WEBINAR

HOW TO INITIATE EU PAEDIATRIC PLANS REGULATORY STRATEGY & WRITING

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WEDNESDAY, OCTOBER 21

NEW YORK 11 AM EDT

PARIS 5 PM CEST

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> STARTING NOW

Welcome !
Presentation

- Yasmine Garnier
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Welcome !
The Speakers

- **Séverine Waterdrinker**
  - *Associate Director, Regulatory Affairs and Scientific Writing*
  - *Broad experience in global development, registration and lifecycle management*

- **Magali Le Goff**
  - *Director, Regulatory Sciences and Scientific Writing*
  - *Leads the Global Scientific Writing team contributing to global development and registration of pharmaceutical products*

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Welcome !
Webinar Duration

- **45 Minutes** initially speaking about the regulatory strategy elements, followed by the process around writing the paediatric scientific document

- **15 Minutes** Q and A session : our experts will answer your questions, **please use the chatbox on the right handside at any time during the presentation**

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EU Paediatric Plans

1. Regulatory Strategy

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Why do we need an EU Paediatric Plan?

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The EU paediatric regulation (1901/2006 and 1902/2006)
A system of **obligations** and **rewards**

For:

- New medicines, or
- Medicines already authorised:
  - Covered by intellectual property rights (patent) if is added:
    - ✓ New indication
    - ✓ New pharmaceutical form
    - ✓ New route of administration
  - Not covered by intellectual property rights and exclusively developed for use in children (PUMA)

Need an agreed PIP, Waiver, Deferral (PDCO opinion + EMA decision)

EMA decisions are made public

PIP Compliance Check vs. EMA PIP decision (studies/ measures and timelines)

The outcome is made public

MAA submission validated only if:

- Results of paediatric studies per agreed PIP (CSR), and/or,
- EMA decision for waiver and/or deferral

Product to be placed on the market with the paediatric indication within 2 years.

A **full** compliance check will lead to a reward (**all** studies completed with results in the label)

New medicine or on-patent authorised medicine	+ 6 months extension to the SPC (patent) *(SPC extension application should be done latest 2 years prior to SPC expiry date)*
Orphan medicine	+ 2 additional years of market exclusivity (in addition to the 10 years)
PUMA	10-year market protection (including 8-year of data exclusivity)

CSR=Clinical Study Report; EMA=European Medicines Agency; MA=Marketing Authorisation; PDCO = Paediatric Committee; PIP=Paediatric Investigation Plan; PUMA= Paediatric-use marketing authorisation; SPC=Supplementary Protection Certificate

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Is a PIP required?

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PUMA => PIP

Assess the patent status and the product type

Define the target MA indication + Check the class-waiver list

https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans/class-waivers

Define if the medicinal product submission is in the regulation's scope

Is it an off-patent product already authorised in EU?

Yes → **No PIP required**

No

Is the product a generic? Hybrid product? Biosimilar? Planned for well-established use approval? Herbal? Homeopathic?

Yes → **No PIP required**

No

Is the targeted indication part of the class waiver list?

Yes: full waiver **(Request EMA confirmation)** → **No PIP required**

No

Is it for:

- A new MA? (see Art. 7)
- A new indication, route of administration or formulation, with a Supplementary Protection Certificate (SPC) or patent qualifying for a SPC? (see Art. 8)

No → **No PIP required**

Yes

For Art. 7 of 1901/2006 amended:
PIP required for all indications developed

Yes

Art.8 of 1901/2006 as amended:
PIP required for all existing and new indications, routes of administration, formulations developed

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Plan the PIP procedure

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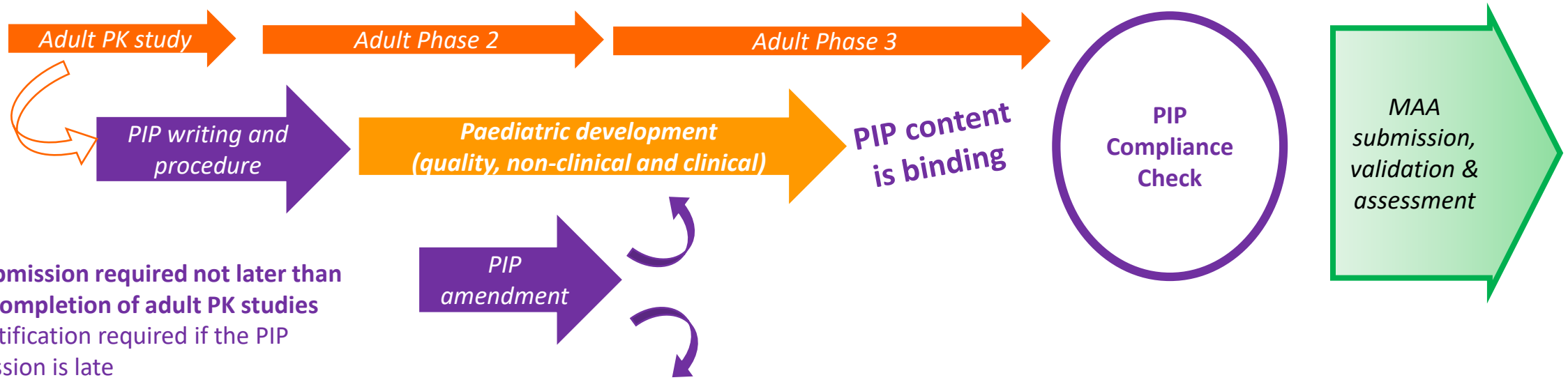
Planning for the PIP procedure

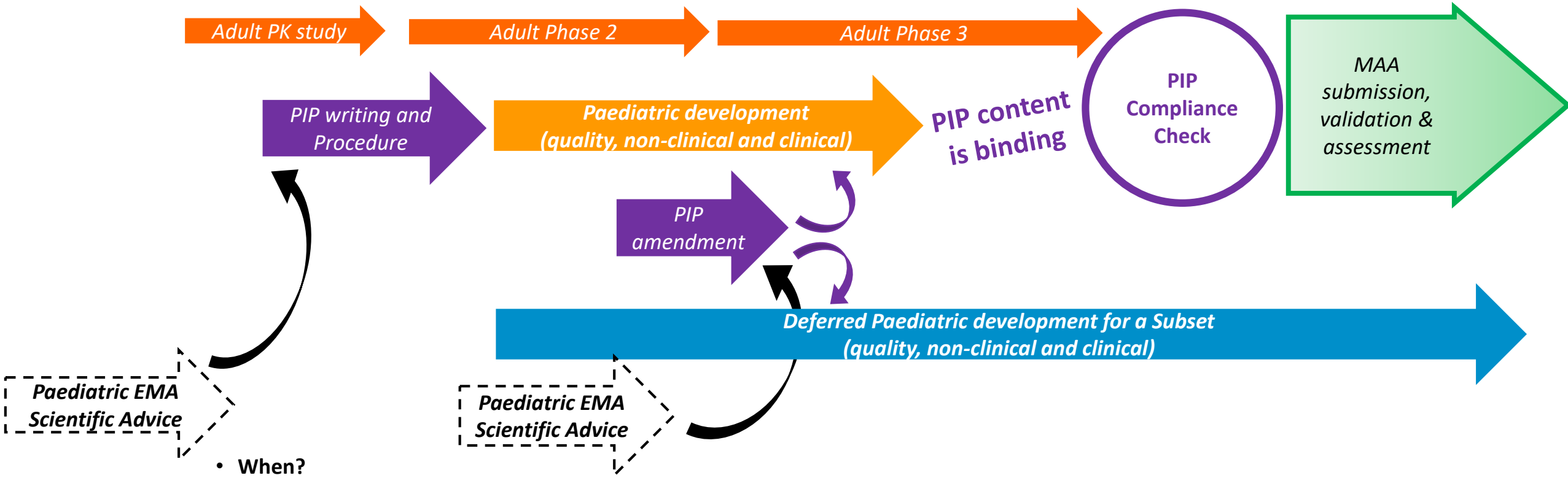


- **PIP submission required not later than upon completion of adult PK studies**
  => Justification required if the PIP submission is late
- **Plan ~ 3-6 months for the PIP writing + 1 year for the PIP procedure**
- **Pre-submission meeting** possible (regulatory and administrative)
- **PDCO re-examination possible** after Day 120 upon request

Deferral Annual Report

MAA= Marketing Authorisation Application; PK=Pharmacokinetic; PDCO=Paediatric Committee; PIP=Paediatric Investigation Plan

PIP & Paediatric EMA Scientific Advice



- **When?**
  - Prior to and/or after the PIP
  - If prior to the PIP: At least 7 months in advance of the PIP submission
- **Which questions?**
  - On paediatric development (quality, non-clinical, clinical)
  - Not on waiver/deferral (PDCO's scope i.e. PIP procedure)
- **Free of charge**

EMA=European Medicines Agency; MAA= Marketing authorisation application; PK=Pharmacokinetic; PDCO=Paediatric Committee; PIP=Paediatric investigation plan

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Tips

- **Make sure the PIP content is aligned to the implemented paediatric development**
  - Submit draft synopsis in early development
  - But amend the PIP with final synopsis during development prior to starting paediatric studies

- **Perform regular internal PIP compliance check during development**
  - Has the targeted indication been modified?
  - Are studies starting as planned?
  - Are study reports available as planned?

