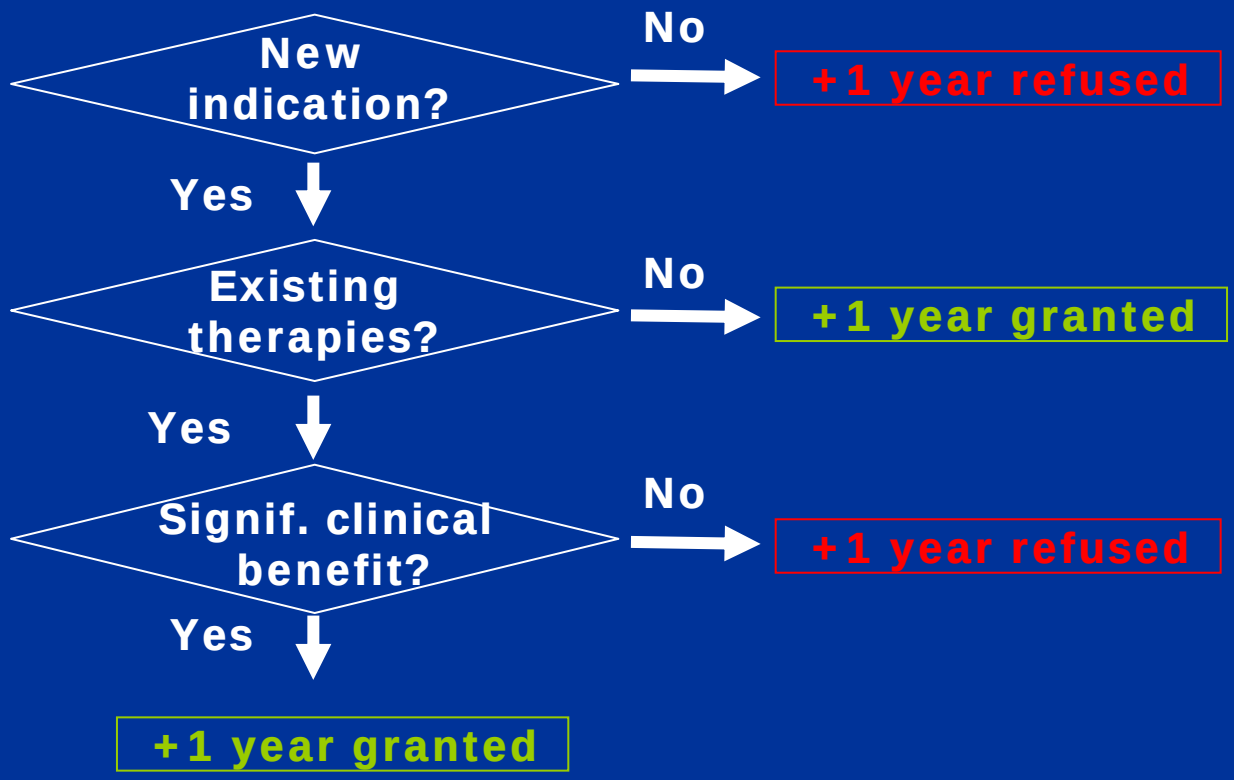
8 + 2 (+1) Data exclusivity Formula for all MA Procedures



Submitted since November 2005

Decision tree

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*

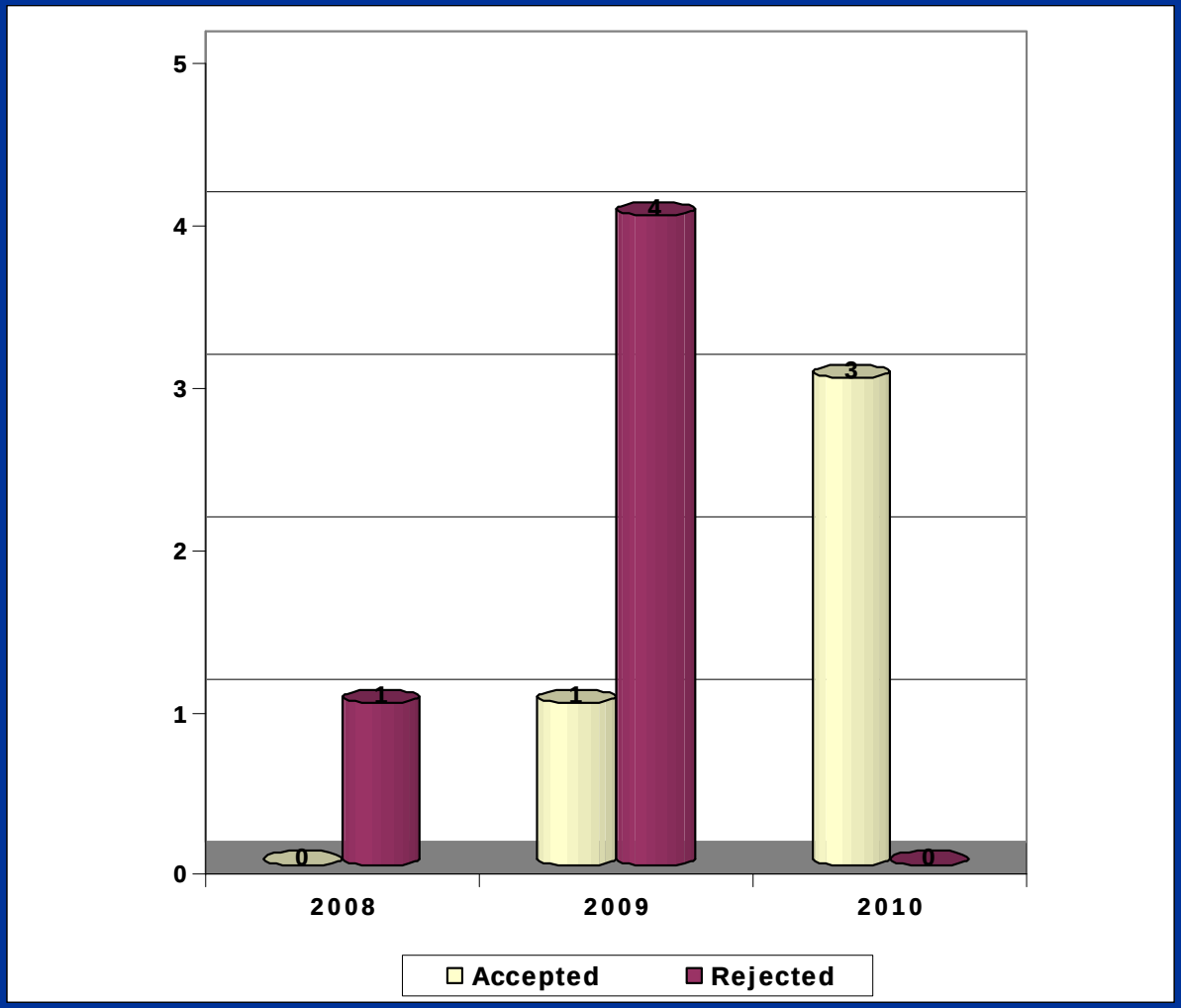
✓ *Response different from other treatments in a substantial part of the target population*

