EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Data exclusivity, market protection, orphan and paediatric rewards

SME info day: Regulatory toolbox for medicines and combined devices developers
EMA, 26 October 2018

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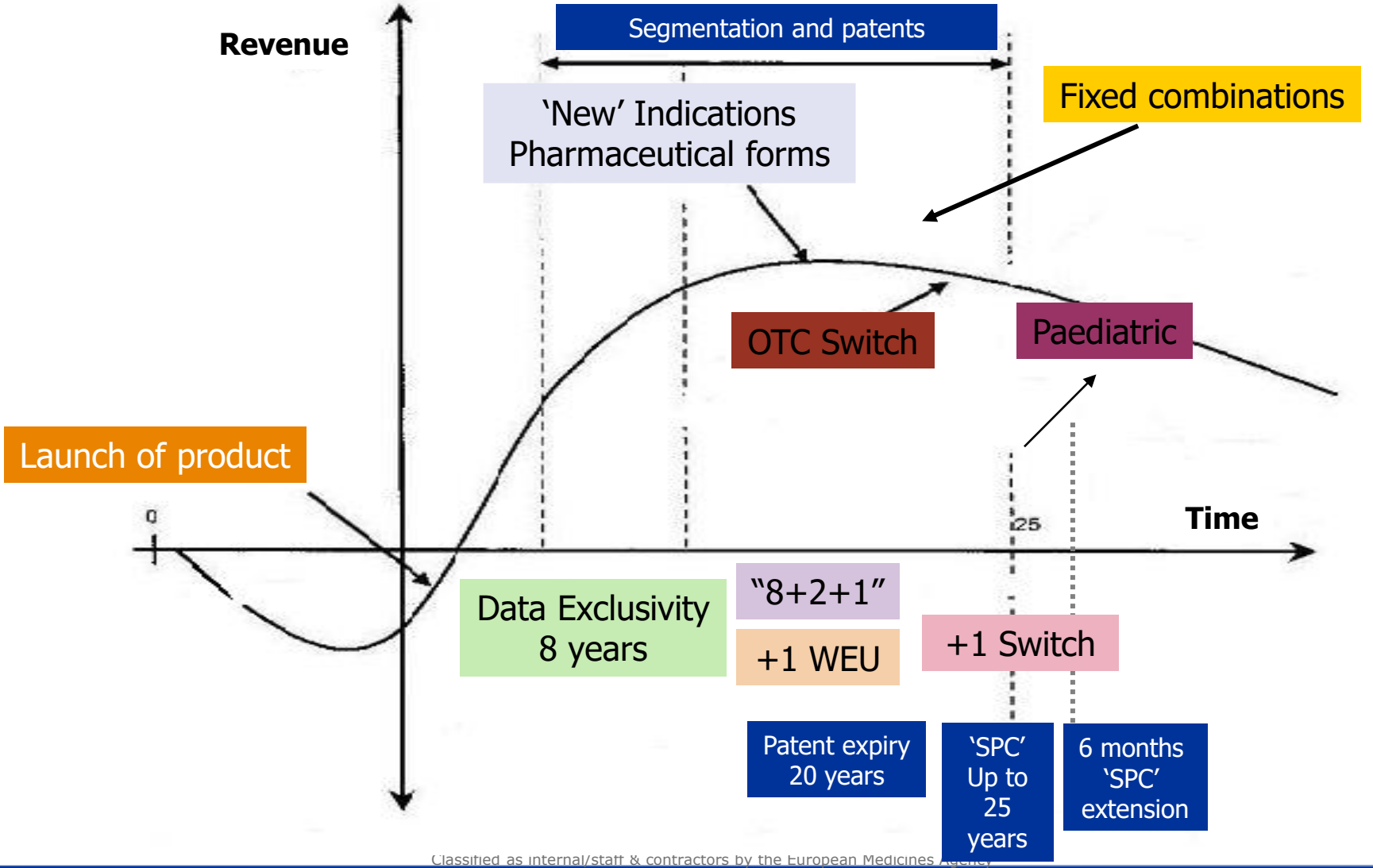
Lifecycle of innovator product



Data exclusivity and market protection provisions

Data exclusivity and market protection

Article 14(11) of Regulation (EC) No 726/2004

'(…) medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an ***eight-year period of data protection*** *and a* ***ten year period of marketing protection****, in which connection the latter period shall be extended to a maximum of* ***11 years*** *if, during the first eight years of those ten years, the marketing authorisation holder obtains an* ***authorisation*** *for* ***one or more new therapeutic indications*** *which, during the scientific evaluation prior to their authorisation, are held to bring a* ***significant clinical benefit in comparison with existing therapies****.'*

8+2 years

Extended by +1 year to a maximum of 11 years

→ This applies to medicinal products containing new or known active substances (notion of **Global Marketing Authorisation**)