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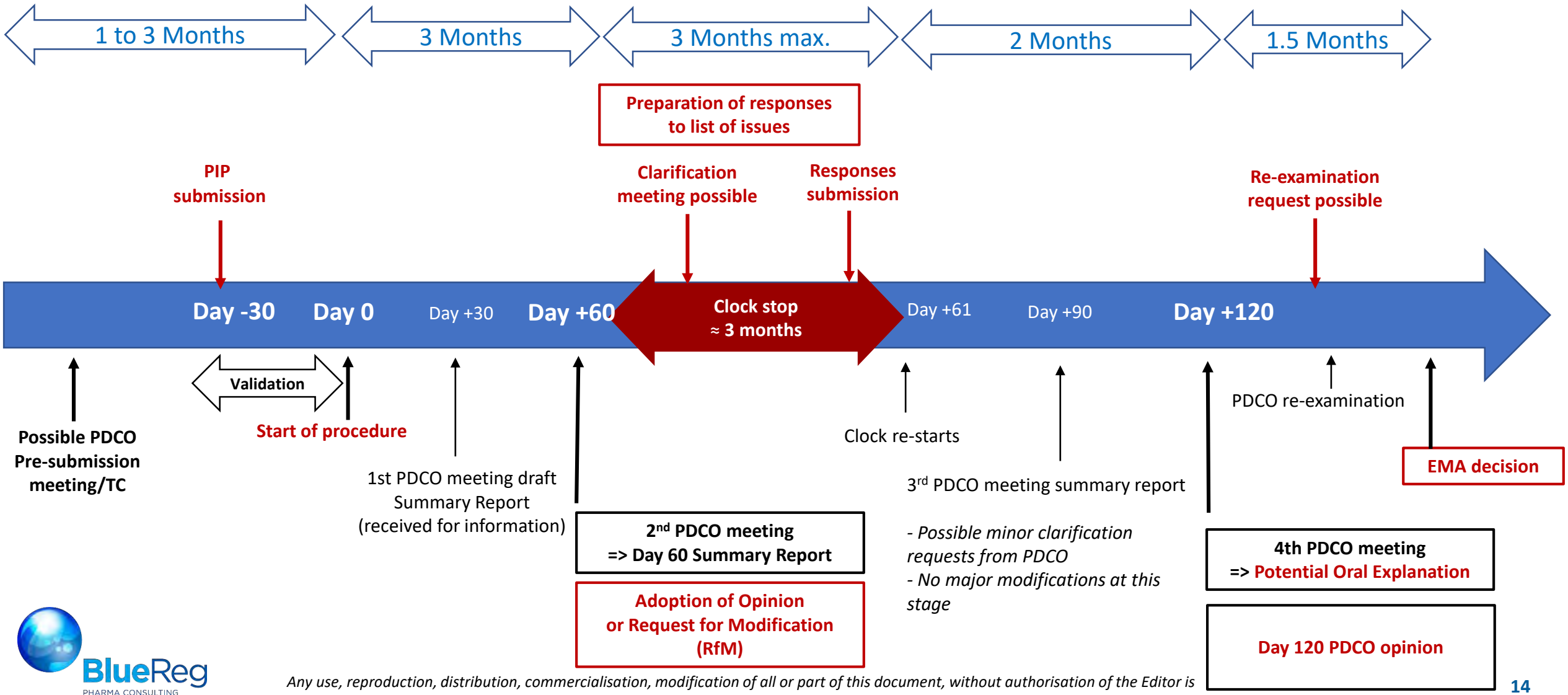
Overview of the PIP procedure

~ 9 months to 1 year

Free of charge



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Which PIP condition?

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Defining the PIP condition
Systematic Approach

- Defining the PIP condition is based on a **systematic approach** assessing:
  1. The proposed/authorised indication(s) and therapeutic area in adults/children
  2. Whether the product is intended for treatment, prevention or diagnosis.
  3. The characteristics of the product i.e. mechanism of action, which determines the expected activity of the medicinal product
  4. The unmet paediatric needs
  5. An independent hierarchical classification of diseases/conditions (MedDRA)

- Both PIP condition and PIP indication are required
  - PIP condition: Treat, prevent or diagnose ‘a condition’
  - PIP indication: Targeted indication in the paediatric population for the purpose of the PIP
  - Several paediatric indications can be within one PIP condition

https://www.ema.europa.eu/en/documents/other/policy-determination-conditions-paediatric-investigation-plan-pip/waiver-scope-pip/waiver_en.pdf

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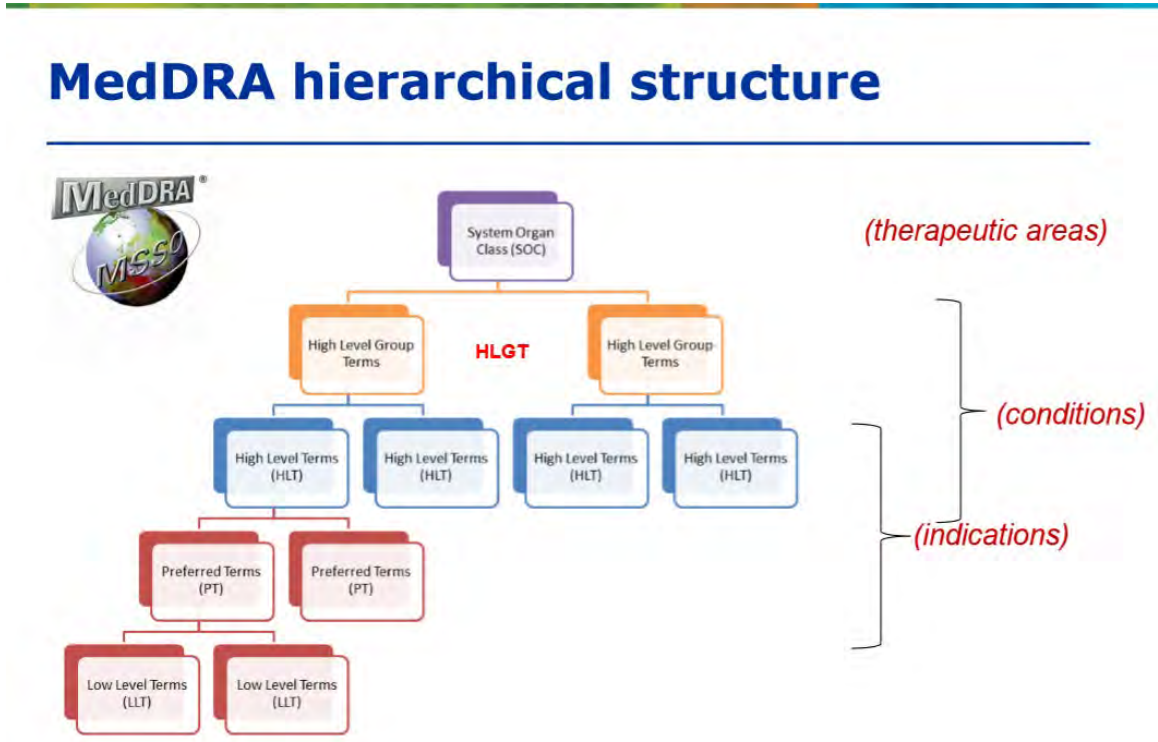
Defining the PIP condition
MedDRA

1. Analyse the proposed indication/therapeutic area and mechanism of action to determine the **High Level Term (HLT).**
    1. Several HLTs, a HLGT or a PT could also be determined.
    2. If several HLTs are defined in step 1, **one reference HLT** will be selected.
    3. If a HLGT is defined in step 1, all HLTs falling under the HLGT will be assessed and **one HLT will be selected** on scientific grounds.
    4. If a PT is defined in step 1, the **corresponding HLT** will be determined as the condition.

2. All PTs falling under the HLT would be considered for the potential paediatric use.

3. PDCO would not go above the condition chosen

4. PIP opinion / waiver will cover all PTs under the HLT



Adapted from presentation on key concepts of the paediatric regulation, Paolo Tomasi.
https://www.ema.europa.eu/en/documents/presentation/presentation-key-concepts-paediatric-regulation-latest-developments-paolo-tomasi_en.pdf
Consulted on 05 March 2020.