Examples

8+2(+1) year market exclusivity

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)*	In the EU there are no approved treatments for relapsed MCL.
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
ISENTRESS (raltegravir) **+1 year refused**	*ART-naïve patients*	Lack of proof of superior efficacy results and safety profile.

Overview of extensions of exclusivity



Orphan Medicinal Products

Development of Orphan Medicines

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

Incentives include

10 years of market exclusivity per therapeutic indication granted for a designated condition

No mix of orphan and non-orphan indications allowed in the same MA (e.g. VIAGRA vs. REVATIO)

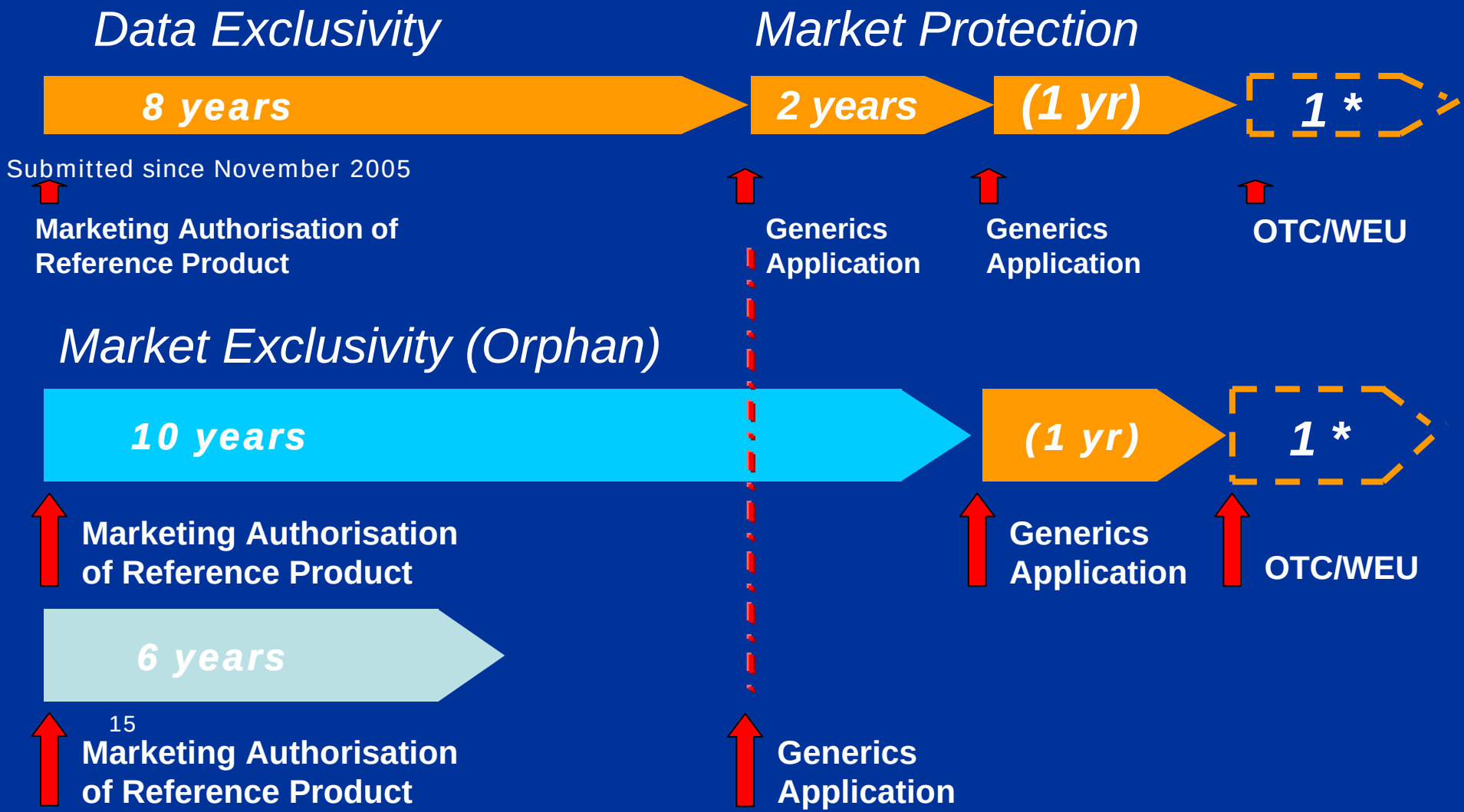
Protocol assistance throughout development

