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# Regulation on medicinal products for paediatric use

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# Regulation on medicinal products for paediatric use

**<u>Findings:</u> approx. 50 % off-label use in paediatrics**

**→ Neonates → 100 %**

**→ Children up to 18 years of age**
**→ usual off-label use**

**<u>Solution:</u> → more paediatric research**

**→ adjustment of the market authorisations**

**→ by compulsion + incentives**

# Regulation on medicinal products for paediatric use

| **Market:** | **MP protected by patent or SPC** | **Orphan medicinal products** | **MP with known substances** |
|---|---|---|---|
| | ↑ | ↑ | ↑ |
| | **Special importance** → **Incentive by patent extension** | **Special significance for serious diseases in children** → **Incentive by extending market exclusivity** | **Significant because known and safe** → **Incentive by data protection** |

# Regulation on medicinal products for paediatric use 1901/2006/EC

**creates:**

**→ New procedure for approval of a paediatric investigation plan**

**→ Duty to research with the sanction of a marketing authorisation ban**

**→ Duty to distribute in favour of children**

**→ Incentive system through patent extension, extension of market exclusivity and data protection**

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# Regulation on medicinal products for paediatric use 1901/2006/EC

**changes:**

→ **Regulation 1768/92/EC**
**- comprehensively to create or extend protection certificates**

→ **Directive 2001/20/EC - Art. 11**
**– Publication of paediatric clinical trials**

→ **Directive 2001/83/EC - Art. 6**
**– Distribution of medicinal products in the EU only if national, decentralised or centralised marketing authorisation exists and the Regulation on medicinal products for paediatric use is satisfied**

→ **Regulation 726/2004/EC - Art. 56**
**Establishment of a Paediatric Committee at the EMEA**

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# Regulation on medicinal products for paediatric use

**Duties of the pharmaceutical entrepreneur:**

- **Paediatric investigation plan**
- **Approval from the Paediatrics Committee of EMEA**
- **Conduct of studies in compliance with the investigation plan**

**Consequence:**

**Art. 7: refusal to grant new marketing authorisation if studies are not in compliance with the investigation plan**

**→ Ban on marketing authorisation also for adults**

# Regulation on medicinal products for paediatric use

**Duties:** **Which medicinal products ?**

**Art. 7 in principle: all new marketing authorisations**

**Art. 8 Line extensions if**

**→ patent exists that comes into question for SPC or extension of SPC**

**Art. 30 Authorisation for paediatric use – PUMA – only if trial is in compliance with the investigation plan (Art. 30 No. 2)**

# Regulation on medicinal products for paediatric use

**Duties:** **Which medicinal products ?**

**Exceptions:** **Art. 9**

- → **Generics**
- → **Bibliographical applications - WEU**
- → **Homeopathic agents**
- → **Trad. phytopharmaceuticals**

**Art. 11 Waiver:** → **Group, e.g. geriatrics and individual cases**

**Art. 20 Deferral:** → **First adults, then children**

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# Regulation on medicinal products for paediatric use

**<u>Paed. Investigation plan</u>** **- Application (Art. 15 et seq.) procedure (Art. 18, 25 et seq.)**

**Approval by Paediatric Committee (Art. 6)**

**- Waivers (Art. 11)**

| **Groups** | **Individual case** |
|---|---|
| **e.g. geriatrics** | **e.g. no benefit** |

**- Deferrals (Art. 20)**

**Requirement: Trial in compliance with investigation plan, not a specific result**

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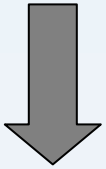
# PIP Approval Procedure
# - PIP Guideline -

**Commission Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies**

**(draft, version January 2007)**

# PIP procedure (1)

→ **Establishment of application and PIP to EMEA/PDCO – Art. 15**



→ **Validation within 30 days by EMEA and preparation of a summary for the PDCO**

- **Request for additional information can put the 30-day regulation out of force**
- **Submission at the latest after completion of the pharmacokinetic studies on adults – Art. 16 (1)**

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# PIP procedure (2)

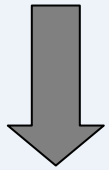
→ **Selection of a rapporteur and opinion of the PDCO within 60 days – Art. 17**

**- does the therapeutic benefit to be expected justify the planned studies?**

**- are the suggested measures suitable?**

**- hearing of PDCO/applicant possible**

**- request for further information possible – Art. 17 ( 2 )**



**Clock stop**

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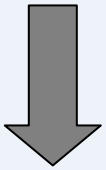
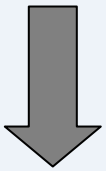
# PIP procedure (3)

