Paediatric Investigation Plans' experience after 10 years: inclusion of the paediatric development early is necessary when requested by regulation

17th Club de phase 1 meeting

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05/04/2018
(slides from Paolo Tomasi, Gunter Egger)

Why is there a EU Paediatric Regulation?

Off-label use

for

=

±

Security risks
& communication

European Paediatric Regulation n.1901/2006 & new tools: PaeDiatric COmmittee at the EMA (PDCO) + PIPs

Population Definition

- Children are NOT small adults
  - ICH E11 (R1) : age categories
    - preterm newborn infants *(*from day of birth to the expected date of delivery plus 27 days*)*
    - term newborn infants (0 to 27 days, en discussion)
    - infants and toddlers (1 month (28 days) to 23 months)
    - "children" (2 to < 6 & 6 to < 12 years)
    - adolescents (12 to < 18 years)
  - Disease (“condition”/ MEDRA) and indication to be defined according to **paediatric needs**

⇒ **To integrate in the paediatric development, according to appropiate variables** (ie. drug, disease, physio-pathology / relevant age-subset)

Population under « maturation » and physiological development

- Different in each age-stage, dev. not linear
  - Neonates: organs / maturation (kidney/liver, % fat, metabolism)
  - Infants, children: CNS, immunity, ….
  - Language, swallowing, motor dev. / walking
  - Bone growth, hormonal / sexual maturation & dev.
  - Adolescents : cognitive / psychosocial

⇒ **Distinction to be done of relevant age-subsets to be defined / BW-BSA**

⇒ **3rd dimension in drug evaluation**

Disease knowledge recent and evolving (particularly in rare diseases)

- Diseases are less known in children (ex: autism, migraine…)
- Less consensus : scientific societes, WG, publications ongoing (ex: ILAE definition of epileptic types/syndromes 2017, neonates seizures INC 2018, initial ages for inclusion vs first diagnosis discussed on orphan diseases; methodological issues on small pop EMA WS 2017)
- Scales for endpoints defined or revised continuously, to be validated according to the ages of the patients under investigation (ex: QOL, MFM vs 6MWT, 4SC in neuromuscular dystrophies, EVA – CHEOPS for pain, …)

⇒ **Importance of published data on epidemiology, disease-registries (natural history), pb?, with data on dose, short and long-term efficacy and safety**