Data exclusivity and Market Protection

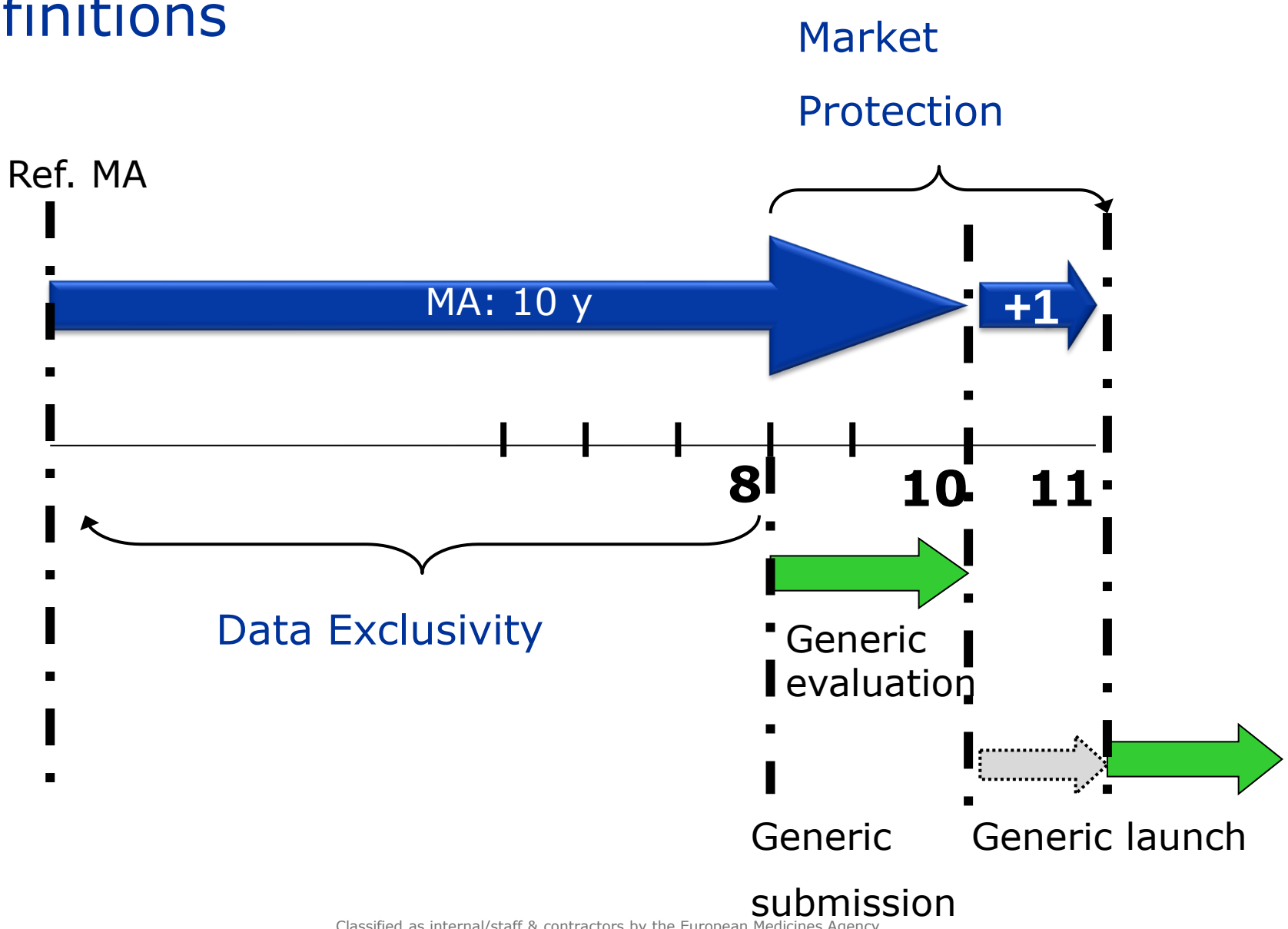
Data exclusivity

= Period of time during which an applicant cannot rely on the data in support of another marketing authorisation for the purposes of submitting an application, obtaining marketing authorisation or placing the product on the market, 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

Definitions



Concept of Global Marketing authorisation (GMA)