→ **Paediatric Committee gives positive or negative opinion possibly after receipt of additional documents (max. 60 days extension of processing time)**



**Art. 18 → Art. 25**

→ **Agency passes opinion of the PDCO to applicant within 10 days of receipt – Art. 25 (1)**

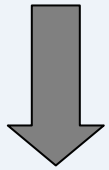


→ **Possibility to file an application for examination within 30 days – Art. 25 (2)**

# PIP procedure (4)

→ **Appointment of a new rapporteur and preparation of a new opinion within 30 days – Art. 25 Abs. 3**

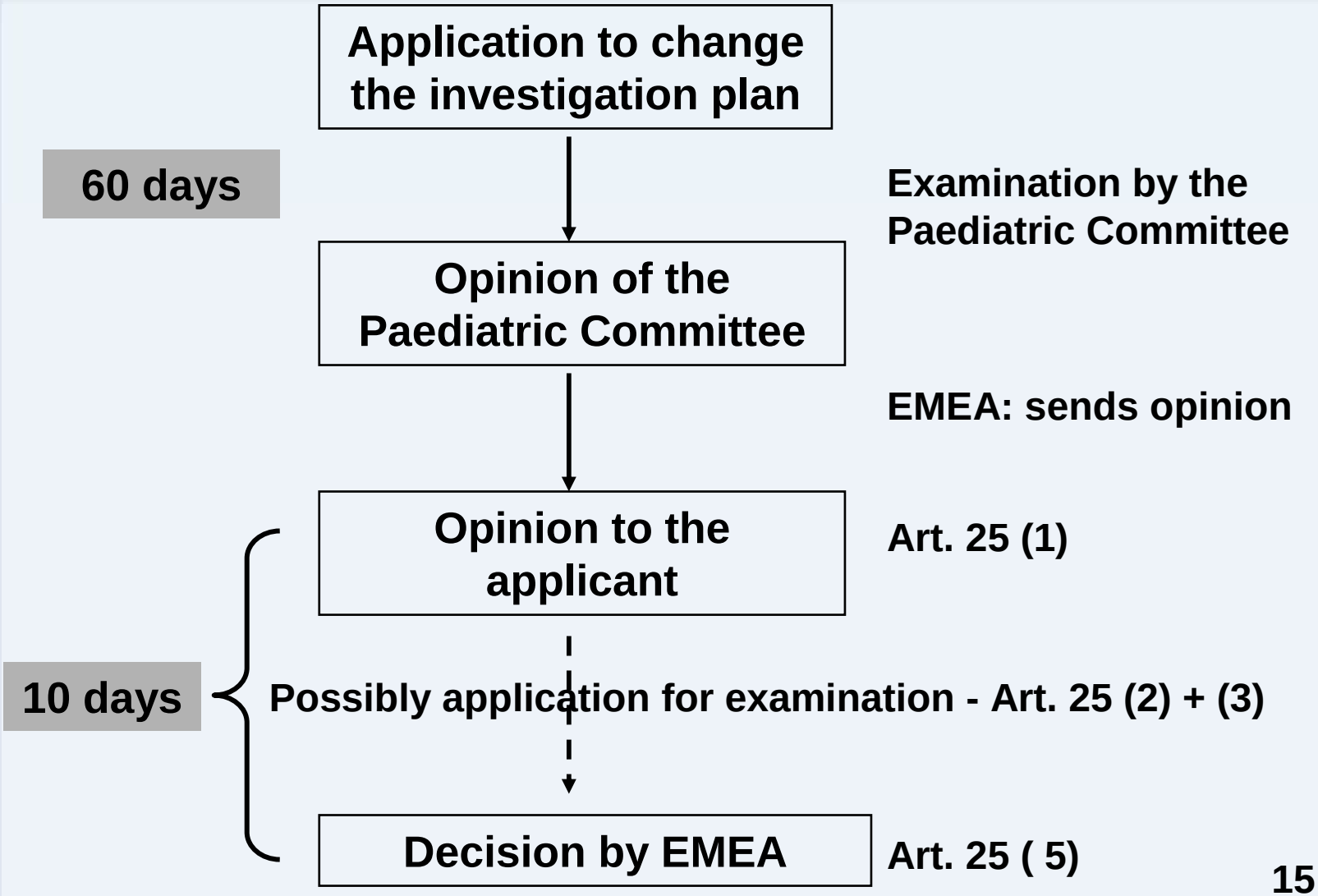
**- second opinion is final**



→ **Decision of the EMEA – not of the EU Commission – on the basis of the opinion within 10 days and information of the applicant - Art. 25 (5)**