⇒ **Standardisation & validation of appropiate scales**

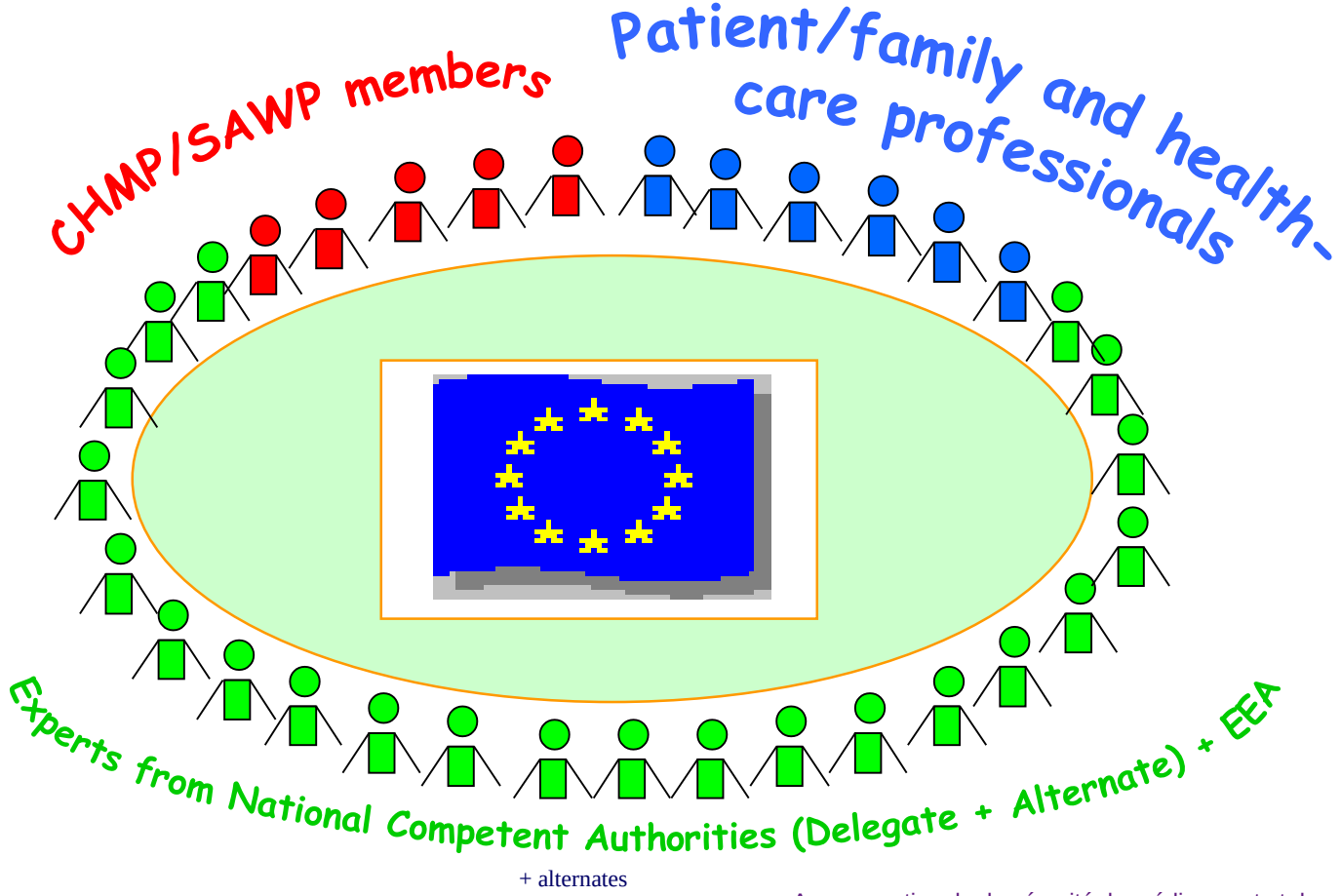
Disease knowledge still variable

- Less frequent:
  - Diseases only existing in children
  - Rare diseases, orphan (ex: genetic deficits with different phenotype / age « subset », metabolic deficits)
  - Different aetiology / diagnostic / evolution in children (ex: chilhood epilepsies, HTA, depression)
- Different patient care (standard of care) / countries - centers:
  - Pharmacology investigation with innovative methods are necessary
  - Contraints of formulation / excipients, swallowing-school attendance

⇒ **Faisability studies / design-timeline, paediatric networks Empr-EMA**

Paediatric Committee (PDCO)

Delegates from European Union MSs (including paediatricians) + Patients & academics representatives + EMA (paediatric coordinators)



Paediatric Committee (PDCO)

- From 2007, within EMA - key role in fulfilment of Paediatric Regulation provisions (link with FDA, etc)
- Main Tasks
  - Assess content of PIPs and requests for waivers/deferrals and provide an opinion
  - Check compliance of an application with agreed PIPs
  - Provide advice on any question relating to paediatric medicines (at the request of the Agency's Executive Director or the European Commission) / WG + Scientific Advice + GL / WPs + PRAC ….
  - Supports EMA on the creation of a European network with specific expertise in the performance of studies in the paediatric population
- The PDCO is not responsible for MAAs & Art. 45-46 review for products for paediatric use, which is responsibility of the CHMP/CMDh NCAs
  - However, CHMP may request the PDCO to prepare an opinion on the quality, safety and efficacy of a product if these data have been generated in accordance with an agreed PIP

Objectives of the Paediatric Regulation

- Informations on paediatric drugs (***even*** if MAA is not granted)
  - ☞ Reports of a completed PIP (on all (non-)clinical studies and quality maesures, except those deferred)
  - ☞ **Mandatory before the MAA submission request**
- Clinical studies in children according to GCP
  - Without non useful CS
  - And…not unnecessary delay of adult MAA

Paediatric Investigation Plan (PIP)

PIP ?

- Document to frame the program of development of medicines

  to ensure their availability for children, from birth to less than 18 years of age, in the requested indication (ie clinical symptomes)

  - Including the strategy and maesures / CS(s) synopis
  - Quality (age-appropiate formulation to be considered from PK Ph1 Adults) and preclinical

- Novel Notions on
  - **medical need**, to be considered earlier in the development,
  - « waiver(s)» partial (per age subsets) or full
  - « deferral(s) » partial on initiation and/or completion of CS-measures

Scope / PIP

- **Centralised, MRP/DC, national procedures**
- **Mandatory before MAA (submission at end of ph1 when PK in adults in known, completion before MAA)**
  - New medicines (article 7) (irrespective of patent status)
  - Autorized / variation type 2 (art. 8) (with SPC -Supplementary Protection Certificate - or patent qualifying for SPC)
    - Indication
    - Formulation ou route of administration
- Exception of PUMA (art. 30): authorised off-patent drugs
  - Volontary procedure
  - Only paediatric population

Not submitted to PIP obligation

- Authorized products without a SPC or patent qualifying for SPC
- Medicinal products authorised under Art 10 and 10(a) of Directive 2001/83/EC
  - Generics, hybrids, biosimilars and through the well-established medicinal use procedure (“Usage bien établit”)
- Medicinal products authorised under Art 13 to 16 of Directive 2001/83/EC
  - Homeopathic and herbal medicinal products

⇒ Attention: nevertheless, products impacted by other aspects of the paediatric regulation, e.g., Article 46

EU Paediatric Regulation: obligations versus incentives

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

**if compliance with PIP, information, approval EU-wide*
#according to GMA concept

PIP structure, Summary Report & PIP Opinion

A: Administrative, informations on the drug (PIP summary)

B: Clinical

- Disease, paediatric specifities vs adults
- Product Information (mode of action) et therapies-SOC
- Discussions therapeutic need/ drug

C: Waivers(s) full / partial

D: Developpement Strategy in children

- Available data (adults and children) and strategy of developpement (age defined subsets, formulation, dose, E&S CS / PK-PD M&S /partial extrapolation, timelines)
- Synopsis measures Q, Précl, Clin. ☞ *« Opinion de PIP » binding*

E: Deferral on initiation/completion of measures-CS

☞ « Summary report PIP » = PIP D0 (& RfM D61) + comments Rapp, Peer-R (coRapp), EMA coordinator ☞ minutes D30, D60, D90, D120 PDCO