Fee reductions for EMA procedures applications

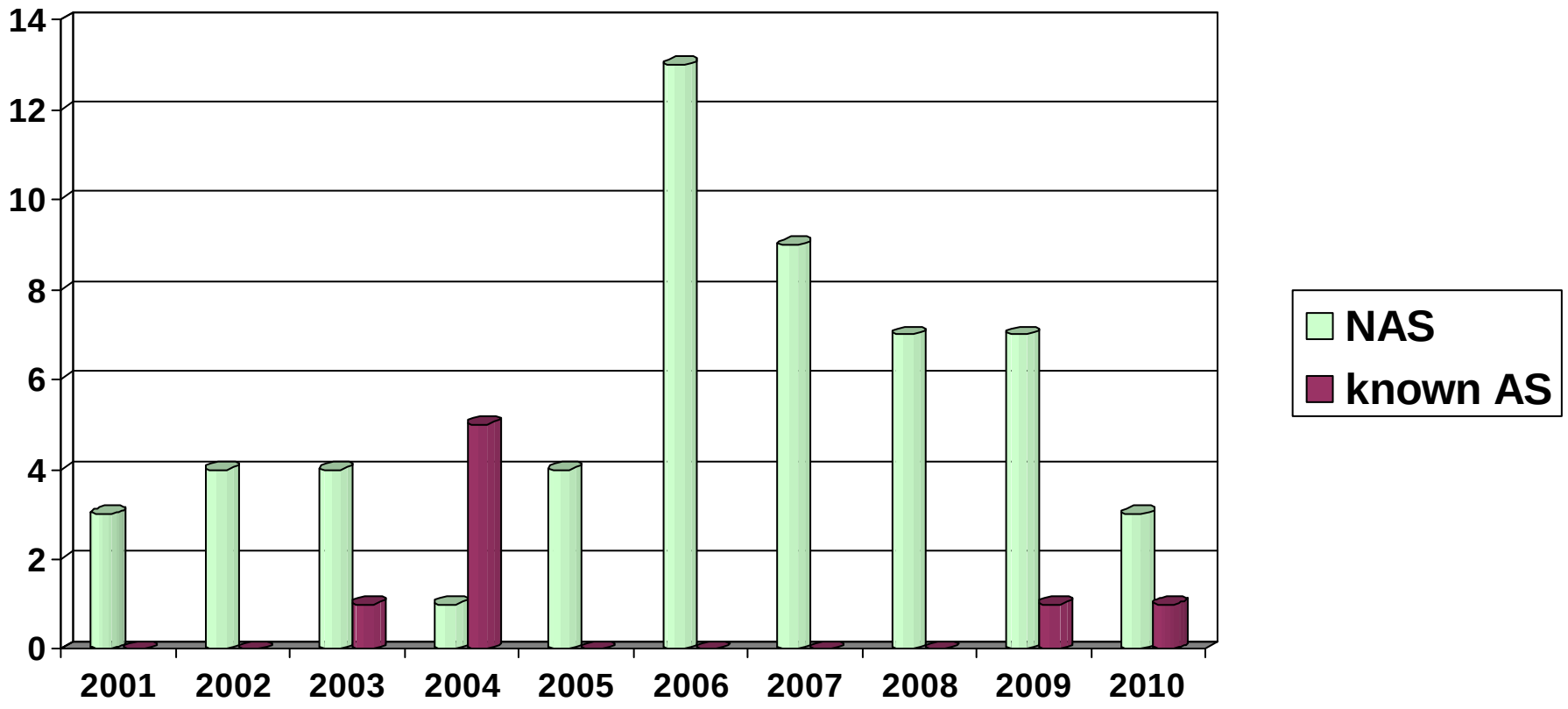
Access to EU research programs (Framework Programme

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

Market exclusivity for Orphan



Active substance status
Orphan medicinal products



Example of Orphan with several ODD and ME periods

Orphan condition	Glivec indication	EC approval
Treatment of chronic myeloid leukaemia (EU/3/01/021)	• *Adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy or in accelerated phase or blast crisis* • *Adult and paediatric patients with newly diagnosed Philadelpia chromosome (bcr-abl) positive (Ph+ for whom bone marrow transplantation is not considered as the first line of treatment*	07/11/2001 19/12/2002 (ext of indication and children)
Treatment of chronic easinophylic leukaemia and the hyper-easinophilic syndrome (EU/3/05/320)	*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.*	28/11/2006

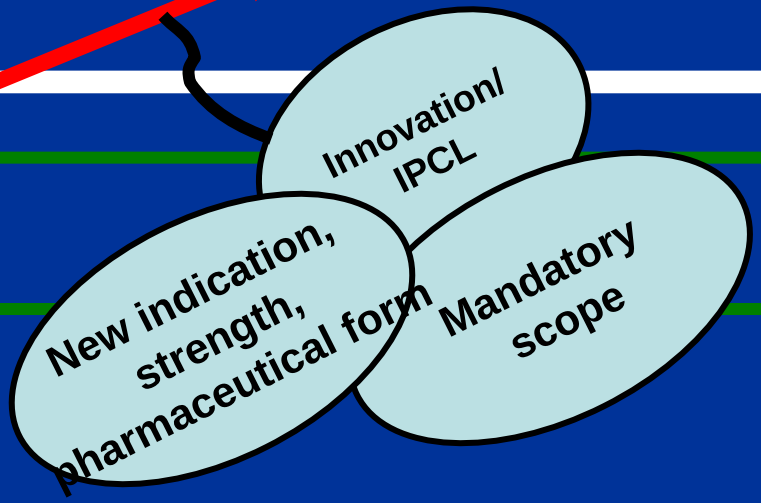
Generic/Hybrid/Biosimilar medicinal product

Two Entry Points for Centralised Generics/Hybrid/Biosimilar

- Automatic access if already authorised Centrally
- Optional access if Innovative/IPCL shown
- Mandatory is within mandatory 'biologicals' scope