→ **Publication**

# Change in the paediatric investigation plan - Art. 22 -



# Regulation on medicinal products for paediatric use

**Transitional provisions for duties of the pharmaceutical entrepreneur**

**Art 57:**

→ **Art. 7 (i.e. ban on marketing authorisation)**
**Applies 18 months after coming into force**

→ **Art. 8 (i.e. ban on marketing authorisation for patent-protected line extensions)**
**Applies 24 months after coming into force**

→ **Art. 31 (i.e. centralised PUMA application)**
**Art. 32 (i.e. labelling as paediatric medicinal product)**
**Applies 6 months after coming into force**

# Regulation on medicinal products for paediatric use

**Transitional provisions for duties of the pharmaceutical entrepreneur**

**Consequences arising from Art. 57:**

→ **Deferrals for the end of research in the investigation plan are mandatory if "PIP compliance" is to be achieved when filing application starting from 2007.**

**The latter is mandatory pursuant to Art. 7, 8 and a prerequisite for incentives pursuant to Art. 28 (3) in connection with Art. 36.**

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# Regulation on medicinal products for paediatric use

**Duties after granting approval:**

**Art. 33**
**Duty to distribute within two years of marketing authorisation**

**→ in the case of marketing authorisation according to approved investigation plan**

**→ incorporation in the EMEA Register**

**Art. 34**
**Vigilance by authorities and pharmaceutical entrepreneur**

**Art. 35**
**Discontinuation of distribution?**

**→ Duties:**

- **Notification to EMEA**
- **Transfer of the marketing authorisation to other pharmaceutical entrepreneurs**

# Incentives for Paediatric Research

**Labelling:**

**Identification**

- **MP authorised for paediatric use in compliance with PIP**
- **all others authorised for paediatric use**

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**The Commission will publish a symbol recommended by the Paediatric Board to be labelled on each pack of MP authorised for paediatric use**

→ **Labelling obligatory 2 years after publication of the symbol**

**Art. 32**

# Regulation on medicinal products for paediatric use
# Rewards and incentives Art. 36 et seq.

**Art 36 (3):**

- **for DP + MRP: duty to grant marketing authorisation in all EU Member States**
- **for centralised authorisation → applies in all EU MS by law**

**Art 37:**

- **for orphan MP → duty to use the centralised procedure**

**De facto compulsion to use the centralised procedure?**
**Increased pressure at all events!!**

**→ Art. 31 permits use of the centralised procedure irrespective of the qualifying features in Art. 3 of EC Regulation 726/2004**

# Protection of Pharmaceutical Innovation

**Patent**

- not always adequate because of

- tests, trials required for marketing authorisation

- duration of NDA procedures i. e. 4-6 years

**SPC**

→ additional protection

- max.15 years but not more 5 years after patent expiry

→ equivalent to patent protection

**Art. 10 – 10 c Dir. 2001/83/EEC**

→ additional protection

- 8 + 2 + 1 years running from the date of first authorisation of the reference product

**within the Community**

- against 2nd applicants, who submitted abridged documentation – generics –

→ no patent protection - 2nd applicants may submit own data

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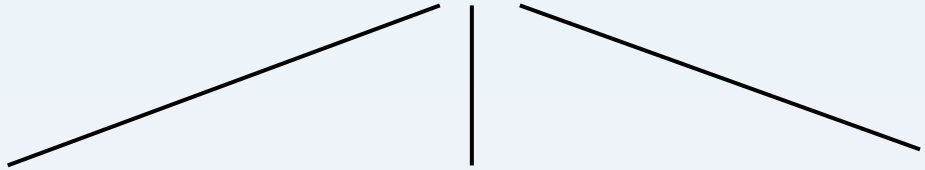
# Utilisation of Innovator's Documentation in an NDA of 2nd Applicants

**Requirements under Art. 10 – 10 C Dir. 2001/83 EEC**



- essential similarity
- consent of the 1st applicant Art. 10 c

bibliographic appl. Dir. 2001/83 Annex IEEC "well established use" for one decade Art. 10 b