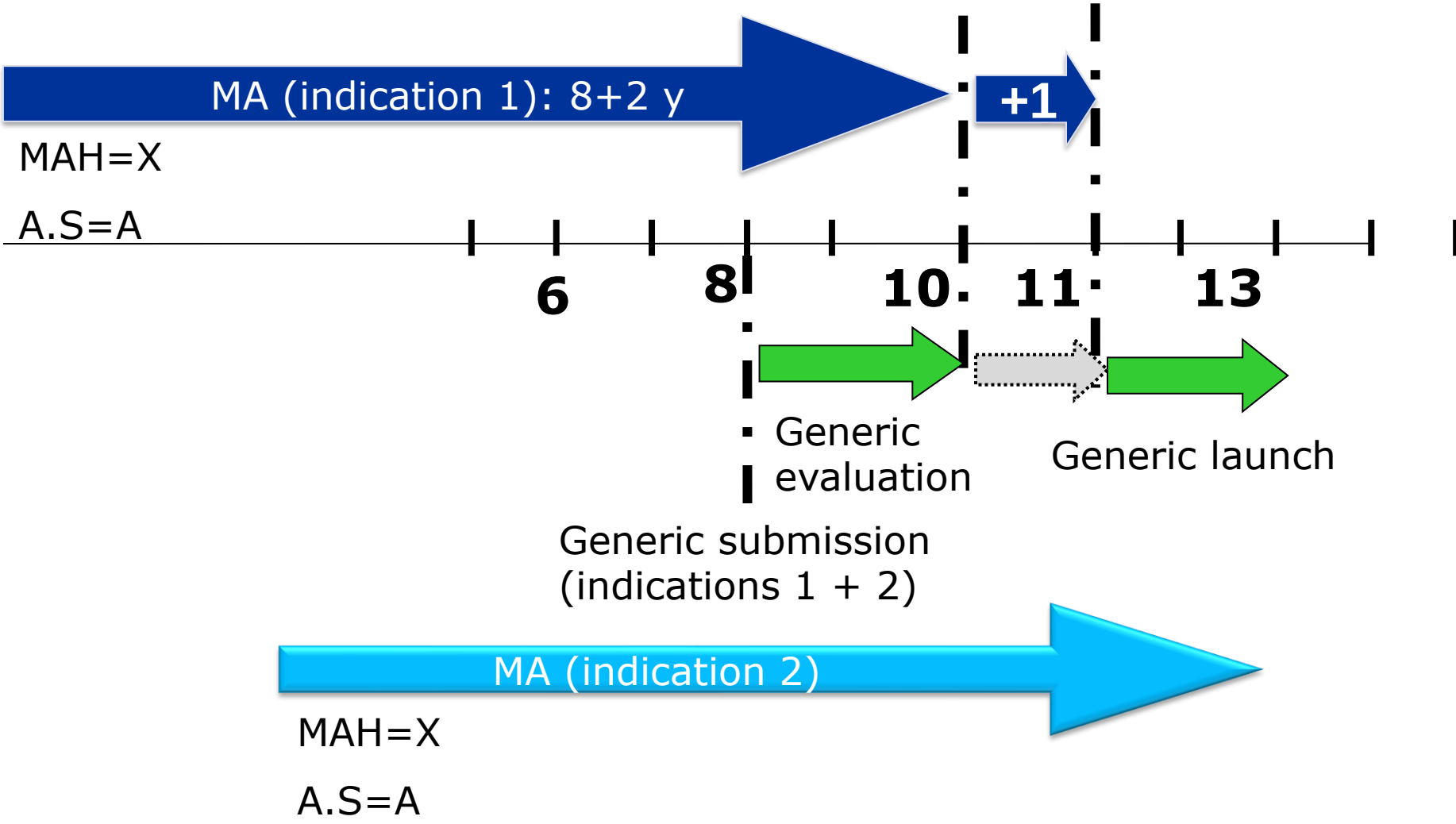
Article 6(1), Directive 2001/83/EC:

'When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, ***any*** *additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations* ***shall be considered as belonging to the same global marketing authorisation,*** *in particular for the purpose of the application of Article 10(1).*

→ This includes authorisations granted through separate procedures and under a different name to the **MAH** of the initial authorisation (=same active substance)

→ Fixed-dose combinations are not considered to fall within the scope of the global marketing authorisation of the already authorised mono-components

Implications of Concept of GMA



New active substance

Article 10, Directive 2001/83/EC

'2.(b) 'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they ***differ significantly*** *in properties with regard to safety and/or efficacy.(…)'*

New active substance, Notice to Applicants

ANNEX I DEFINITION OF A NEW ACTIVE SUBSTANCE

A new chemical, biological or radiopharmaceutical active substance includes:

- a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use n the European Union;

- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised in a medicinal product for human use in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised;

- a biological substance previously authorised in a medicinal product for human use in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process;

- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised in a medicinal product for human use in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union.

Regulatory consequences of determination of NAS

A. If significant differences in safety and/or efficacy demonstrated vis-à-vis reference active substance – New active substance, i.e. **not** part of GMA of initial MA

B. If **NO** significant differences in safety and/or efficacy demonstrated vis-à-vis reference active substance – Known active substance, i.e. part of GMA of initial MA, for the same Applicant