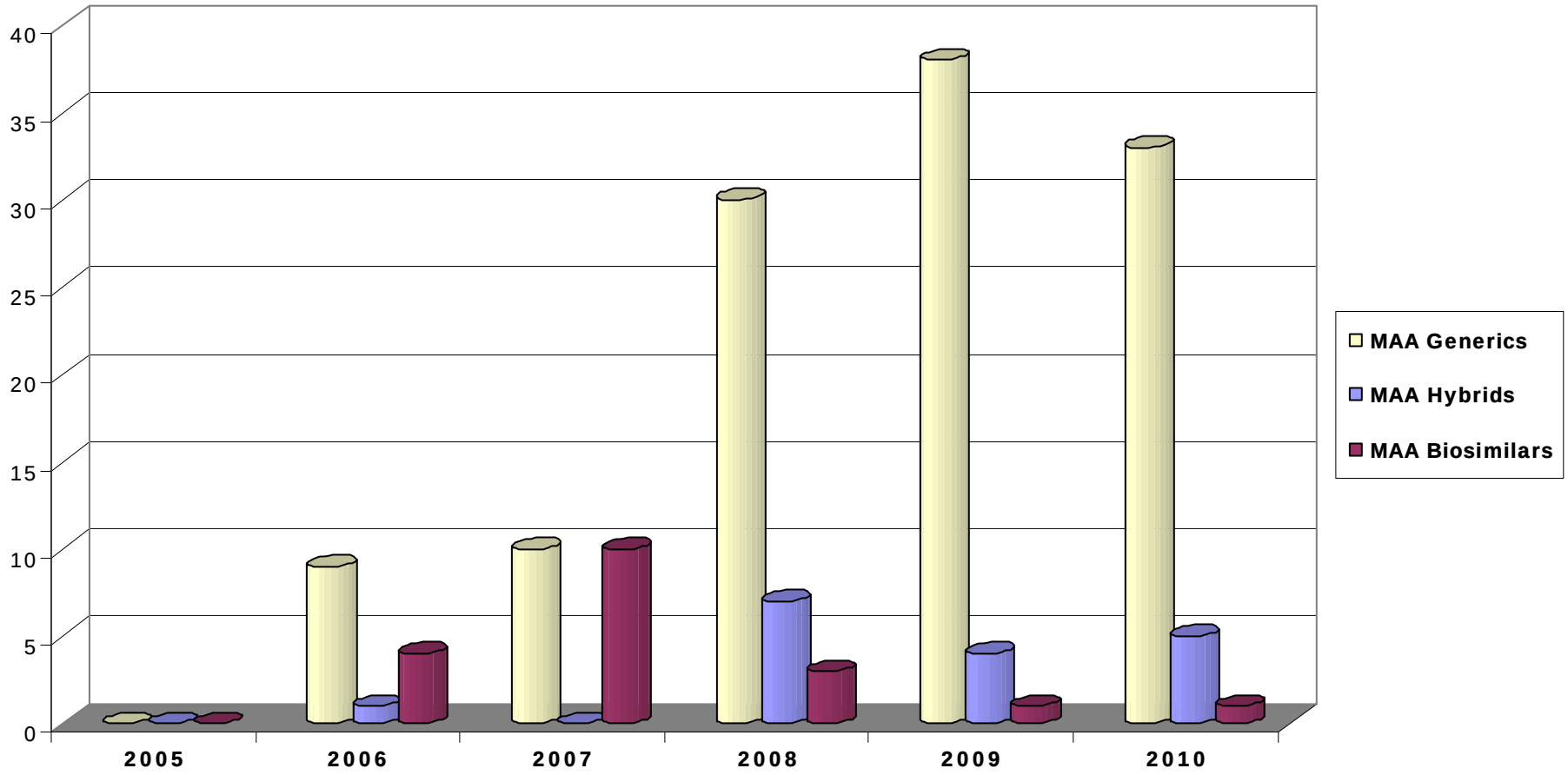
CAP RMP → **CAP Generic/Hybrid/Biosimilar**