- generic application
- expired protection term Art. 10 Abs. 1

**no consent of the 1st applicant is required**

# Orphan Medicinal Products – OMP
# EU Reg. 141/2000

**MARKET Exclusivity Art. 8**

- **for 10 years no other application accepted by EU and MS for a**

  **similar medicinal product**

- **Reduction to 6 years if criteria are no longer met**

- **<u>Exemptions:</u>**
  - **informed consent application**
  - **insufficient supply**
  - **a similar product is superior**
    **Def.: Art. 3 EU Reg. 847/2000**

- **<u>Wide definition of “similar medicinal product"</u>**

  **≠ Essential similarity in the case of Art. 4, No. 8, Lit a, iii**

  **→ Def. : Art 3 EU Reg. 847/2000**

  **efficient protection against "Me Toos"**

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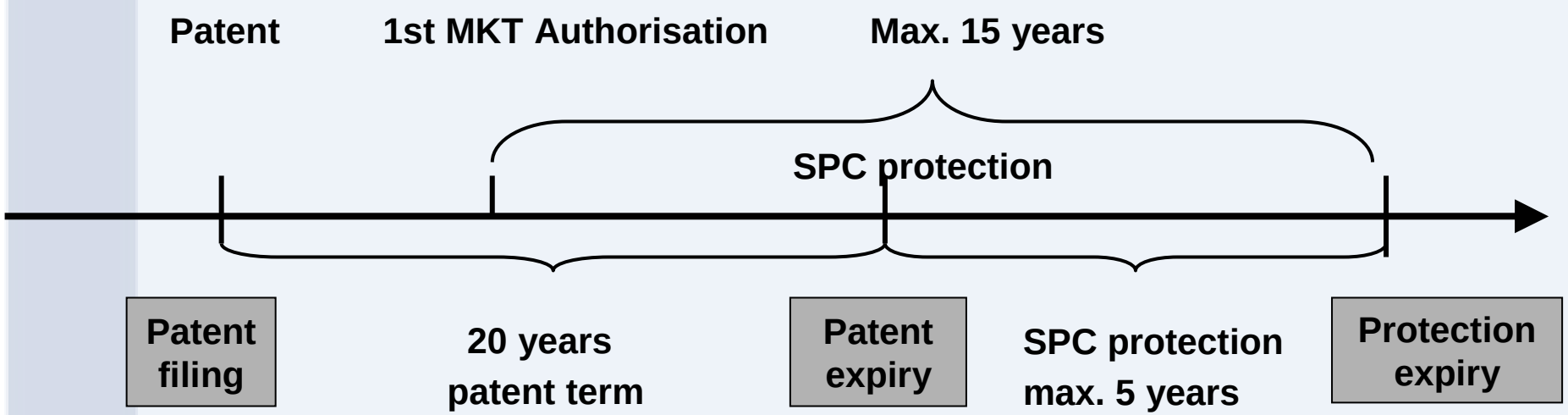
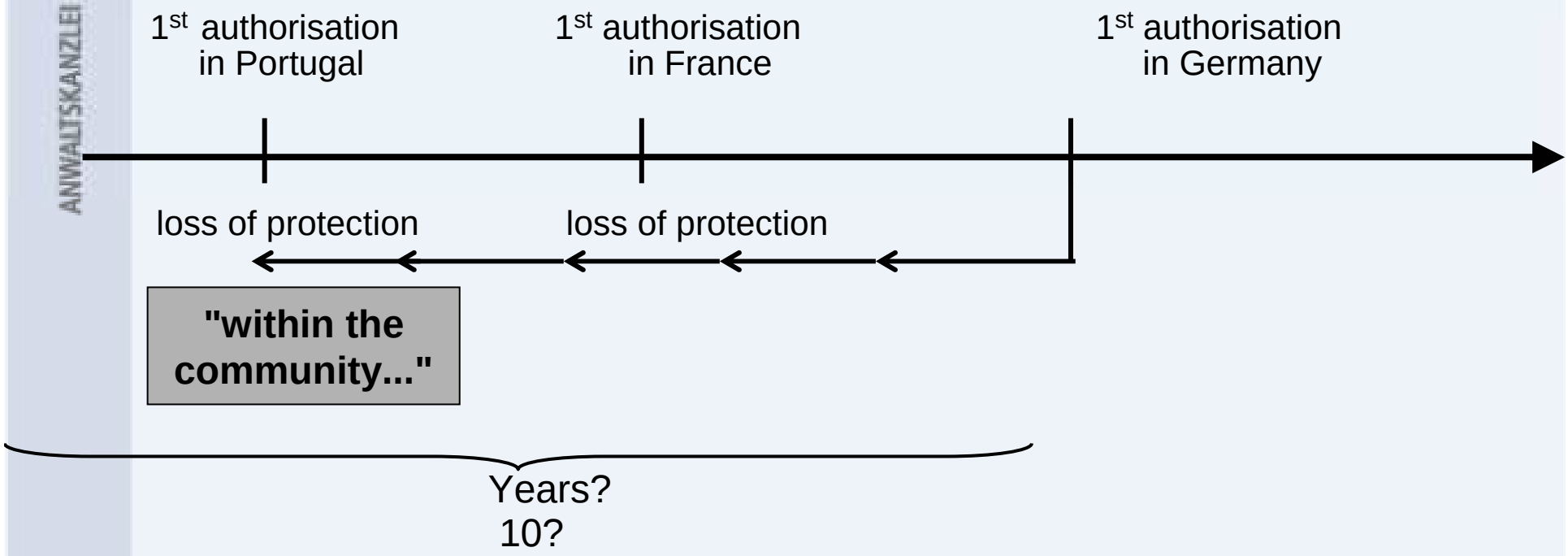
# Supplementary Protection Certificate - SPC -
## EC Regulation ⟶ National Patent Law