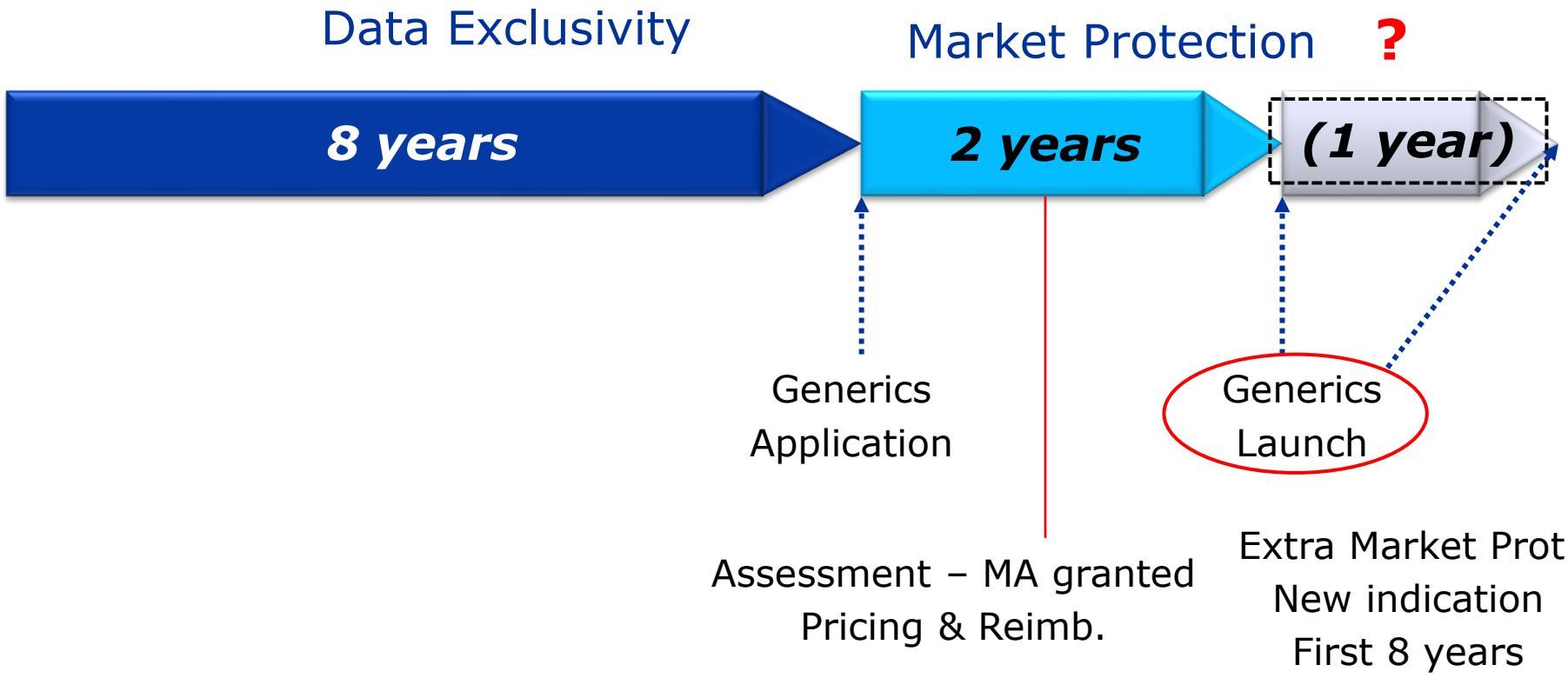
Provisions on **extended** market protection and data exclusivity

+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)*

+ 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 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)*

8+2(+1) Formula



- *Paediatric reward does not apply in case +1 year marketing protection is granted*

Market protection extension

Article 14(11) of Regulation (EC) No 726/2004

'(…) medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an eight-year period of data protection and a ten year period of marketing protection, in which connection the latter period shall be extended to a ***maximum of 11 years*** *if, during the* ***first eight years*** *of those ten years, the marketing authorisation holder obtains an* ***authorisation*** *for* ***one or more new therapeutic indications*** *which, during the scientific evaluation prior to their authorisation, are held to bring a* ***significant clinical benefit in comparison with existing therapies****.'*

Extended by +1 year to a maximum of 11 years

First 8 years

One or more therapeutic indications

Significant clinical benefit in comparison with existing therapies

→ This applies to medicinal products containing new or known active substances (notion of **Global Marketing Authorisation**)

Significant clinical benefit in comparison with existing therapies

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

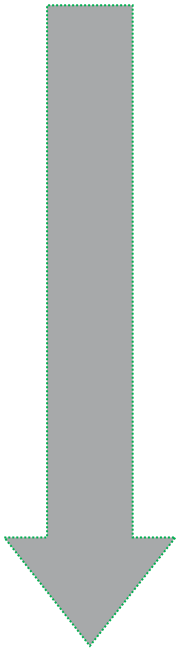
Key questions

1. Is it a new indication?
2. What are the existing therapies?
3. How does it compare to existing therapies?

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 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 more 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 is not considered existing therapies!

How does it compare to existing therapies?