Pediatric specifications / SmPC

- 4.1 indication or extension
- 4.2 new posology or amendement
- 4.3 ou 4.4 new pediatric information
- 4.8 nouvelle security data/results in pediatric CS
- 5.1 « waiver » or « deferral » to specify, ou new data
- 5.2 new data
- 5.3 new juvenile (non-clinical) data

→ Obligation to specify in the SmPC all the information collected/analysed following the PIP developments / CS

PIP opinion

PIP opinion template
1. waiver: condition
2. Paediatric investigation plan
2.1 condition – indication
Age subsets
Pharmaceutical form
Measures
Quality-related studies
Non-clinical studies
Clinical studies
Extrapolation, modelling and simulation studies
Other studies
Other measures
3. Follow-up, completion and deferral of PIP
4. Details of agreed measures
5. Potential long-term safety or efficacy issues for RMP/PV

Synopsis CS (cf. template PIP)

Clinical studies - Study identifier(s) (nb: «ongoing»)	**<Study number> <Text>**
Study design features and main objectives	
Study population and subset definition	
Number of study participants by paediatric subset (e.g. age, sex, severity or stage)	
Study duration for participants	
Dosage, treatment regimen, route of administration	
Control(s)	
Primary endpoint(s) with time point(s) of assessment	
Main secondary endpoint(s) with time(s) of assessment	
Statistical plan including study conduct and analysis	
Other	
Plan for specific follow-up (not part of this study)	
External Data Safety Monitoring Board	
(Date of initiation)	
Date of completion (last patient, last visit)	