# Start of Protection Term for SPC and Data Protection



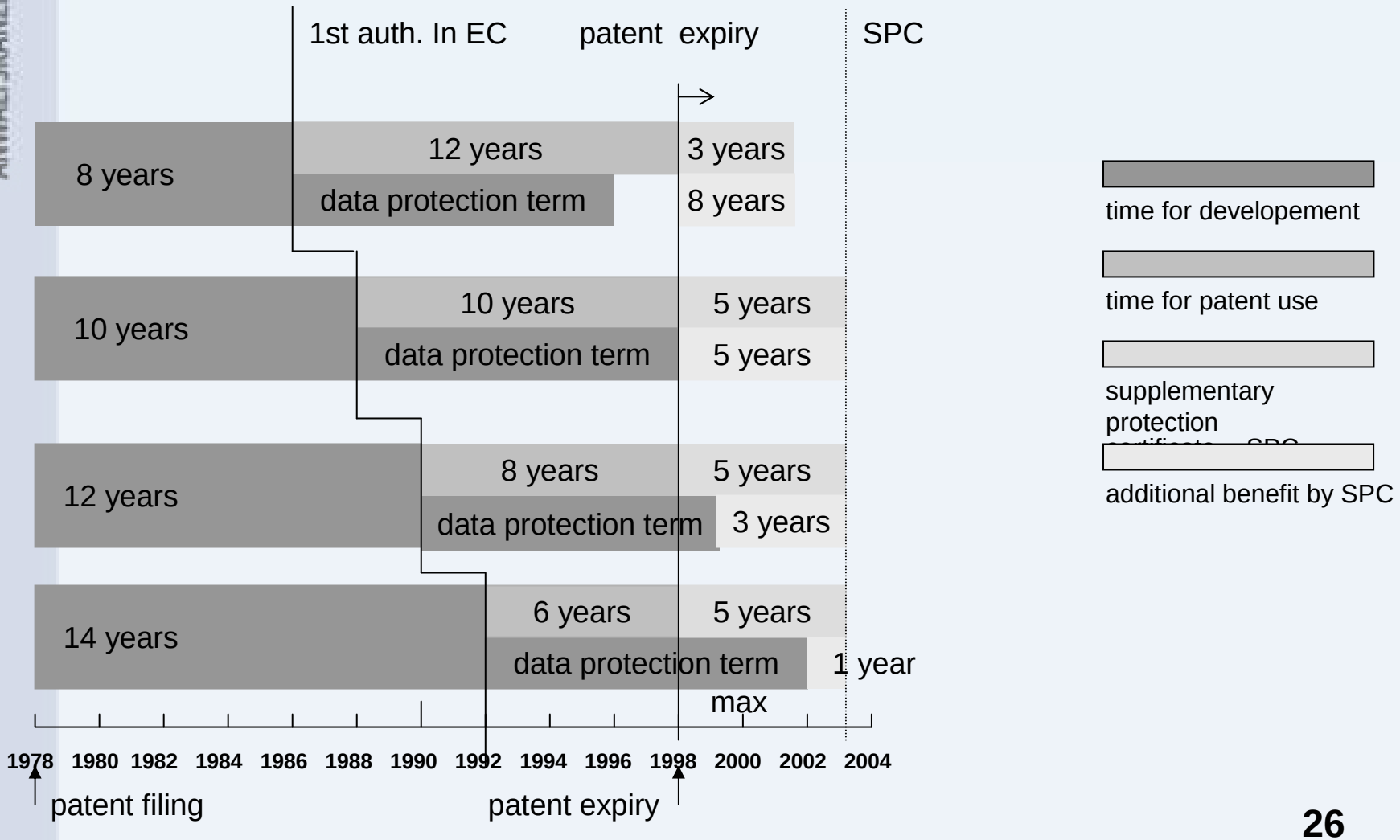

also in Member States other than those in which the application is made