Justification of significant clinical benefit may be based on:

- **Improved efficacy**
- **Improved safety**
- **Major contribution to patient care**

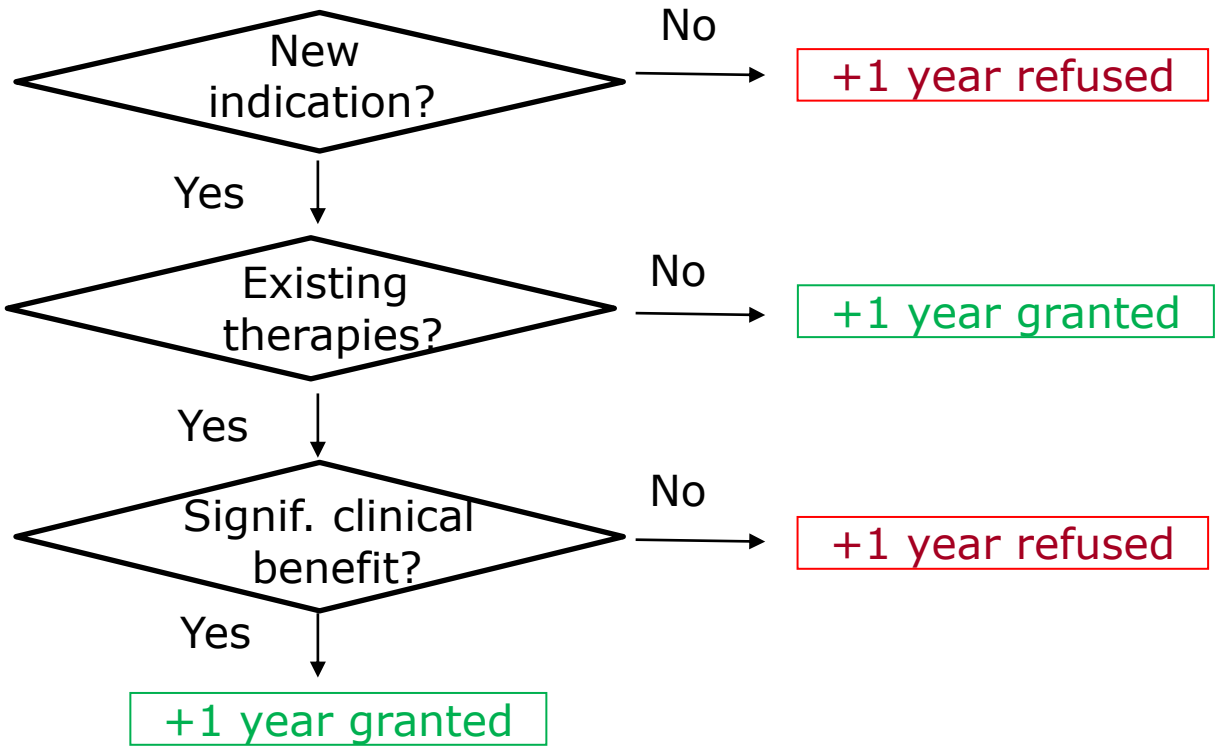
*To be assessed by **CHMP** at time of authorisation of a new therapeutic indication where the applicant claims significant clinical benefit in comparison with existing therapies*

Justification of significant clinical benefit

Improved efficacy	Improved safety	Major contribution to patient care
• Using clinically meaningful endpoint(s) in adequate and well-controlled clinical trials • Same level of evidence needed to support a comparative efficacy claim for two different products • Direct comparative clinical trials preferred	• Normally requires substantiation by large and robust data • Relative safety profile to be globally assessed preferably through comparative trial(s) • Safety benefits to be shown in a specific, prospective study quantifying risk for each therapy	• New mode of administration (e.g. ease of self-administration) • New route of administration • Treatment alternative (e.g. ≠ principal mechanism of action) • Response ≠ from other treatments in a **substantial** part of the target population

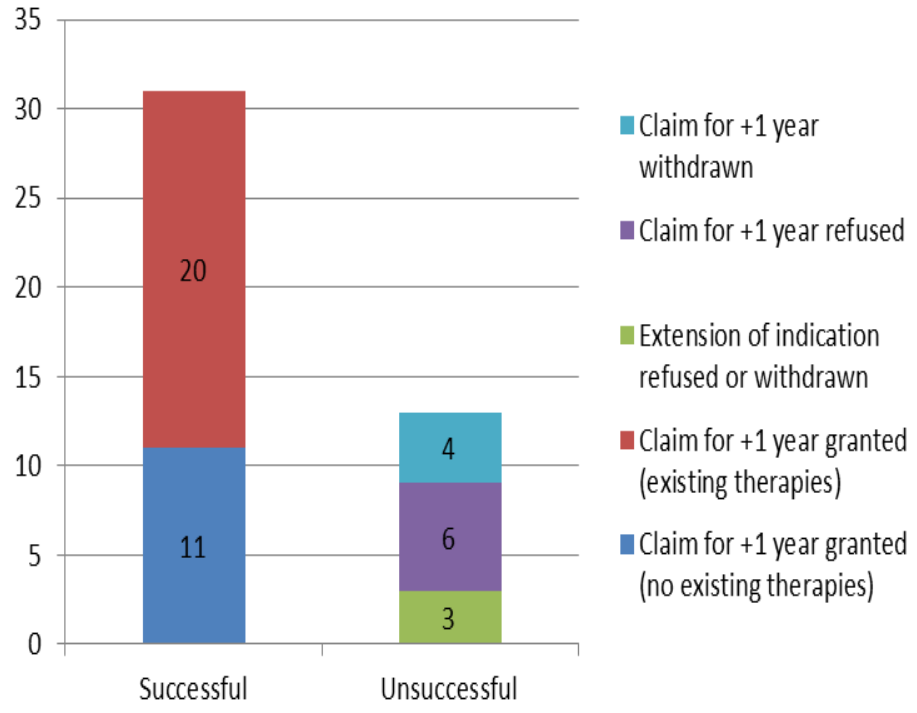
Decision tree

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]