Defining the PIP condition

Example of waiver refused

Target PIP indication	PIP Condition	Reasons for waiver refusal	Paediatric development required
None since waiver request. « In adults », **reduction of residual risk of cardiovascular events in adult patients with type-2 diabetes mellitus as add on to statin therapy**.	**Reduction of residual cardiovascular events in patients with diabetes** Should be "elevated lipid levels"	- The product is not likely to be ineffective or unsafe - The disease/condition does occur in the paediatric population - Measures are justified by the expected therapeutic benefit and clinical trials are feasible - The product may represent a significant therapeutic benefit as the needs are not met - Clinical studies may fulfil a therapeutic need of the paediatric population.	• The scope of the PIP should not be limited to the condition proposed by the applicant, because **the actual aim of this product is the treatment of elevated lipid levels in the blood. The reduction of CV complications is a consequence of the treatment.** • **The condition should be « elevated lipid levels »** which does affect children, and the product could potentially address an unmet medical need. • In addition, it is important to find out whether a lipid lowering treatment **started early in childhood would reduce** the cardiovascular risk that may lead to events in adulthood only.

Defining the PIP condition
EMA inventory of needs for paediatric medicines

- Objectives of the inventory:
  - For sponsors to identify opportunities of pediatric development
  - For the PDCO to judge the need for medicines and studies when assessing PIP, waivers and deferrals

- The lists of medicines are available by therapeutic class and provide the product name with its related need(s)

https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/needs-paediatric-medicines

Anaesthesiology
Cardiovascular
Diabetes (types I and II)
Endocrinology
Gastroenterology
Immunology
Infectious diseases
Nephro-urology
Neurology
Obstructive lung disease
Oncology
Ophthalmology
Pain
Psychiatry
Respiratory
Rheumatology

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EU Paediatric need published by the EMA

Examples

Ophthalmology:

Notes

For the designation of the products International Non-proprietary Names (INN) are used whenever possible. Products are listed in alphabetical order within the product classes, not in order of priority.

If not stated otherwise, the needs concern all paediatric age-groups.

The shaded products represent those where a positive decision has been adopted on a Paediatric Investigation Plan (PIP). For further information please consult the EMA website.

Product	*Needs*
Anti-infectives	
Quinolone eye drops	Data on safety and efficacy <1 year of age
Corticosteroids	
Dexamethasone	Data on safety and efficacy of intravitreal formulations
Mydriatics & Cycloplegics	
Atropine sulfate	Data on safety and efficacy
Cyclopentolate HCL	Preparation with better tolerability/acceptability ("non-stinging") Data on safety and efficacy <3 months of age
Antiglaucoma	
Betaxolol	Data on safety and efficacy
Bimatoprost	PIP agreed for "Treatment of glaucoma"
Latanoprost	PIP agreed for "Treatment of glaucoma"
Timolol	Age-appropriate, preservative-free preparation
Travoprost	PIP agreed for "Treatment of glaucoma"
Diagnostics and perioperative preparations	
Acetylcholine chloride	Data on safety and efficacy
Apraclonidine	Data on safety and efficacy under 12 years of age
Diclofenac sodium	Data on safety and efficacy
Antineovascularisation agents	
Anti-VEGF mAb	Safety and efficacy in the treatment of retinopathy of prematurity (ROP)
Immunosuppressants	
Ciclosporin	PIP agreed for "Treatment of vernal keratoconjunctivitis"

Asthma and obstructive lung disease:

BETA 2-ADRENERGIC DRUGS	
SALBUTAMOL	
Authorised indication	Asthma, reversible pulmonary obstruction
Authorised age group	All age groups (oral solution not licensed in < 2years)
Authorised dose	0.25 to 0.5 mg per age via inhalation (aerosol/powder) Nebulised: 0.05-0.15 mg/kg x 4, oral: 1-4 mg (dep on age) x 3-4 Maximum 8 drops (4 mg)
Authorised formulation	Tablets, oral solution, aerosol for inhalation, powder for inhalation, solution for nebulisation, i.v. solution
Needs[1]	Data on pharmacokinetics (PK), efficacy and safety in bronchopulmonary dysplasia in the neonate
FENOTEROL	
Authorised indication	Acute asthma, reversible pulmonary obstruction, prevention of exercise induced obstruction
Authorised age group	> 4 years
Authorised dose	100 – 200 µg up to four times daily
Authorised formulation	Aerosol for inhalation, solution for nebulisation
Needs	Data on pharmacokinetics (PK), efficacy and safety in children < 4 years
TERBUTALIN	
Authorised indication	Acute asthma, acute pulmonary obstruction (obstructive bronchitis)
Authorised age group	All age groups
Authorised dose	Per os: 0.075 mg/kg, powder/aerosol: 0.25-0.5 mg, nebulised: 2.5-5 mg, i.v.: 25 µg/kg per 24h
Authorised formulation	Oral solution, aerosol for inhalation, solution for nebulisation, i.v. solution
Needs	Data on pharmacokinetics (PK), efficacy and safety in children < 6 months Data on long term safety

The list will specify which kind of data would be needed but neither the design, nor the number of studies (e.g. PK, efficacy). The lists will indicate the need for 'age-appropriate' formulations, without specifying which one, to keep options open and room for innovation.

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Should the PIP include a paediatric development, a waiver and/or a deferral?

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Assess competitors

- **For competitors** with close targeted indications, therapeutic areas and mechanism of action:

  ⇒ Assess PIP conditions, waivers, class waivers, deferrals, paediatric development

- **For specific conditions related to the targeted indication:**

  ⇒ Perform a search in the EMA website and obtain the EMA PIP decision for the products

- Check whether **class waivers** used for competitors **had been revoked**

https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans/class-waivers

Condition	Product	Waiver	Deferral	Paediatric development
Name	Name	Age subset: waiver granted or refused Add reasons for the waiver: * lack of significant benefit * no significant therapeutic benefit since clinical studies not feasible * disease/condition not occuring in this age group * product unlikely to be safe Year of the EMA decision	Yes/No	Age subset With quality, non-clinical and clinical studies (study types: PK/PD, bioavailability, food effect, safety, efficacy, dose-finding, M&S)

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For all age subsets, assess if **waivers** are relevant

- **Waiver** can be applied if there is evidence showing any of the following:
  - The product or class is likely to be **ineffective or unsafe** in part of, or all the paediatric population
  - The disease or condition **occurs only in adult populations**
  - The product **does not represent a significant therapeutic benefit** over existing treatments for paediatric patients
- You need a clear disease condition in the paediatric population and knowledge of existing treatments.
- As an example:

Age subset	Age range	Reason for the waiver request			
		Lack of efficacy	Lack of safety	Disease/condition not occuring in this subset	Lack of significant benefit over existing treatments in this subset
Preterm newborn infants or neonates	From day of birth to the expected day of delivery + 27 days			**YES**	

For all age subsets, assess if **deferrals** are relevant

- **Deferrals** should be **justified on scientific and technical grounds, or on grounds related to public health:**
  - If appropriate to conduct studies in adults prior to initiating studies in children
  - If studies in the paediatric population will take longer to conduct than in adults
  - If additional non-clinical data are considered necessary prior to starting studies in children
  - If major quality problems prevent development of the relevant formulation(s)

- As an example for studies that take longer to conduct than in adults

Age subset	Age range	Study identifier	Description	Area (quality, non-clinical, clinical)	Date of initiation (FPI) and deferral requested (Y/N)	Date of completion (LPLV) and deferral requested (Y/N)	Other dependency
Term newborn infants	0 to 27 days	xxx	xxx	New formulation + non-clinical juvenile program + 2 paediatric studies	N	**YES**	
Infants (or toddlers)	1 to 23 months	xxx	xxx		N	**YES**	
Children	2 to 11 years	xxx	xxx		N	**YES**	

FPI=First patient included in the trial; LPLV=Last patient last visit

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For the paediatric development of the remaining paediatric subset(s), assess relevant guidelines

Examples

Quality guidelines	• Reflection paper on **formulations of choice for the paediatric population** (EMEA/CHMP/PEG/194810/2005) • Guideline on **pharmaceutical development of medicines for paediatric use** (EMA/CHMP/QWP/805880/2012 Rev.2)
Non-clinical guidelines	• ICH guideline S11 on **nonclinical safety testing in support of development of paediatric pharmaceuticals** (EMA/CHMP/ICH/616110/2018), Step 5 • Guideline on the need for **non-clinical testing in juvenile animals** of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005)
Clinical guidelines/ reflection paper/ concept paper	• ICH E11 (R1): Clinical investigation of medicinal products in the **paediatric population** (EMA/CPMP/ICH/2711/1999) • **Role of PK** in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004, Corrigendum) • Guideline on the reporting of physiologically based pharmacokinetic (PBPK) **modelling and simulation** • Reflection paper on the use of **extrapolation in the development of medicines for paediatrics** (EMA/189724/2018) • Clinical trials in **small populations** (CHMP/EWP/83561/2005) • Conduct of the **PV** for medicines used by the paediatric population (EMA/CHMP/PhVWP/235910/2005-rev.1), Section 5
Disease-specific guideline	• See **CHMP disease-specific guidelines and some paediatric addendum** (e.g. acute heart failure, hypertension, lipid disorders, paediatric oncology, pulmonary arterial hypertension, bacterial infections) • See **disease-specific guideline on paediatric development** (e.g. juvenile idiopathic arthritis)
Neonate (term and preterm) guidelines	• Guideline on the investigation of medicinal products in the **term and preterm neonate** (EMA/536810/2008) • Impact of **brain / liver / lung & heart / renal immaturity** when investigating medicinal products intended for neonatal use