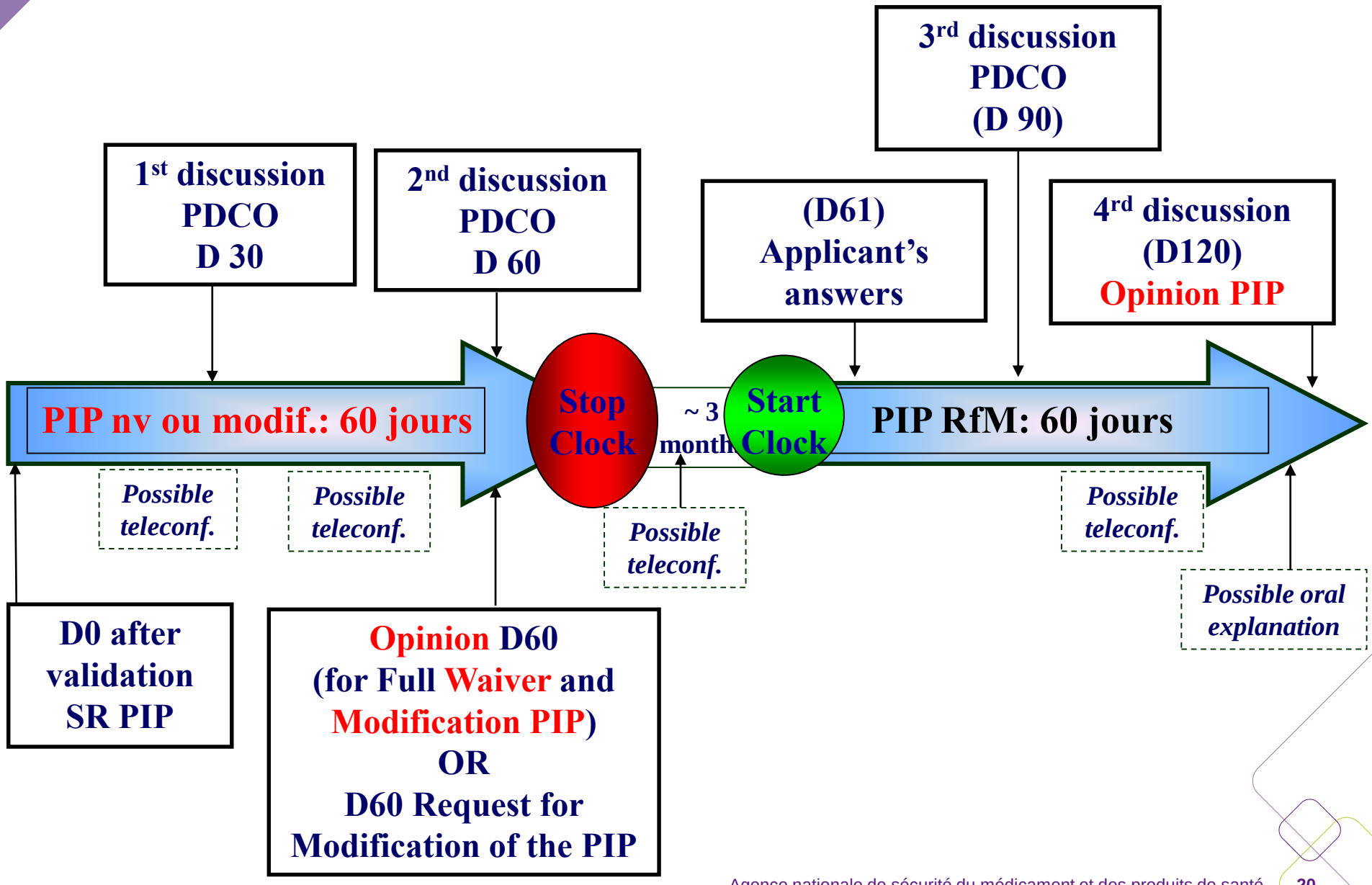
EMA/PDCO for PIP assessment

- EMA Paediatric Coordinator
  - Contact person for the sponsor for the whole PIP procedure
  - Provides critical review and coordinates the preparation of the summary report
- PDCO Rapporteur and Peer Reviewer
  - Conducts critical review of the PIP
  - Provides scientific expertise with comments of the Applicant's PIP
  - Identifies scientific issues and proposal for discussion by the Committee
- Working Groups: Formulation (FWG), Non-clinical (NcWG), MSWG & EWG (other EMA committees, WG) (FDA pediatric clusters)

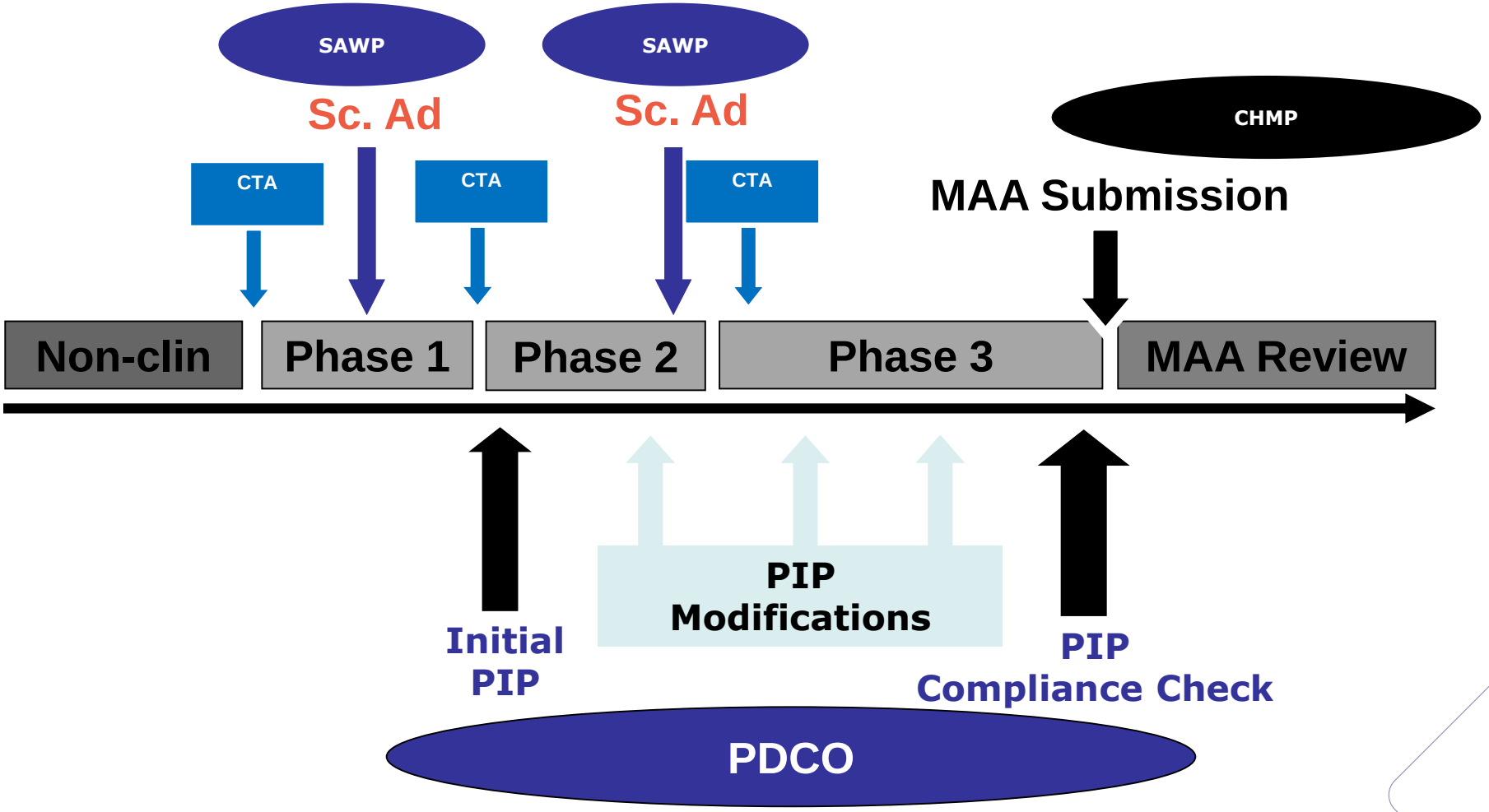
☞ **Summary report PIP (assessment) → PIP opinion (decision) assessed by the PDCO**

☞ **To be provided (SR PIP D120 + detailed opinion, ± D60 SR/opinion PIP modifications) for CS submission at ANSM**