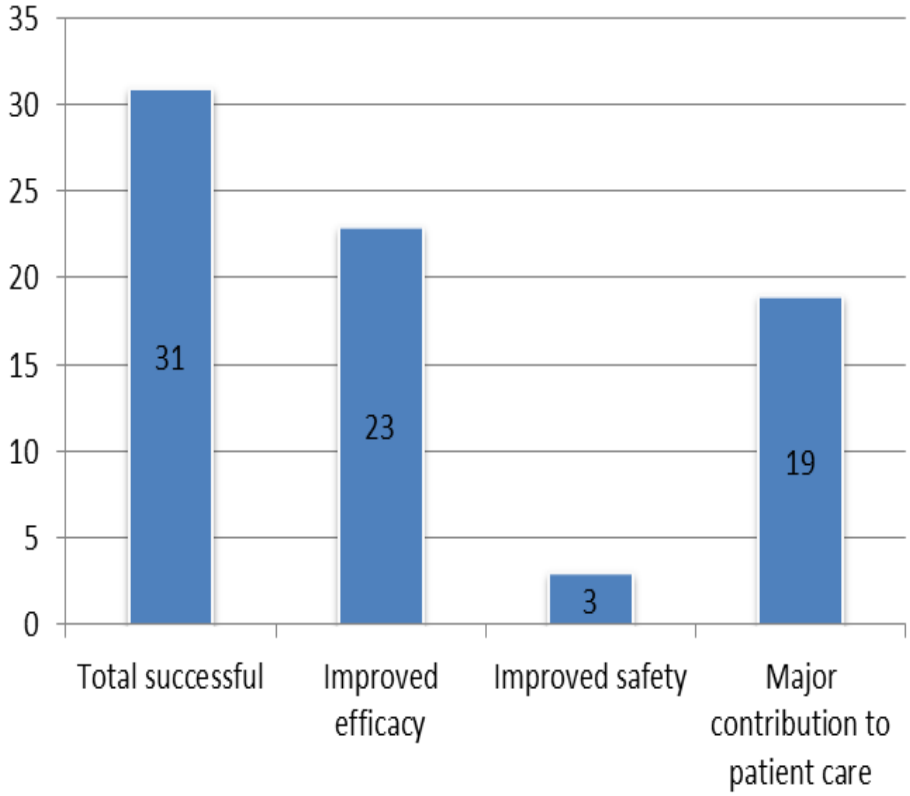


EMA experience - +1 year of marketing protection

Overview of claims received



Grounds for accepting the claims



Data exclusivity "1 year switch"

Legal basis – Article 74a of Directive 2001/83/EC

Where a change of classification of a medicinal product has been authorised on the basis of ***significant pre-clinical tests or clinical trials****, the competent authority* ***shall not refer to the results of those tests or trials*** *when examining another application by another applicant for or holder of MA for a change of classification of the same substance* ***for one year after the initial change was authorised.***

- Change of classification
- Significant pre-clinical tests or clinical trials
- Data exclusivity for one year

Data exclusivity "1 year for a well-established substance"

*Where an application is made for a **new indication** for a **well-established substance**, a non-cumulative period of **one year** of data exclusivity shall be granted, provided that **significant pre-clinical or clinical studies** were carried out in relation to the new indication.*

- New indication
- Well-established substance
- Significant pre-clinical tests or clinical trials

→ No experience yet in the centralised procedure with this incentive
→ Incentive for development of new indications whilst data protection would not apply

European orphan legislation

- Lack of appropriate treatment – ' *Patients suffering from rare conditions should be entitled to the same level of treatments as other patients'*
- Market often economically not interesting
- Lack in return of investment

•1983 – US Orphan Drugs Act

•1993 – Japanese legislation for Orphan Drugs

•**1999- EU 'Orphan' Reg. No 141/2000**

Aim of the Regulation:

Stimulate R&D of orphan products by providing appropriate incentives

Incentives for orphan medicines

- 10 year **market exclusivity*** (protection from similar medicines in same indication)
- + 2 years of market exclusivity for completion of the paediatric investigation plan (PIP)
- Protocol assistance throughout development
- Access to centralised procedure
- Fee reductions

* Can be reduced to 6 years post-authorisation if criteria no longer met

Impact of authorised orphan medicines

Other medicines (orphan or not) for the same or overlapping indication must:

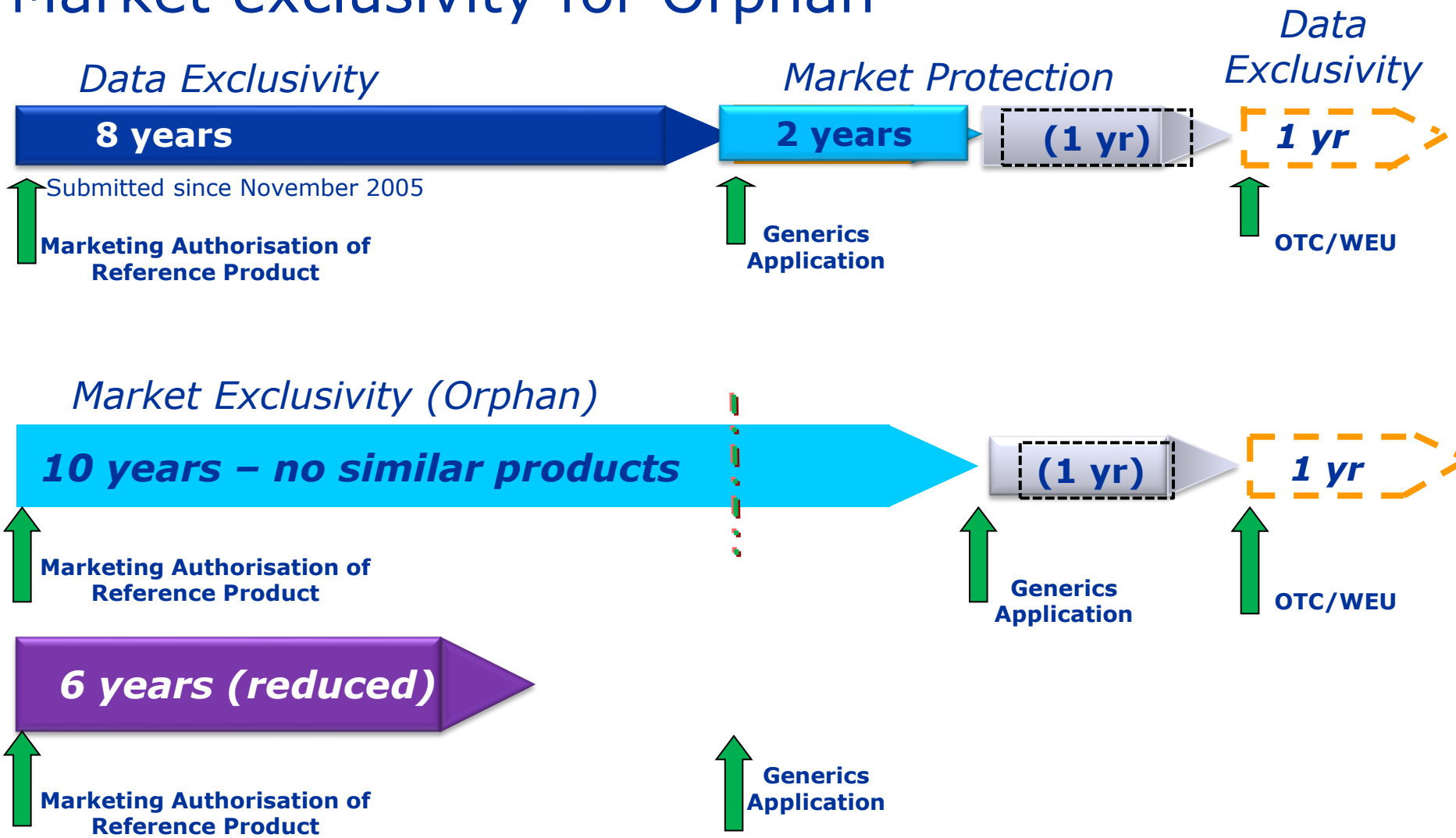
- Demonstrate that the medicine is **not similar**, or
- Justify a **derogation** if:
  - Consent from MAH of orphan product
  - MAH of orphan product unable to supply sufficient quantities
  - It's established that the second product is clinically superior (e.g. safer or more effective)