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Summary of paediatric development, waiver, deferral

Example

Age subset [1]	Age range [1]	Partial Waiver [2]	Paediatric Study Prior to MAA Submission	Partial Deferral [3]
Preterm newborn infants or neonates	From day of birth to the expected day of delivery + 27 days	Yes (disease not occuring)	NA	NA
Term newborn infants	0 to 27 days	No	No	Yes (studies taking longer in children than in adults) Proposed development plan for deferred studies (initiated before but completed after MA submission)
Infants (or toddlers)	1 to 23 months	No	No	
Children	2 to 11 years	No	No	
Adolescents	12 years to 18 years	No	Yes Proposed development in adolescents	No

[1] As defined by ICH-E11 guideline and addendum on Clinical Investigation of Medicinal Products in the Paediatric Population
[2] Registration can occur without paediatric development for some or all subsets of the paediatric population
[3] Registration can occur without initiation / completion of 1 or more paediatric studies

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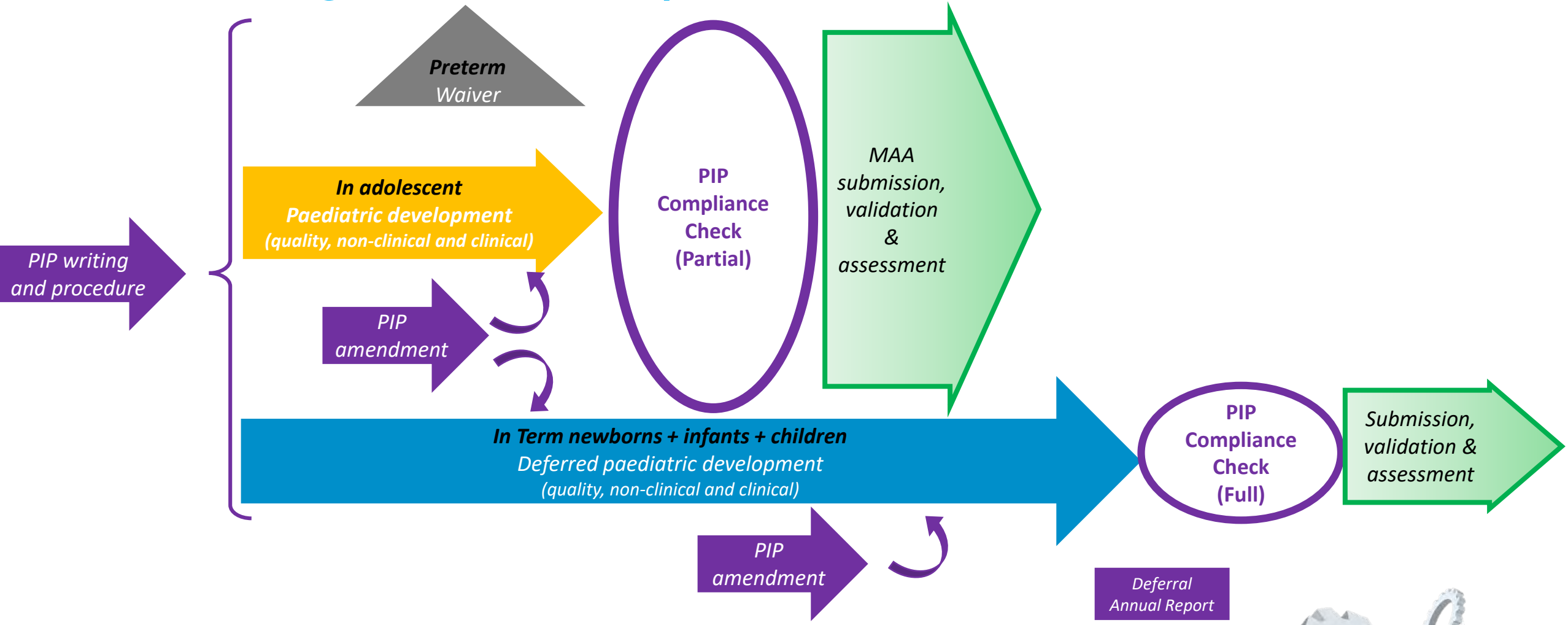
Planning for the PIP procedure - Example



MAA= Marketing authorisation application; PK=Pharmacokinetic; PDCO=Paediatric Committee; PIP=Paediatric investigation plan

Content of the PIP Application

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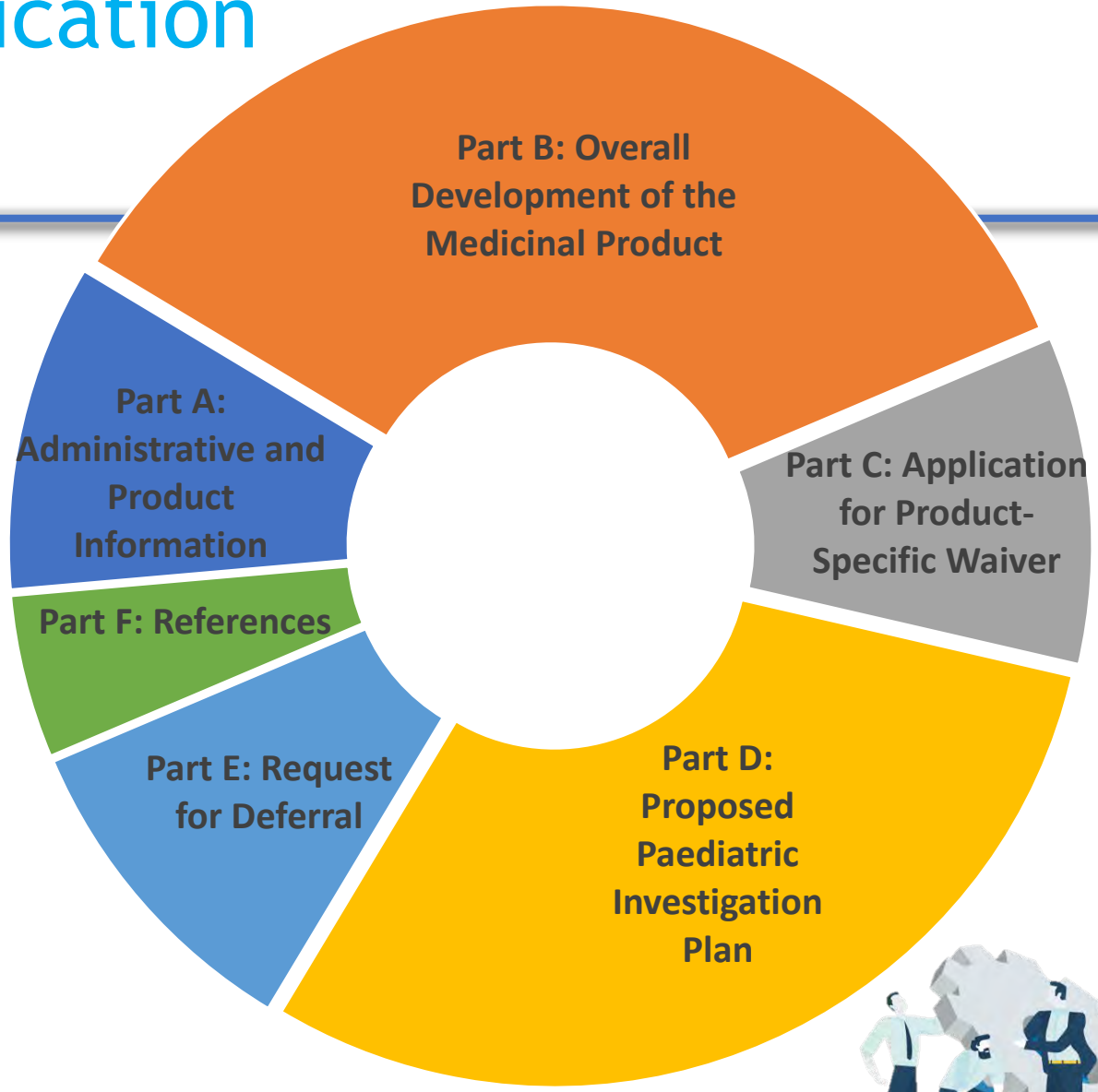
Content of the PIP Application

- **Part A: Administrative and Product Information**
  - Electronic application form
  - Key Elements Form

    Summarises the planned paediatric development
- **Parts B to F: Scientific Document**
  - Development plan
  - Waiver application
  - Deferral request



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Part A: Key Elements Form

Is a summary of the planned paediatric development

Quality Measure	Non-clinical Study	Clinical Study	Modelling and Simulation Study	Extrapolation Study
Pharmaceutical form for paediatric use	Study type	Study type + Design + Objectives	Model description	Study description
Description and objectives for development	Objectives	Study population + Number of participants	Model type	Objectives
Completion date	Test system/species, age	Study duration	Date used to build the model	Methodology
	Route of administration/doses	Treatment details	Model methodology and software	Study population and subset definition
	Dosing duration	Endpoints and timepoints of assessment	Covariates	Number of study participants by paediatric subset
	Initiation and completion, with additional requirements	Statistical plan	Model qualification	Initiation and completion, with additional requirements
		Data Safety Monitoring Board	Initiation and completion, with additional requirements	
		Initiation and completion, with dependencies		