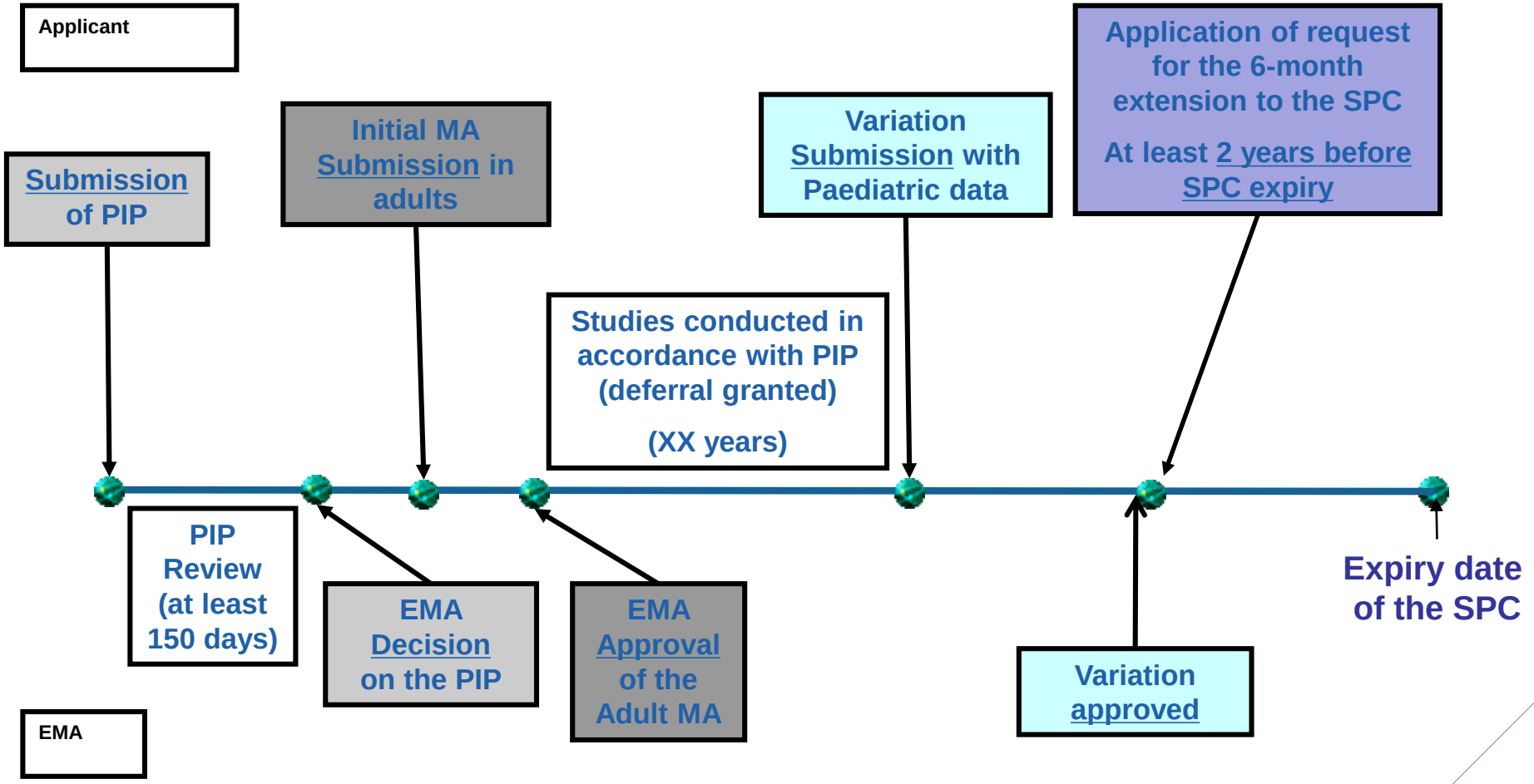
Timelines PIP



PIP Submission Timelines (SA / sc. Qs/ Eps)



Timelines from PIP submission to SPC expiry



Compliance Check on the agreed PIP

- Compliance check request is to be done before submission of MA application, exceptionally can also be conducted in parallel
  - In the latter case, validation is suspended until compliance is verified

- The compliance request procedure will last 2-3 months
  - Letter of Intent (-1 month)
  - Compliance request submission
  - PDCO opinion within (30 or) 60 days of receiving the request
    - By the EMA-coordinator and the Rapporteur
    - If partial compliance, issue of a compliance report within 10 days
    - If final compliance Issue of a compliance report and opinion on compliance within 10 days

- Compliance check is different than data assessment
  - "Yes" or "No" on the binding elements
  - No negotiation, no clock stop, no re-examination

AntiEpileptic Drug development: time of dev. on specific indications, driven by the adult

ADULT POP. (symptomes)

Partial Onset Seizures (focal)

PGTCS with IGE

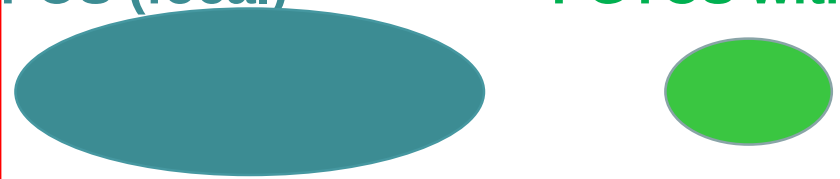
Time of dev vs. Patient expiration

⇒ ***Partial extrapolation could allow better fulfulliment of all needs (chilhood epilepsies / neonatal seizures can be the most severe ones)***

⇒ ***Chiron, Behrouz et al, CNS Drugs 2013***

PAEDIATRIC POP. (symptomes & types)

POS (focal) **PGTCS with IGE**



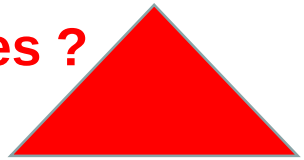
=> efficacy extrapolation? Ok ≥4 y. FDA – EMA / Experts-Sg. Learning ociety (ILAE)

Epilepsy syndromes with generalized epilepsy

Chilhood types epilepsies ?