EC-wide uniform protection term

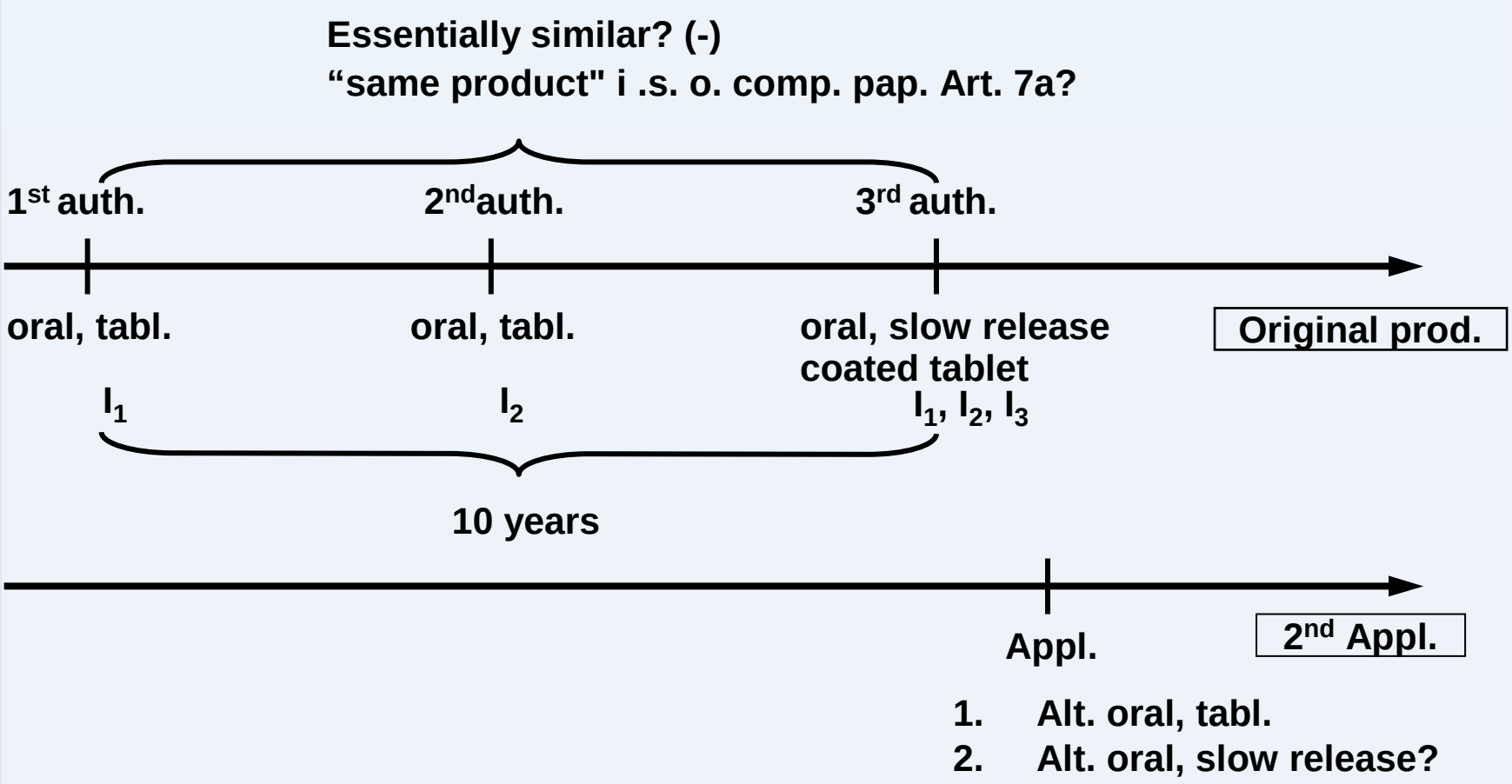
Period of exclusivity will be reduced by the varying duration of NDA procedures