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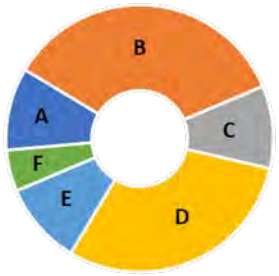
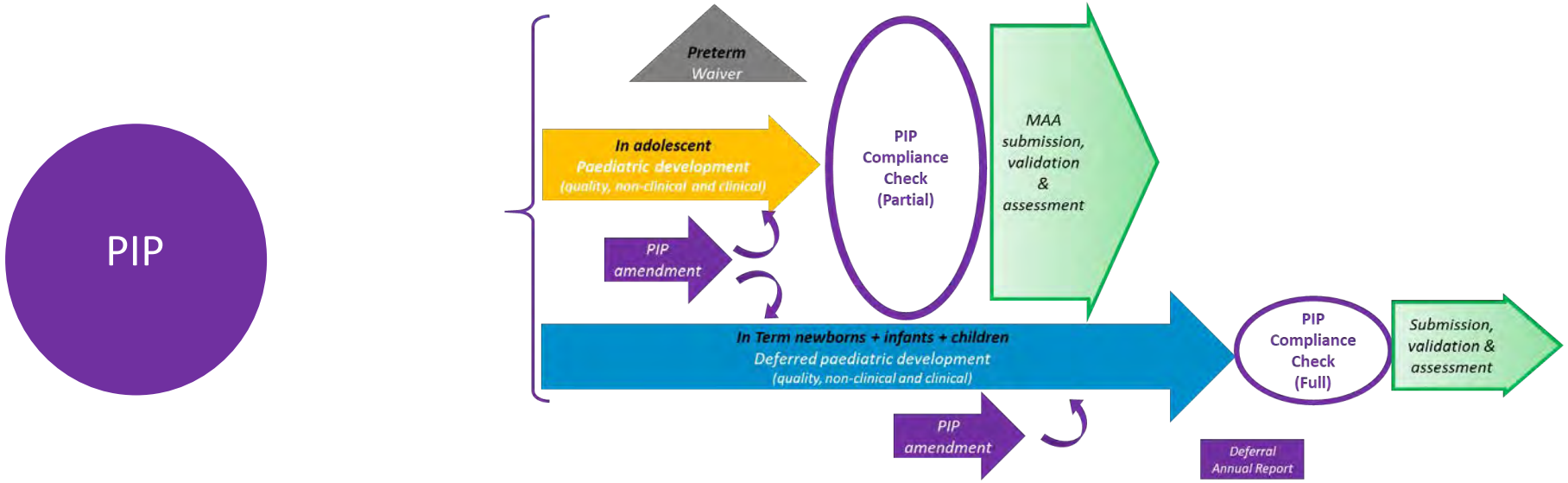


Overview of possibilities

Content of the PIP application	Part A Administrative + Product Information	Part B Overall development of medicinal product	Part C Waivers	Part D Proposed paediatric development	Part E Deferrals	Part F References
Paediatric development all subsets	YES	YES	-	YES	YES/NO	YES
Product-specific waiver all subsets	YES	YES	YES	-	-	YES
Partial waiver	YES	YES	YES	YES	YES/NO	YES
Deferral all subsets	YES	YES	-	YES	YES	YES
Paediatric development+ partial waiver+ deferral	YES	YES	YES	YES	YES	YES

Content of the PIP Application: Example



Application	Part A Administrative + Product Information	Part B Overall development of medicinal product	Part C Waivers	Part D Proposed paediatric development	Part E Deferrals	Part F References
Paediatric development+ partial waiver+ deferral	YES	YES	YES: In PRETERM newborn infants or infants	YES: In adolescents + TERM newborns or infants, infants/toddlers, and children	YES: In TERM newborns or infants, infants/toddlers, and children	YES

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EU Paediatric Plans

2. Writing the Paediatric Scientific Document

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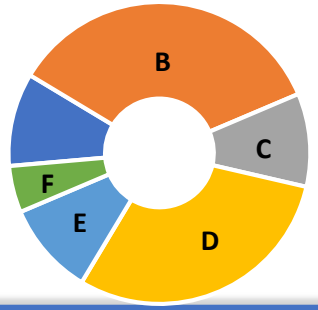

Overall approach for Parts B to F

Use of the 'Template for scientific document' (*template in a word format on EMA website*)

- Concise, stand-alone document (recommended length for Parts B-E: 50 pages)
- If multiple conditions, Parts B-E to be repeated in this order for each condition

Practical aspects

- Involved team: Regulatory, CMC, non-clinical, clinical, medical experts
  Statistician, writer and publisher
- Hybrid between an Investigator's Brochure, development plan, protocol and literature review
- Plan ~3-6 months
- Useful document: EMA/PDCO Summary Report Template (available on EMA website)

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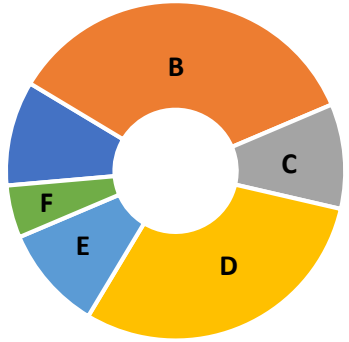
Paediatric Scientific Document: Application Summary



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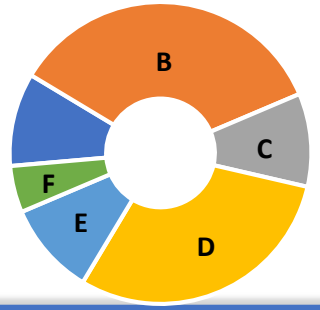

Paediatric Scientific Document Application Summary

- Objective: ‘to inform about the main aspects of the proposal for a PIP and/or waiver’
- Similar to a synopsis
- Limit of 750 words

Active·substance(s),·class·and·mechanism·of·action:·<Text>·*Brief·description·of·mode·of·action,·including·expected·differences·between·children·and·adults.*¶

Product·name:·<Text>·*if·already·authorised·in·the·EEA*¶

MAH·/·applicant:·<Text>·*Name·of·applicant*¶

Authorised·indication(s):·<Text>·*in·children·and/or·adults*¶

Planned·indication(s)·in·adults:·<Text>·*as·mentioned·in·the·PIP·scientific·application*¶

Condition:·<Text>·*as·mentioned·in·the·PIP·scientific·application·should·be·relevant·to·the·mechanism·of·action.·Refer·to·the·policy.·State·whether·it·is·"treatment",·"prevention"·or·"diagnosis".*¶

Proposed·indication(s)·in·children:·<Text>·*as·mentioned·in·the·PIP·scientific·application*¶

Potential·benefit·for·children:·<Text>·*Outline·of·potential·significant·therapeutic·benefit·for·this·medicinal·product·in·relation·to·unmet·needs·in·children.·A·brief·justification·for·waiver·or·deferral·request·may·also·be·included.*¶

Clinical·development:·<Text>·*Summary·of·proposed·studies·(type,·age,·numbers),·including·short·justification·for·proposed·study·programme·(underlying·strategy).·Make·transparent·links·to·paediatric·networks·and·communities.·Explain·how·feasibility·of·proposed·studies·is·ensured.*¶

Pharmaceutical·form:·<Text>·*Identify·if·there·is·a·need·for·development·(based·on·proposed·age·groups·and·indication).·If·potentially·yes,·describe·plans·including·timing·of·availability·of·age-appropriate·formulation·for·paediatric·studies.*¶

Route·of·administration:·<Text>·*Use·EDQM·standard·terminology*¶

Non-clinical·plans:·<Text>·*Brief·overview·of·how·proposed·non-clinical·study·programme·and·/·or·existing·data·support·studies·and·use·in·children.·Summarise·proposed·non-clinical·studies·or·justify·absence·of·proposed·studies.*¶

Extrapolation:·<Text>·*If·there·is·a·possibility·to·extrapolate·efficacy·from·adults·to·children·or·from·older·to·younger·children,·this·should·be·elaborated.·Data·related·to·extrapolation·of·safety·information·from·adults·to·children·can·also·be·included.·Modelling·of·PK·and/or·PD·if·used·for·decision-making·should·be·mentioned.*¶

Waiver(s),·deferrals:·<Text>·*Justification·for·product-specific·waiver·or·partial·waiver·in·relation·to·proposed·paediatric·subsets.·Summarise·milestones·of·proposed·paediatric·studies,·if·relevant,·in·relation·to·adult·development.*¶