LGS, Dravet S, Infantile Spams, TuberoSC, others

Neonatal seizures ?



« age appropiate formulation » development

- Age-appropiate / size-shape of (mini-)tablets, oral liquid < 6 y.
- Composition: excipients
- Acceptability / palatability: endpoint on CS
- Volume(s) of administration, infusion rate
- Device of accurate dosage
- Waste of expensive drugs

☞ Formulation Working Group (FWG) of PDCO

☞*Guideline on pharmaceutical development of medicines for paediatric use 2014*

☞*Updated Excipients rec. (SWP)*

Experiences with the EMA guideline on pharmaceutical development of medicines for paediatric use

- University: **mini-tablets** / oral solution
  - 517 patients 6 months - 6 years, Düsseldorf
    - Mini-tablets: 2 mm, coated or not
    - Versus syrup
  - Results :
    - At all ages, mini-tablets are better accepted vs oral solution
    - Little difference if coated or not
    - Well tolerated
  - Systems of maesure for counting mini-tablets exist.

Excipients labelling EMA

« Excipients in the label and package leaflets of medicinal products for human use » (CPMP/463/00) (PDCO, SWP, BWP, QWP, ..)

- Updated information, thresolds
  - Paediatric population…

- Including Q&A

- Aspartame, benzyl alcohol, benzoic acid & benzoates, benzalkonium chloride, gluten, boric acid, cyclodextrins, ethanol, fragrance allergens, fructose and sorbitol, phosphates, propylene glycol & esters, sodium laurylsulfate & sodium

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000387.jsp&mid=WC0b01ac05808c01f6

Pre-clinical development

- Cf. non-clinical data on adults, ± available data /
  - Pharmacology: mode of action, safety
  - Pharmacokinetics
  - Toxicology: single and multiple doses, genotoxicity, cancerogenicity, reprotoxicity (fertility, embryo-foetal development , pre-post-natal dev.)...

→ dedicated studies in immature animal ?

- Non Clinical Working Group (NcWG) of PDCO
- *Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005)*
- *Oncology review: signals distincts from CS in adults, allowing to identify the targets to monitor in CS*

Specificities of Clinical Development

- To integrate the paediatric development « asap, end Ph1 », and by age-subsets
  - From end of pharmacokinetic studies in adults
- Design of the CS with rationale/justification
  - Dose regimen determination: PK/PD CS / IA for confirmation (*M&S & extrapolation*)
  - Selection and validation of efficacy criteria *(ex: DMD, Depression)*
  - Selection of traitement /control *(placebo or SOC ? < 2 y?)*
  - Folllow up monitoring - Pharmacovigilance *(>2-5 y?)*
  - Faisability and appropiate recruitment : selection of « paediatric » centres

⇒**Objective: MAA**

⇒ **ie EMA website: paed. Workshops-expert meetings-Scientific guidelines, EMA publications and PIP/M&S/Extr. templates**

PK-PD in children

◆Volumes & timepoints blood sampling CS:

guideline EC 2008 "ethical considerations for clinical trials on medicinal products conducted with the pediatric population"

- limites

  3 % of total blood volume (BV) during a period of 4 weeks

  1 % BV at any single time

  BV ~ 80 to 90 ml/kg body weight ☞ 3% ~ 2,4 ml

◆Pharmacodynamic markers

- Need of appropiate PD markers, comparative data from Adults CS or other paediatric CS is useful (dose rationale)