NAP RMP

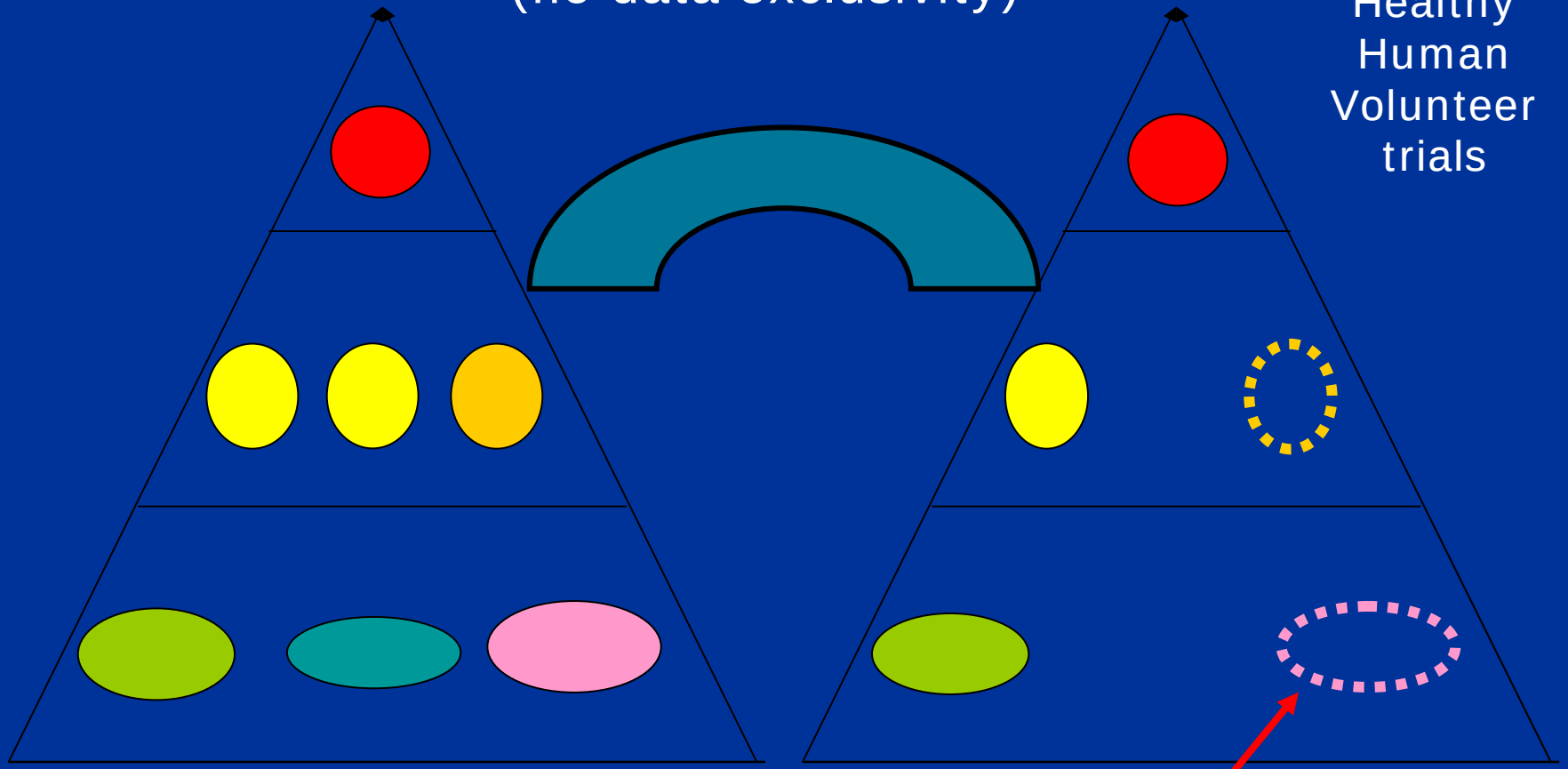


NAP=nationally authorised product

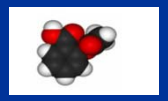
Generic, Hybrids and Biosimilar MAAs 2005-2010



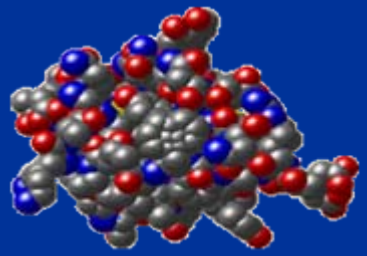
Abridged application – generic (no data exclusivity)



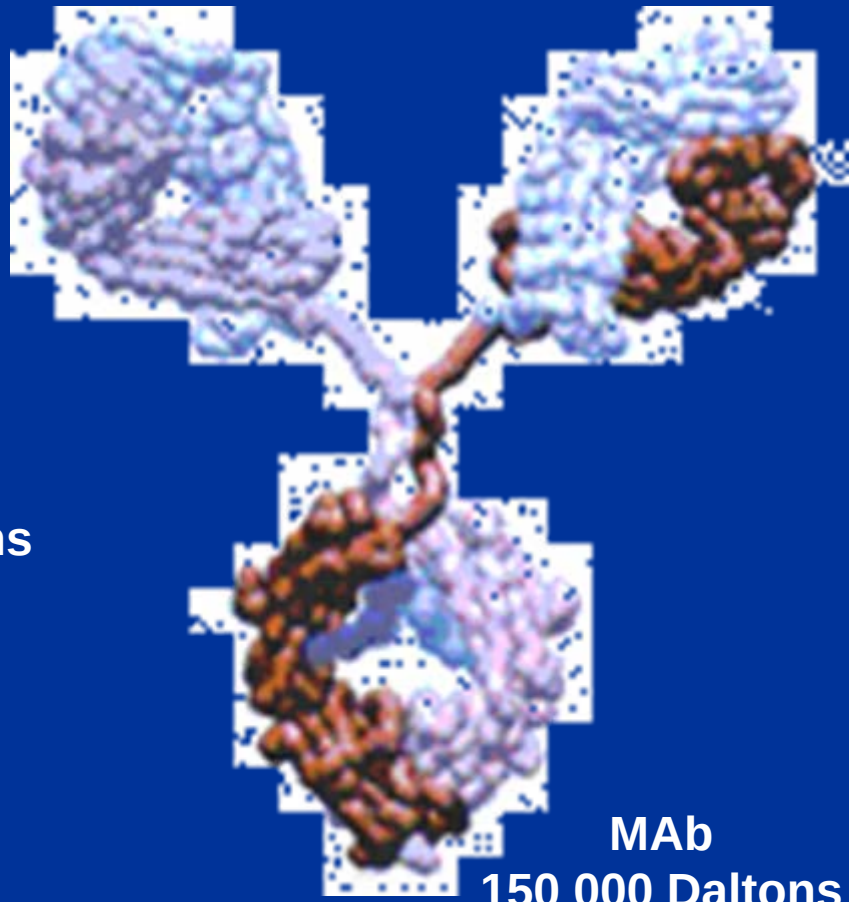
Why „biosimilar“ (and not „biogeneric“)?