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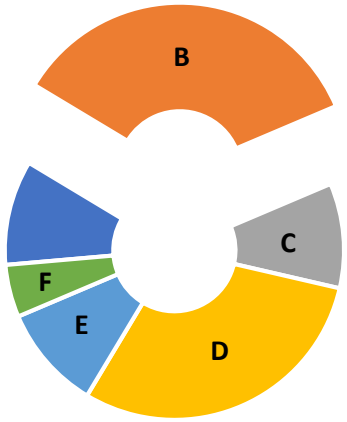
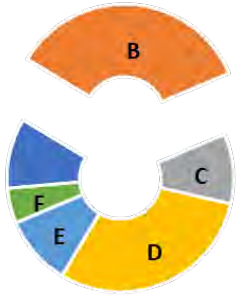
Paediatric Scientific Document
Part B - Overall Development





Part B: Overall Development of the Medicinal Product

B.1. Discussion on **Similarities and Differences** in the Condition Between Populations, and **Pharmacological Rationale**

B.2. Current Methods of **Diagnosis, Prevention or Treatment** in Paediatric Populations

B.3. Significant **Therapeutic Benefit** and/or Fulfilment of **Therapeutic Needs**

Key points

- Known or expected similarities and differences in the condition and drug effects between
  - **Paediatric subjects vs. adults**

  AND
  - **Paediatric subsets**
- **Epidemiology of disease** in paediatric population
- Current means of diagnosis, prevention or treatment
- Discussion of therapeutic benefit and need

Practical aspects

- **Literature** search generally required
- **High-level overview** of the product
- **Source documentation:** review articles, guidelines, medical/association recommendations

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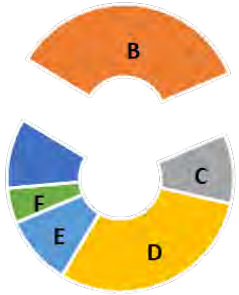

Part B: Overall Development of the Medicinal Product

B.1. Discussion on Similarities and Differences in the Condition Between Populations, and Pharmacological Rationale

B.1.1. Similarities and Differences in the Condition Between Populations

Key points

Known or expected similarities and differences **between adults vs. paediatric subjects AND between paediatric subsets** in:

- Seriousness of disease
- Aetiology and pathophysiology of disease
- Clinical manifestations and prognosis
- Epidemiology (of great importance in case of waivers)

Key points/issues

- **Prevalence/incidence** of the condition in paediatric population in **EU**
  - Identify recent, paediatric- and EU-specific prevalence/incidence data
  - Wide differences between epidemiological studies
- **Earliest age of disease onset**

Practical aspects

- Literature-based information
- Tabular overview of epidemiological data
- **Sources of information:**

  Review articles

  Epidemiological studies from International Organisations or Medical Associations

  National or Regional Registries

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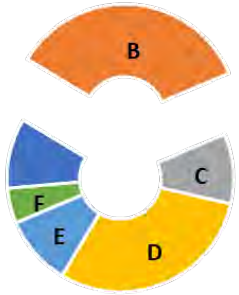

Part B: Overall Development of the Medicinal Product

B.1. Discussion on Similarities and Differences in the Condition Between Populations, and Pharmacological Rationale

B.1.2. Pharmacological Rationale

Key points

Known or expected similarities and differences **between adults vs. paediatric subjects AND between paediatric subsets** in:

- Pharmacological properties
- Known or suspected mechanism of action
- Absorption, distribution, metabolism and excretion
- Drug-drug interactions, food effects

Practical aspects

- Experience with **same class competitors**
- Focus on known effects associated with mechanism of action and drug class, unique paediatric safety concerns, potential adverse events of interest
- Setting the scene for the proposed paediatric measures

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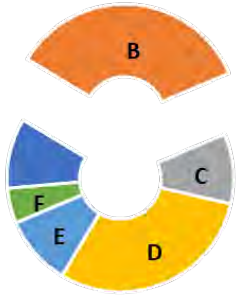

Part B: Overall Development of the Medicinal Product

B.2. Current Methods of Diagnosis, Prevention or Treatment in Paediatric Populations

Key points

- **Currently available treatments**: treatments authorised in paediatric population, standard of care (including unauthorised treatments)
- Therapeutic options **other than medicinal products**

Practical aspects

- **Possible subsections**:
  - Diagnosis of disease
  - Disease prevention
  - Treatment of disease
- **Important points on existing treatments:**
  - Authorised vs. non-authorised in paediatric subjects
  - Treatment differences between age groups
- **Sources of information**: review articles, guidelines, medical/association recommendations, textbook or paediatric drug prescription patterns
- **Potential for active comparators** in proposed paediatric studies

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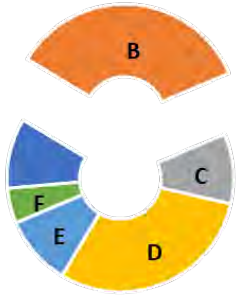

Part B: Overall Development of the Medicinal Product

B.3. Significant Therapeutic Benefit and/or Fulfilment of Therapeutic Need

Key questions

- Is there any **unmet need** and does your product **satisfy this need**?
- Does your product have a **significant therapeutic benefit over existing treatments**?

Practical aspects

- Include **a comparison** of medicinal product in question with current methods for diagnosis, treatment and prevention to assess potential significant therapeutic benefit
- **Therapeutic need may be listed in 'EMA Inventory Paediatric Needs' and 'WHO Model List of Essential Medicines for Children'**

'Potential significant therapeutic benefit' could be based on one or more of the following:

- Offers **a reasonable expectation for safety and efficacy to treat condition** where no authorised treatment is available
- Is **associated with expected improvement in efficacy and/or safety** compared to standard of care
- Provides an **improved dosing scheme or method of administration,** leading to improved efficacy, safety or compliance in children
- Represents a **new clinically relevant age-appropriate formulation**
- Has **a different mechanism of action** with a potential advantage in terms of improved efficacy or safety
- Existing treatments are **not satisfactory** and alternative methods **with better benefit-risk balance** are needed
- Associated with an **expected improvement in quality of life**

If a significant therapeutic benefit or unmet needs are identified, conclusion on the need to have a PIP should be drawn.

If relevant, discussion of:

- **Feasibility of performing clinical studies** in the proposed condition
  Lack of feasibility might be a ground for waivers.
- Whether expected therapeutic benefit **justifies paediatric studies** in the proposed condition
- Whether **new data are needed** when there are existing data
  PDCO will not endorse data replication.

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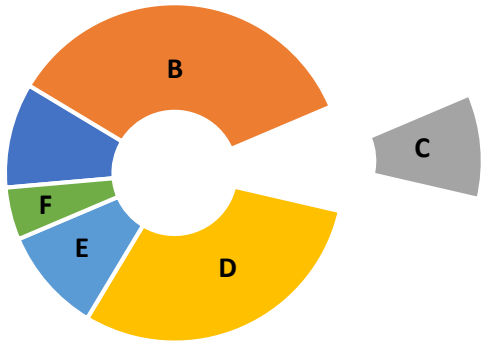
Paediatric Scientific Document
Part C - Product-Specific Waiver(s)



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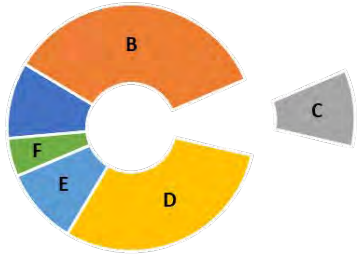

Part C: Product-Specific Waiver

C.1. Overview of the **Waiver Request**
C.2. **Justification** for a Product-Specific Waiver
C.2.1. Applications Based on a **Likely Lack of Safety or Efficacy** in Part or All of the Paediatric Population
C.2.2. Applications Based on the **Disease or Condition Not Occurring** in the Specified Paediatric Subset
C.2.3. Applications Based on **Lack of Significant Therapeutic Benefit**

Key points

- Waiver request for entire paediatric population or only selected paediatric subsets
- All paediatric subsets should be covered by a waiver request or a PIP proposal

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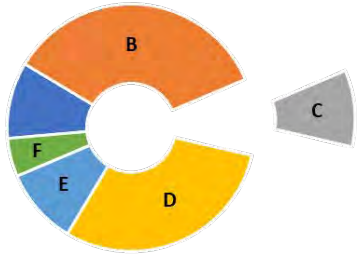

Part C: Product-Specific Waiver

C.2. Justification for a Product-Specific Waiver

C.2.1. Applications Based on a Likely Lack of Safety or Efficacy in Part or All of the Paediatric Population

Key justification

- May be based on **pharmaceutical rationale** (Section B.1.) or **preliminary data** suggesting lack of efficacy or safety (from non-clinical models and studies and/or literature)

- Grounds for '**Lack of efficacy**' should take into account:
  Seriousness of condition (Section B.1.)
  Availability of other methods/treatments (Section B.2.)