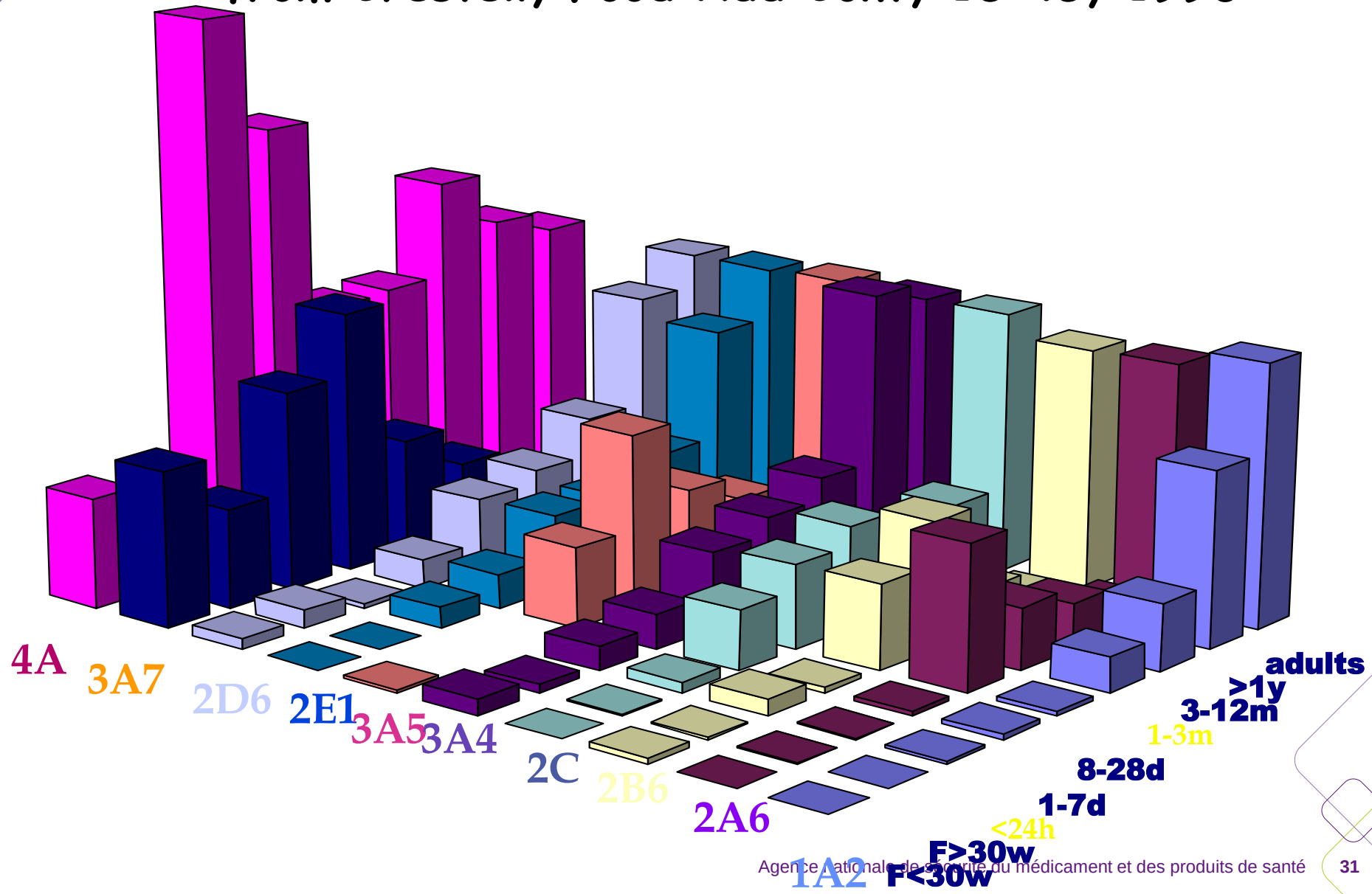
☞ Sparse sampling / Population PK/PK-PD – PBPK

☞ Sensitive assays / micro-sampling techniques (<0.5 - 1 ml)

☞ PD to be considered from Ph1-Ph2

Age-based changes in CYP activity

from Cresteil, Food Add Cont, 15:45, 1996



Modelling & Simulation + Extrapolation : optimizing dose & designs

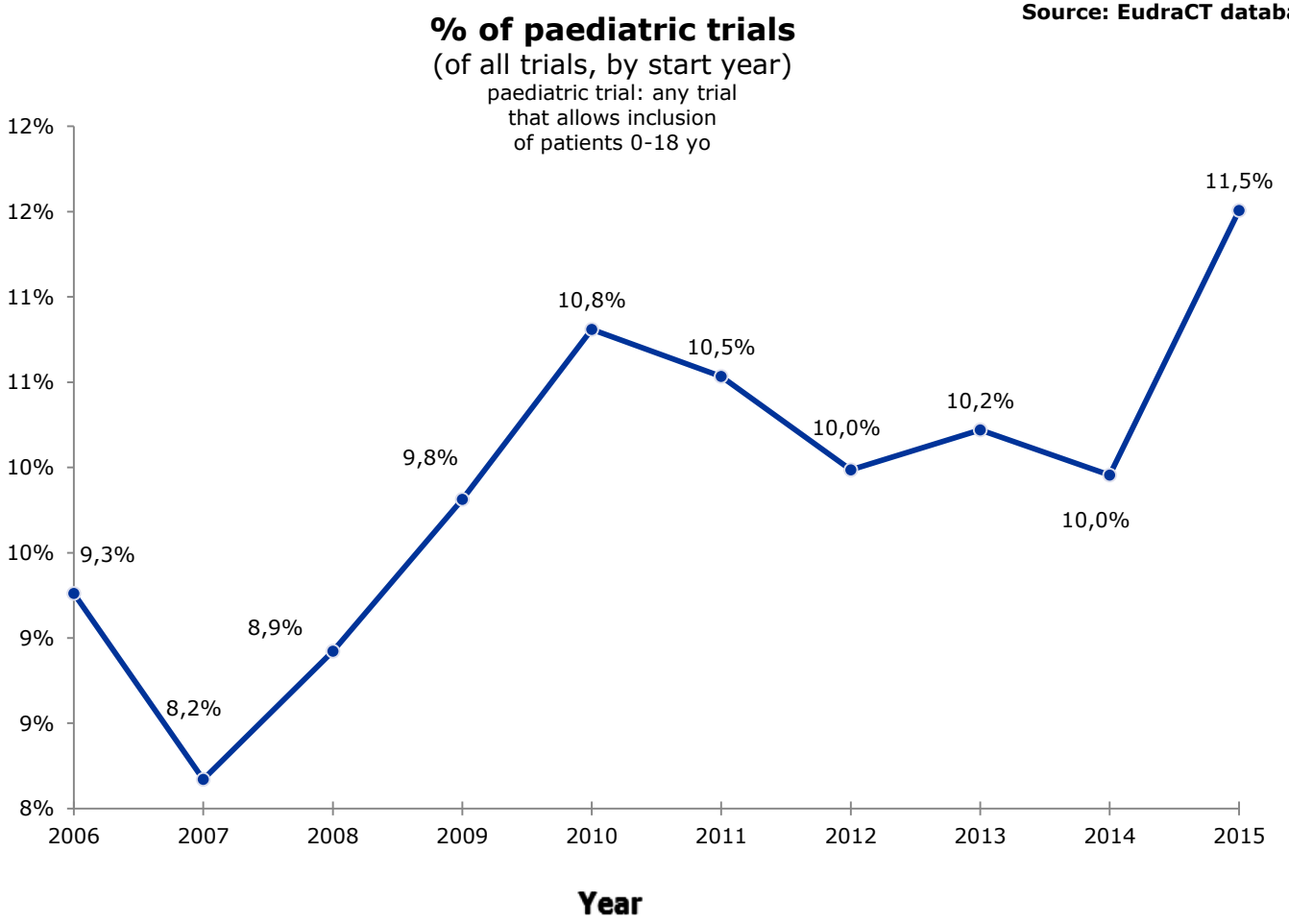
- Innovative methods M&S combined, with all data available (including other indications), to identify the initial dose in children
  - Pop PK & PD - Bayesian
  - PBPK & PD – Systems pharmacology (< 2 y. particularly)
- PKPD studies or Ph3 / adaptative design
- Validation of predicted PK/PD dose – E – S
  - Real data, process to be updated (design, interim analysis)