Aspirin
180 Daltons



Insulin
5 700 Daltons



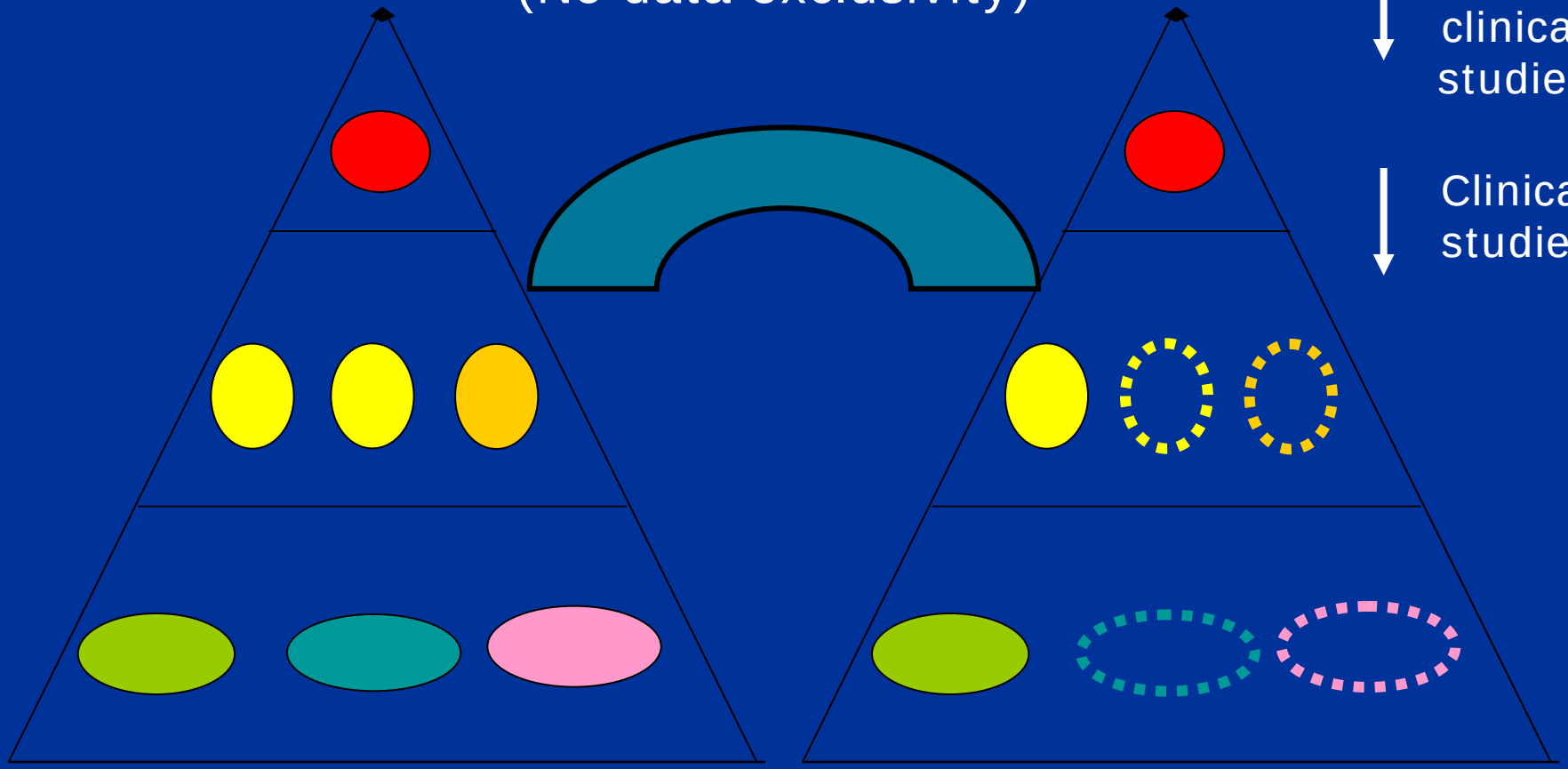
MAb
150 000 Daltons

How far can we go?

What do we need to know?

Abridged application – Hybrid/Biosimilar

(No data exclusivity)



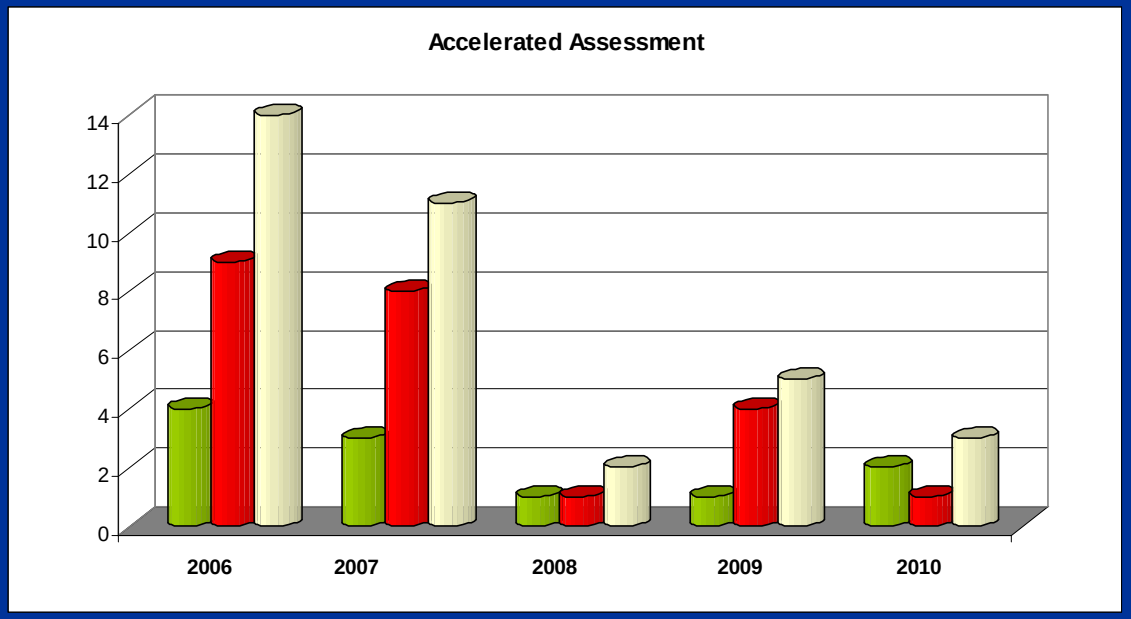
Reference Product

Early access tools

Accelerated Assessment Requests 2006-2010

May be requested for medicinal products of **major interest from the point of view of public health** and in particular from the **view point of therapeutic innovation**