- Grounds for '**Lack of safety**' may include:
  Known or suspected **issues with pharmacological properties** of drug or class
  Safety issues identified in non-clinical or clinical studies

Practical aspects

- **Absence of available data on safety or efficacy in the paediatric population is not accepted as the sole justification for a waiver**

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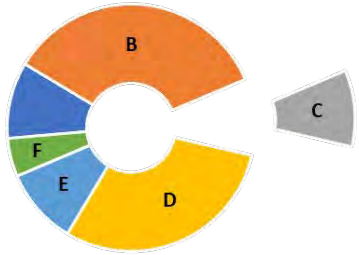

Part C: Product-Specific Waiver

C.2. Justification for a Product-Specific Waiver

C.2.2. Applications Based on the Disease or Condition Not Occurring in the Specified Paediatric Subset

Key justification

- Disease or condition for which the specific product is intended **occurs only in adults**
- Based on **detailed description of incidence/prevalence** in different populations

Practical aspects

- References to Section B.1.
- For waivers covering **the entire paediatric population** ⇒ Focus on **earliest age of onset for the condition**
- For waivers covering **only specific paediatric subsets** ⇒ Focus on **incidence/prevalence data**

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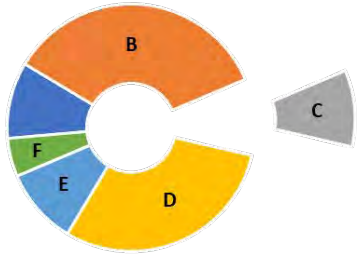

Part C: Product-Specific Waiver

C.2. Justification for a Product-Specific Waiver

C.2.3. Applications Based on Lack of Significant Therapeutic Benefit

Key justification

- Product **does not represent a significant therapeutic benefit** over existing treatments for paediatrics
- Based on **detailed discussion of existing treatment methods**

Practical aspects

- References to Section B.2. (Current treatments) and Section B.3. (Therapeutic benefit/need)

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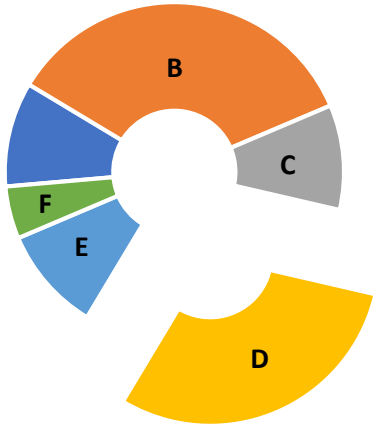
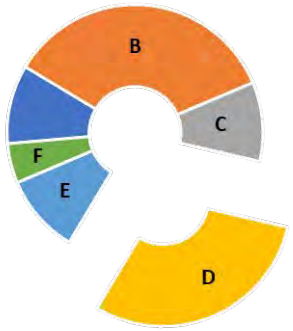
Paediatric Scientific Document
Part D – Paediatric Investigation Plan





Part D: Paediatric Investigation Plan

D.1. **Existing Data** and **Overall Strategy** Proposed for the Paediatric Development
D.2. Paediatric **Formulation** Development
D.3. **Non-Clinical** Studies
D.4. Paediatric **Clinical** Studies
D.5. **Other** Studies

Key points

Minimum for non-clinical and clinical studies

- Study type, study design with objectives
- Species (non-clinical) and target population (clinical)
- Age
- Number of animals (non-clinical) and patients (clinical)
- Route of administration, dosages and duration of treatment
- Assessments and endpoints

Scientific Advice obtained? Implemented?

If product already assessed by CHMP, were there any issues impacting paediatric development?

Practical aspect

Study synopses/outlines provided in the PIP application for all pharmaceutical, non-clinical and clinical studies (even for deferrals)

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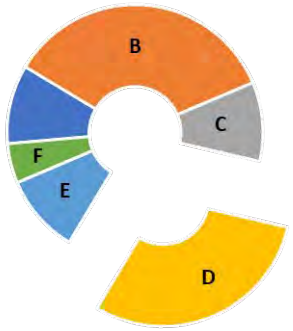

Part D: Paediatric Investigation Plan

D.1. Existing Data and Overall Strategy Proposed for the Paediatric Development	
D.1.1. Paediatric Investigation Plan Indication	• **Not necessarily identical to the adult indication** • Should specify whether **product is intended for diagnosis, prevention or treatment** of the condition in question
D.1.2. Selected Paediatric Subsets	List all paediatric subsets not covered by waiver(s)
D.1.3. Information on Quality, Non-Clinical and Clinical Data	• Summary of **development strategy in adults with relevance to paediatric development** • **Tabular outline** of planned studies in adults • Review of **any information on the product in paediatrics** (scientific/medical references, use outside the terms of a MA, medication errors, accidental exposures or known class effects)

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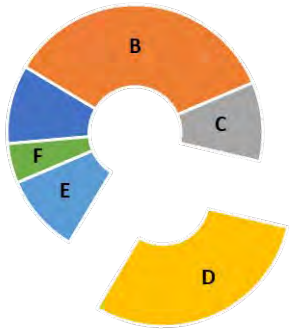

Part D: Paediatric Investigation Plan

D.2. Paediatric Formulation Development	
D.2.1. General Strategy	• Focus on **existing/proposed formulation** development • Address **critical issues for paediatric population** Form Strength Excipients Taste-masking and acceptability (including palatability) Route of administration
D.2.2. Summary of All Planned and/or Ongoing Measures in the Pharmaceutical Development	• **Tabular list** of planned and/or ongoing measures intended to address issues discussed in Section D.2.1. • Use of the Key Element Form

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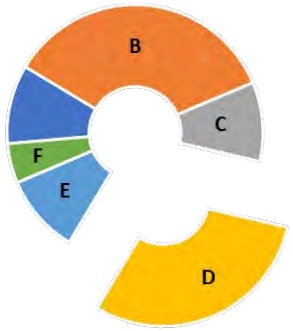

Part D: Paediatric Investigation Plan

D.3. Paediatric Non-Clinical Studies	
D.3.1. General Strategy	• Focus on **non-clinical strategy** to support paediatric use • **Juvenile studies to be considered** (species and age to be justified) if insufficient data from human safety or animal studies • Should be discussed: **Pharmacology** **Toxicology**
D.3.2. Summary of All Planned and/or Ongoing Non-Clinical Studies	• **Tabular list** of proposed non-clinical studies discussed in Section D.3.1. • Use of the Key Element Form

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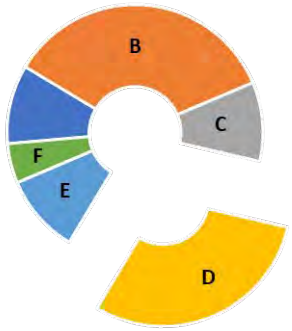

Part D: Paediatric Investigation Plan

D.4. Paediatric Clinical Studies	
D.4.1. General Strategy	• Focus on **clinical paediatric strategy** in relation to the development in adults • Studies should be **performed first in the least vulnerable groups** whenever possible
D.4.2. Paediatric PK/PD Studies	• PK/PD studies, population PK modelling and simulation
D.4.3. Clinical Efficacy and Safety Studies	• Discussion on whether **specific dose-finding studies** are needed • **Appropriate efficacy and safety endpoints** in each of the relevant paediatric subsets • **Appropriate and feasible study designs** (e.g. use of placebo or active control) • Use of **less invasive methods** (to protect paediatric population)
D.4.4. Summary of All Planned and/or Ongoing Clinical Studies	• **Tabular list** of proposed clinical studies discussed in Section D.4.2. and Section D.4.3 • Propose **binding timelines for initiation and completion of each study** • Use of the Key Element Form
D.4.5. Details of the Planned and/or Ongoing Paediatric Clinical Studies	• **Protocol-like information** • Reference to Part F where protocols or synopses may be added

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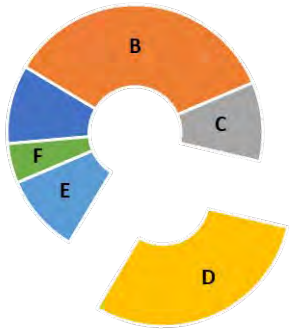
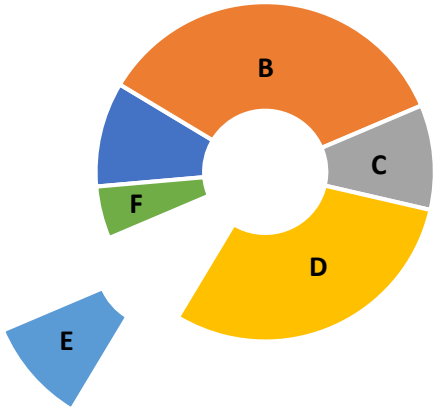
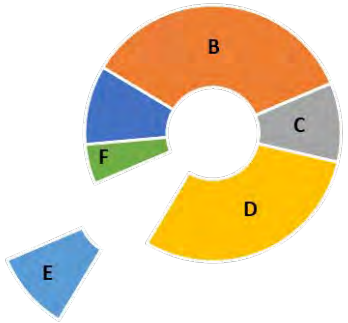


Part D: Paediatric Investigation Plan

D.5. Other Studies	
D.5.1. Modelling and Simulation Studies	Justify proposed objectives, data to be used, and methodology
D.5.2. Extrapolation Studies	Justify proposed objectives, data to be used, and study population