Market exclusivity principles

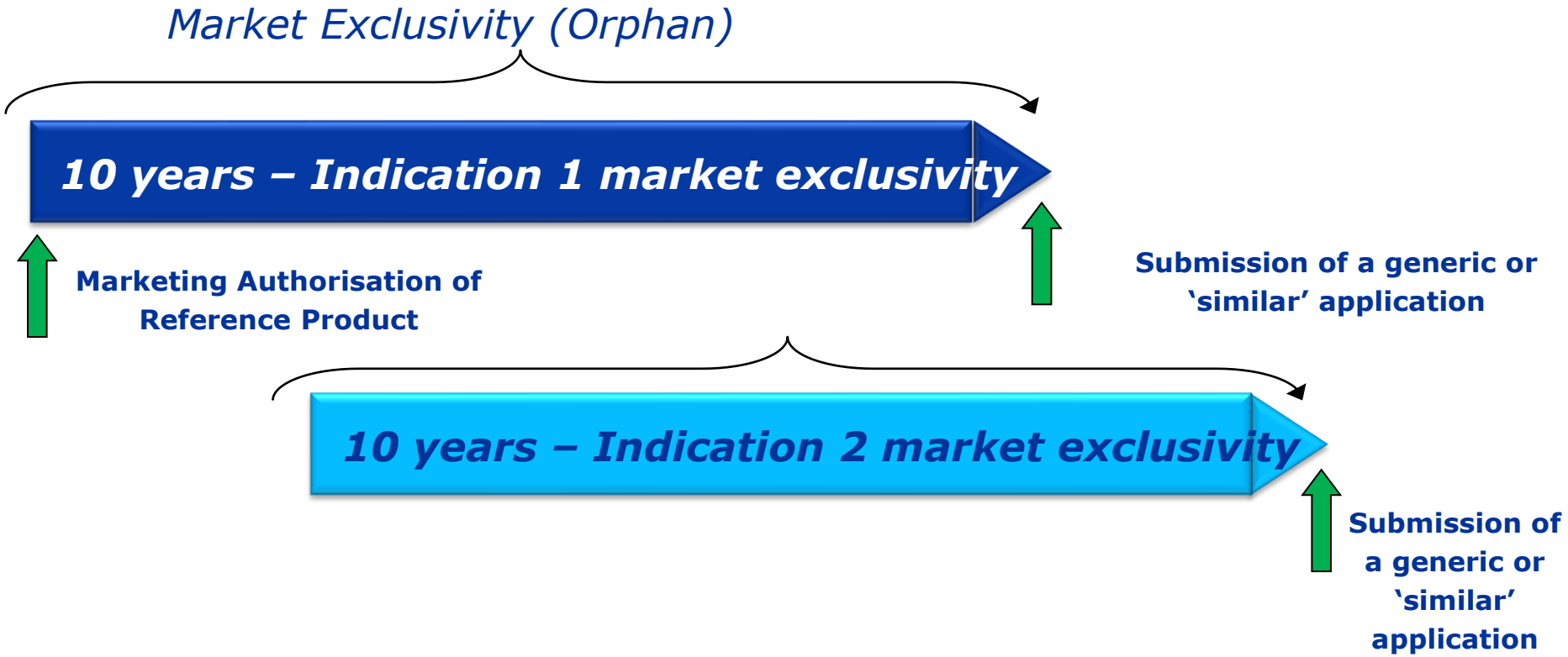
- Market exclusivity in Orphan Regulation **runs in parallel** with normal rules on data exclusivity and market protection
- Therapeutic indication for a **separate orphan designation** benefits from 10 years market exclusivity
- No mix of orphan and non-orphan indications in the same MA allowed
- However,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



Market exclusivity for Orphan



Note: Only if therapeutic indications are for separate orphan designations

Paediatric Medicines

Development of paediatric medicines

Obligation

- To study drugs in children for new products or new indications

Agree Paediatric Investigation Plan (PIP) by Paediatric Committee (PDCO)

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

PIP related obligations vs incentives

Type of MP	Obligation	Incentive	Compliance with PIP
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	Necessary for validation of application*
Off patent Medicine	None (voluntary PIP possible for PUMA)	8+2 years of data protection for PUMA	Necessary for validation of PUMA application

#according to GMA concept ** Except for Art. 10 and Art 10a applications*

Conditions for paediatric rewards

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

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

"Negative" PIP results do allow the reward

Paediatric Use Marketing authorisation (PUMA)

- Exclusively paediatric indications!
- 8+2 data and market protection for off patent medicine
- Financial incentive - partial fee exemption for PUMA
- Optional access to the Centralised procedure
- Capitalise on the invented name

PUMA granted through centralised procedure:

- Buccolam (midazolam) – 05/09/2011
- Hemangiol – 23/04/2014
- Sialanar – 15/09/2016
- Kigabeq – 20/09/2018

Incentives & support for (early) access to medicines

Brineura

- For late infantile neuronal ceroid lipofuscinosis type 2
- Very rare, congenital disease leading to death by 10 – 16 years of age
- No existing treatments
- slows the progression of motor and language decline

R&D support

- Innovation Task Force
- **Scientific Advice***
- **Paediatric development***
- PRIME
- SME support

Regulatory pathway

- **Accelerated assessment***
- Conditional MA
- **MA under exceptional circumstances***
- Compassionate use
- ATMP certification

Incentives

- **Data exclusivity***
- **Market protection***
- +1 year
- **Orphan Market exclusivity***
- 2 year extension
- SPC extension
- **Reduced fees***

* Incentives/support applied to Brineura

Study on pharmaceutical incentives and rewards – Key findings

- Average development time increased (10 -> 15 years)
- Effective protection period declined (15 -> 13 years)
- 51% of sample patent last to expire
- 45% of sample has been granted an SPC
- EU has most attractive pharma incentives regime in comparison with other jurisdictions
- Positive relationship between effective protection period and level of pharma R&D

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If you have any questions please submit them via ASK-Ema, the Agency's request for information on-line service.