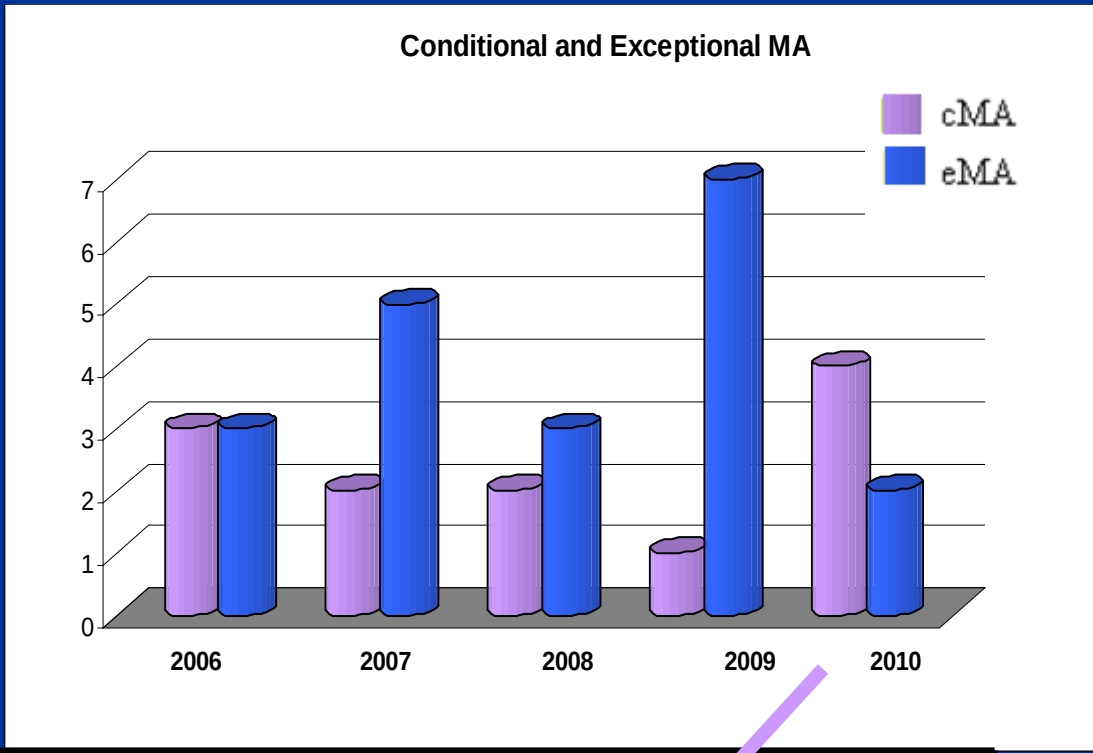
Possibly **CHMP Opinion at Day 150** or switch to normal TT



(2006: Soliris, 2007: Isentress, 2009: Vpriv)

Conditional MA

- Comprehensive (clinical) data not available, to be provided after approval
- Must fulfil scope (orphan drugs, emergency threats, serious and life-threatening diseases) and requirements
- Approval valid for 1 year, renewable

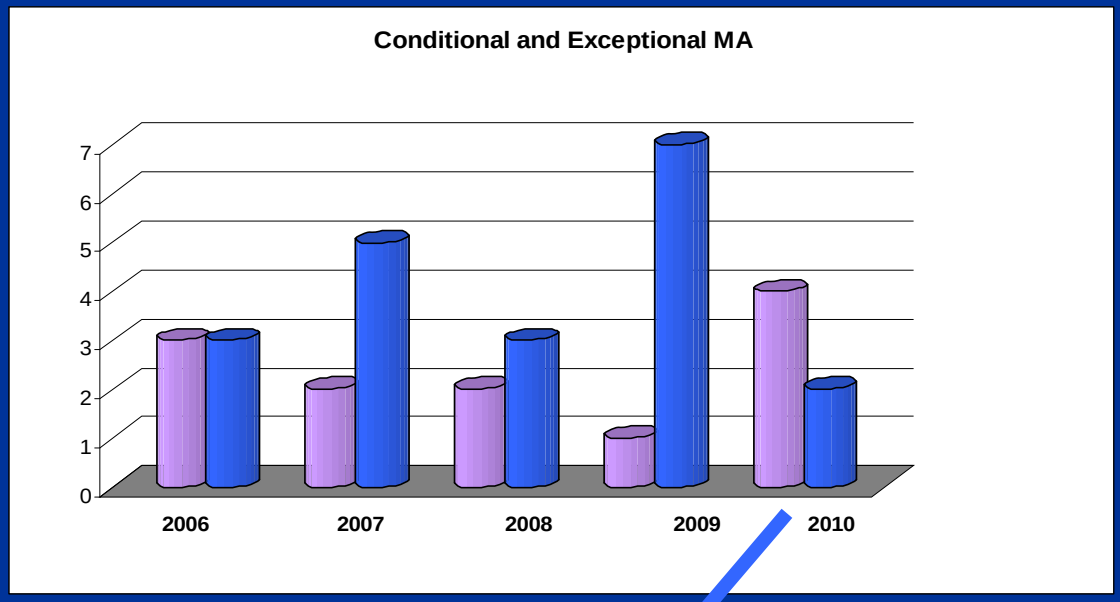


Arepanrix	Vaccine	J	Split Virion
Arzerra	Chronic lumphocytic leukemia	L	ofatumumab
Votrient	Renal cell Carcinoma	L	pazopanib
Humenza	H1N1 vaccine	J	Split virion