Paediatric Scientific Document
Part E - Deferral(s)





Part E: Deferral(s)

E.1. **Timelines of Measures** in the Paediatric Investigation Plan

Key points

- **When it is not planned that a study/measure will be initiated or completed before the submission of the corresponding MAA in adults**
- Deferrals may be granted based on **scientific, technical grounds, or on grounds related to public health**
  - Appropriate to conduct studies in adults before initiating studies in paediatrics
  - Studies in paediatric population will take longer to conduct than studies in adults
  - Need of additional non-clinical data
  - Resolution of paediatric formulation issues
- Use the **strategy and timelines** developed in Part D as basis for deferral
- Specify timelines of measures in **tabular format** (example provided in EMA template)

Practical aspect

Final study reports needed for compliance check

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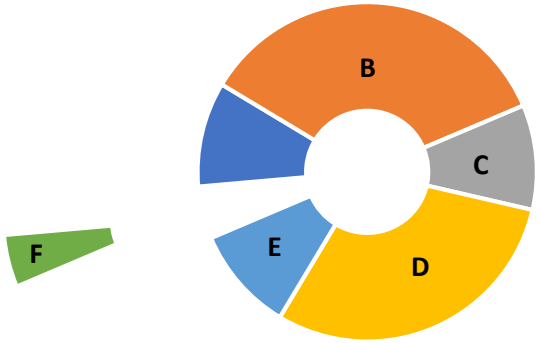
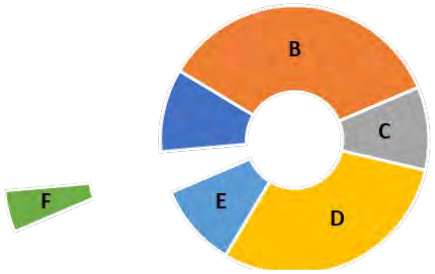
Paediatric Scientific Document
Part F - References





Part F: References

List of all literature references, articles, bibliography etc. related to scientific discussion

Practical aspects

Subsections

- References (published literature/guidelines/websites)
- Investigator's Brochure and synopses/protocols of the listed studies
- Latest approved SmPC and RMP for a product already authorised
- Scientific Advice relevant to paediatric development (given by CHMP or competent National Health Authorities)
- Any written request by FDA and/or any advice/opinion/decision relating to paediatric information given by Competent Authorities outside the EU
- Any commission decision on orphan designation

Additional subsections for long and complex tables (e.g. epidemiological data, current treatments, tabular summaries of studies)

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Methodology Summary

Regulatory Strategy

- ✓Is a **PIP required**? If so:
- ✓Plan the **reward strategy**
- ✓Plan the PIP **procedure**
- ✓Define the PIP **condition**
  - Indication, mechanism of action, paediatric needs, MedDRA
- ✓Define whether the PIP should include a **paediatric development, a waiver and/or a deferral**
  - Assess competitors, epidemiology, existing treatments, give advice on development plan
- ✓Prepare **Part A of** the PIP application
  - Electronic application form and Key Elements Form

Writing the Paediatric Scientific Document

- ✓Complete the **Application Summary**, outlining the overall approach in paediatrics
- ✓Complete **Part B** with similarities and differences between adults vs. paediatrics and between paediatric subsets, and identification of a therapeutic benefit/need
- ✓Complete **Part C** for full/partial waiver
- ✓Complete **Part D** for paediatric development
  - ✓Quality, non-clinical and clinical measures
- ✓Complete **Part E** for deferral requests (to be justified)
- ✓Compile **Part F** with References/Annexes

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Q and A Session !

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Q and A Session

Question 1: Are there any adapted PIP procedure for covid-19 related treatments and vaccines?

Yes, PIP procedures are facilitated for covid 19 related treatments and vaccines. There are no pre specified PIP submission deadlines and scientific documentation can be agreed on a case-by-case basis. Expedited reviews of PIP applications and compliance checks were implemented, e.g.:

- Review timelines are reduced (to 20 days minimum), but exact timelines depend on PIP complexity and responses to questions,
- EMA decision timeline is reduced (to 2 days),
- Compliance checks can be reduced (to 4 days).

Of note, the timing for scientific advice is reduced as well (to 20 days).

For more information, see:

https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans#accelerated-procedure-for-covid-19-treatments-and-vaccines-section

Post-webinar note:

FDA and EMA have issued a common commentary on submitting iPSP and PIP for prevention and treatment of covid 19, to speed up the development and approval.

https://www.ema.europa.eu/en/documents/other/fda/ema-common-commentary-submitting-initial-pediatric-study-plan-ipsp-paediatric-investigation-plan-pip_en.pdf

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Q and A Session

Question 2: What are the paediatric requirements in the UK after the Brexit?

On 1st September 2020, the MHRA released guidance presenting the general approach to UK PIP. This guidance stated:

- Simplification of the PIP application process with an expedited assessment where possible.
- Required scientific content and assessment remain in line with EMA guidance documents.
- Northern Ireland will continue to be part of EU PIP system.
- Applicants should include information relevant specifically to the UK, in particular with respect to any areas of unmet therapeutic need that the product intends to cover in the UK.
- Guidance addresses the common scenarios that may occur when UK paediatric procedure is submitted to the MHRA after 1st January 2021.
- Different scenarios depending on whether an EU PIP is already approved or not, or ongoing as of 1st January 2021 are discussed in guidance. Please refer to guidance or contact BlueReg at contact@blue-reg.com for more information.

Links to recent MHRA published guidelines:

https://www.gov.uk/guidance/procedures-for-uk-paediatric-investigation-plan-pips-from-1-january-2021#general-approach-to-uk-paediatric-investigation-plans

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/910265/Guideline_on_the_format_and_content_of_applications_for_agreement_or_modification_of_a_Paediatric_Investigation_Plan.pdf

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Q and A Session

Question 3: What are the differences between US vs. EU requirements for paediatric plans?

Because of time constraints, the answer mainly focused on the EU PIP vs. US PSP differences in terms of scientific document/content:

• Scientific document structure/headings differ between US PSP and EU PIP, but high level of similarities in the topics to cover and scientific information to be presented/discussed.

• Main difference is on the presentation of product characteristics, its mechanism of action and its development in adults. Less information is required regarding these points in the US PSP than in the EU PIP since the FDA paediatric requirements are discussed at EoP2 (i.e. later than in EU), meaning that in the US, at the time of the paediatric requirements, the Applicant would have already interacted with the Agency on these points.

Post-webinar note:

The FDA and EMA common commentary cited above (https://www.ema.europa.eu/en/documents/other/fda/ema-common-commentary-submitting-initial-pediatric-study-plan-ipsp-paediatric-investigation-plan-pip_en.pdf) presents a tabular comparison of the information that is often included in each section of the iPSP and the PIP, showing substantial overlaps in the 2 documents.

Also, in the US drug regulation, paediatric patients are defined as children younger than age 17 whereas in EU, the age limit is 16-18 years, depending on the region.

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Question 4: How do we request the compliance check?

If no Paediatric Investigation Plan was agreed for that PIP condition (i.e. product-specific waiver), no compliance check will be required since there will be no measures/timelines to check against.

If a Paediatric Investigation Plan was agreed, it is strongly recommended to apply for it at least 2 months prior to the planned submission of the MA. You will need to submit the compliance check request together with study reports, evidence of study initiation (i.e. signed declaration of the principal investigator) and for provide some sections of the Module 2 for quality measures.

See also: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-procedure-paediatric-investigation-plan-compliance-verification-european-medicines_en.pdf

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Question 5: What is the content of a Deferral Annual Report?

The objective of the deferral annual report is to provide an update on the progress of the paediatric development. This is done by completing a specific template.

You will need to check the date for sending the report:

- There is no need to submit annual reports before the MA is granted.
- Dates for sending the annual report will be depend on whether the medicine is already authorised or not, and on the initially agreed PIP decision date.

See also: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/paediatric-medicines/annual-report-deferrals

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Question 6: In marketing authorisation applications with exceptional circumstances, can the PIP be the missing document/study (providing a valid justification)?

We would need additional information to better understand why you are raising this question.

We wonder whether your situation could in fact refer to a PIP waiver request on the ground of ‘lack of feasibility for conducting studies’ (e.g. recruitment capacity), in which case you would still need to submit a PIP application and provide the EMA decision in your MAA.

Please do contact us at contact@blue-reg.com should you need further assessment/advice on your specific situation.

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Question 7: What kind of justifications for a "late" submission of a PIP during development of a medicinal product did you use in the past? Based on your experience which percentage of pharmaceutical/biotech companies really meet the requirement to start PIP during or just after Phase 1 PK studies?

We see cases of development programs stopped and re-initiated, explaining the delay in submitting the PIP. We also see cases with developments focused on US registrations first, and subsequently expanded to EU registrations. The justification is required in the PIP application form, so the teams should explain the situation of their product development on a case-by-case basis.

Based on our experience, new developments aiming at global registrations consider the EU PIP requirement timelines. However, we also regularly see late justifications explained by the development history of the products, without having a clear representative percentage to provide.

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