EC-wide coordination of the NDA procedures is necessary

# Influence of data protection term according to Art. 10 Para 1(a) iii Dir 2001/83 EEC



# Line extensions of the original MP



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# New regulations for Line Extensions

**Art. 6 para. 1 Dir. 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).*"**

→ **See also Annex II Variation Regulation**

**§ 25 Abs. 9, S. 2 AMG**

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# New provisions for line extensions

**Art. 6 (1)**

- → **All variations are <u>one</u> (1) marketing authorisation within the meaning of Art. 10**
- → **Protective period only once with initial marketing authorisation**
- → **No protection for line extensions**

  **Exception.: PUMA**
- → **Special provision for new indications with known substances**
- → **AMG (German Drug Act) Section 25 (9)**

# Incentives for paediatric research I
# Concept of the EU Commission

## Regulation on MP for paediatric use – PU -

**MP protected by patent or SPC**

↓

**6 months extension**

**if studies conducted in compliance with PIP**

**Art. 36**

**Orphan MP market exclusivity**

↓

**2 years extension**

**if studies conducted in compliance with PIP**

**Art. 37**

# Incentives for paediatric research II
# Concept of the EU Commission

**Paediatric Use Marketing Authorisation**

➡ **PUMA**

- **MP not protected by patent or SPC**
- **MA exclusively for paediatric use, incl. strength, pharmac. form, rate of admin.**
- **If studies conducted in compliance with PIP**

**Art. 30**

# Incentives for Paediatric Research III

**Regulation for MP on PU**

→ **Data protection** **~ Art. 10 Dir. 2001/83/EC**

**~ Art. 14 (11) Reg. 726/2004/EC**

→ **8 + 2 + 1 (non interim regulation!)**

→ **Protection for a line extension**

**It may retain the name of**

**the original (Art. 30 (4)**

**Art. 38**

# Proof of “PIP compliance”

**Prerequisite for all incentives!**

**Proof: Art. 28 (III)**

**→ all measures of PIP satisfied**

**→ study results in SmPC**

**→ examination in marketing authorisation procedure**

**→ explicit confirmation in the marketing authorisation notice**

**→ from when possible? Transitional provisions?!**

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# Proof of “PIP compliance”

**Order:**

1. **Paed. investigation plan**

   → **application starting from July/August 2007 at the earliest**

2. **Approval procedure**

   → **Duration? 3 – 6 months**

3. **Start and end of the studies**

4. **Approval in the marketing authorisation procedure**

5. **Application for Patent extension via SPC – 6 month before expiry**

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# Proof of “PIP compliance”

**Significance for Art. 7 + 8 i.e. marketing authorisation bans**

→ **Art. 7 (i.e. marketing authorisation ban)**
**applies 18 months after coming into force**

→**Art. 8 (i.e. marketing authorisation ban for patent-protected line extensions)**
**applies 24 months after coming into force**

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# Proof of “PIP compliance”

**Consequences arising from Art. 57**

→ **Deferrals for the end of research in the investigation plan are compelling if “PIP compliance” is to be achieved for the filing of application starting from mid-2008.**

**The latter is compelling pursuant to Art. 7 and 8 and prerequisite for incentives pursuant to Art. 28 (3) in connection with Art. 36.**

# Regulation on medicinal products for paediatric use

**Transitional provisions - incentives for existing studies**

**Art 45: - existing studies must be submitted**

**- consideration in investigation plan and in the marketing authorisation (+)**

**but Art. 45 (3):**

**rewards and incentives only**

- **essential**
- **studies approved in an investigation plan**
- **completion after the Regulation on medicinal products for paediatric use has come into force**

# Regulation on medicinal products for paediatric use

**Transitional provisions - incentives for existing studies**

**Patents Agency will request proof of significance, Art. 36 (2) and Art. 37 make reference to Art. 28 (3)**

⇨ **The significance is determined in a binding manner in the marketing authorisation and incorporated in the notice of marketing authorisation. This is a prerequisite for granting rewards.**

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**Thank you for your attention!**