http://www.ema.europa.eu/pdfs/human/regaffair/50995106en.pdf

Exceptional Circumstances MA

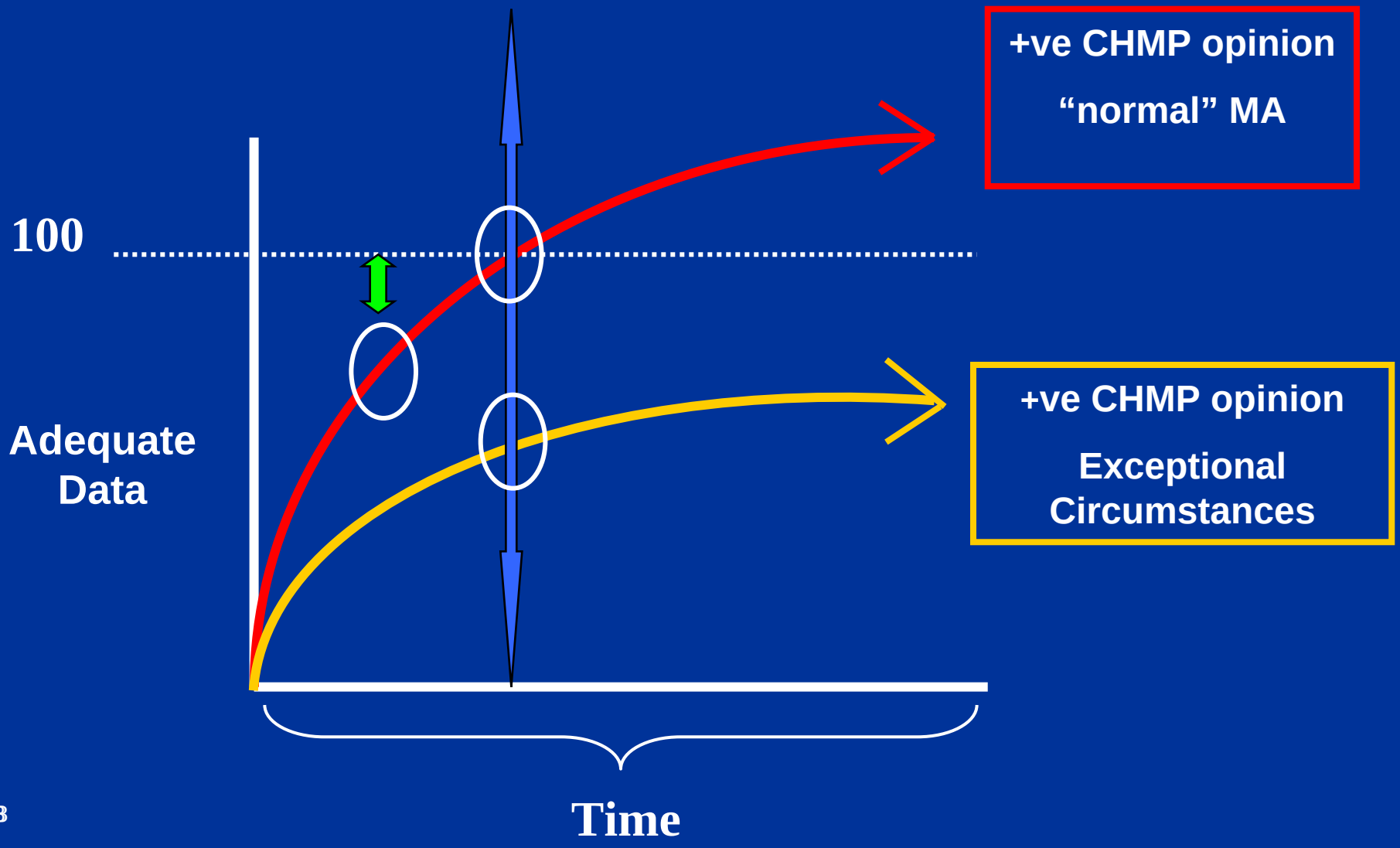
- Comprehensive data not available and cannot be provided
- Must meet criteria (rarity, medical ethics, state of scientific knowledge)
- Approval valid for 5 years, annual re-assessment



Pumarix	Vaccine	J	Split Virion

http://www.emea.europa.eu/pdfs/human/regaffair/50995106en.pdf

Normal vs. Conditional or Exceptional MAs



Paediatric Medicines

Development of paediatric medicines

Obligation

To study drugs in children for new products or new indications, 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 application

Reward

6 month ext of supplementary patent certificate

extra market exclusivity for orphan (2 years)

PUMA (Paediatric Use Marketing Authorisation) Incentives for old products →

8+2(+1) data/market protection

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

Paediatric SPC extension

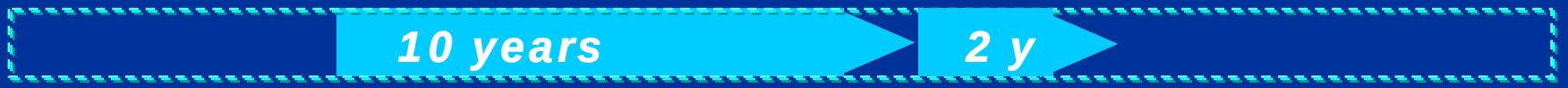
"Protects any invention with commercial application (idea of innovation)"

"Operates at the very beginning of the development of a medicinal product, Long before submission of an application"

OR

Paediatric Orphan Market exclusivity

Market exclusivity (orphan + paediatric)



Examples of compliance statement

Year	Companies	Products: Invented name (international non-proprietary name)
	Centrally authorised products	
2008	Merck Sharp and Dohme	Cancidas (caspofungin)
2009	Schering-Plough Europe	Rebetol (ribavirin)
2009	Bristol-Myers Squibb Pharma EEIG	Orencia (abatacept)
2010	Novartis Europharm Ltd	Zometa (zoledronic acid)
	Art. 29 Paediatrics	
2008	Merck Sharp and Dohme BV	Cozaar and associated names (losartan)
2009	Astra Zeneca AB	Arimidex and associated names (anastrazole)
2009	Novartis Pharma AG	Diovan and associated names (valsartan)
2010	Pfizer Limited	Sorties and associated names (atorvastatin)
2010	Pfizer Limited	Xalatan and associated names (latanoprost)

Conclusions

Explore different Regulatory strategies to maximise existing legislative incentives

Engage in early discussions of strategies with the Competent Authorities and with Rapporteurs

Benefit from Scientific and Regulatory Affairs Advice also on:

- Data exclusivity provisions
- Early access tools ‘conditional/exceptional’
- Dossier requirements for ‘hybrid’ or ‘biosimilars’
- …

Zaïde Frias

Head of Regulatory Affairs

Tel: +44 (0) 207 523 7019

zaide.frias@ema.europa.eu

EMA
7, Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

www.ema.europa.eu

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20/04/2011 **NicOx S.A. withdraws its marketing authorisation application for Beprana (naproxcinod)**

The European Medicines Agency has been formally notified by NicOx S.A. of its decision to withdraw its application for a centralised marketing authorisation for the medicine Beprana (naproxcinod), 375 mg hard capsules. ... Read more

19/04/2011 **European Medicines Agency holds first stakeholder forum on the implementation of the new pharmacovigilance legislation**

On 15 April 2011, the European Medicines Agency held a stakeholder forum on the implementation of the new pharmacovigilance legislation with a broad cross-

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