→ GL framework : dose-finding workshops (M&S/Extrapolation WG), GL extrapolation EMA, FDA ped. pharmacology 2015

- EMEA/CHMP/EWP/147013/2004 Corrigendum Guideline on the role of pharmacokinetics in the development of medicineal products in the paediatric population
- EMA/CHMP/458101/2016 Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation
- EMA/178564/2017 Reflection paper on the use of quantitative tools for extrapolation in paediatric medicines development
- EMA/199678/2016 Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

Paediatric clinical trials

Source: EudraCT database



10-year Report to EC on the Paediatric Regulation

High-quality paediatric research

- More than 700 PIPs are ongoing
- ~100 PIPs have been completed
- Support across European network for paediatric matters and collaboration of committees / working parties / working groups (CHMP, PDCO, PRAC, COMP, CAT, SAWP, MSWG, FWG, NCWG, CMDh)

→ Systematic review of paediatric developments

10-year Report to EC on the Paediatric Regulation

Context

- Delays in completion and results reporting of clinical trials under the Paediatric Regulation in the European Union: A cohort study 2010-2014

(Thomas J. Hwang, Paolo A. Tomasi, Florence T. Bourgeois) Plos medicine March 2018
PLoS Med 15 (3): e1002520. https://doi.org/10.1371/journal.pmed.1002520

- 326 paediatric clinical trials for 122 novel medicines authorised by the EMA
- 76% (247/326) of paediatric studies not planned to be completed at initial MA
- Rate of completion CS : 23% (56/247) for those planned completed after MAA *vs* 86% (68/79) for trials planned to be completed before authorisation (adjusted hazard ratio 0.11; 95% CI 0.06±0.19).
- Completion dates for 50% (162/326) postponed by a median of 2.2 year
- 38% (124/326) of paediatric studies completed as of 30 November 2017
- Among completed studies, publication reported in a public registry or in the peer-reviewed literature for 85% (105/124) at a median of 1.1 y. after study completion, and 60% (74/124) were published in a peer-reviewed journal

(Limitations: medicines not authorised by the EMA and possible trials to be completed or published in the future)

FDA

- **Best Pharmaceutical for Children Act (BPCA) 1997**
- **Pediatric Research Equity Act (PREA) 2003**
  - ☞ **Pediatric Study Plans, 2012/13, to be submitted early in the dev.**

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf

- **Research to Accelerate Cures and Equity for Children Act (RACE) 2017**

requires companies developing targeted cancer drugs for adults to develop those drugs for children with cancer as well

Thank you

http://ansm.sante.fr/Activites/Medicaments-en-pediatrie

Differences EU (Paediatric Regulation) / USA (BPCA-PREA-FDAA)

	US BPCA (Best Pharmaceutical for Children Act) 1997	**US PREA** (Pediatric Research Equity Act) 2003	**EU 2006**
Development	**Optional**	**Mandatory**	**Mandatory** ***(optional for off-patent)***
Instrument	**Written Request**	**Paediatric Study Plan (PSP, 2012) if deferral**	**Paediatric Investigation Plan (PIP)**
Waiver	**N/A**	**3 grounds**	**3 grounds**
Timing	**End of phase 2**	**End of phase 2**	**End of phase 1**
Reward	**6 months exclusivity**	**-**	**Main: 6 months SPC extension (patent)**
New drugs (section 505)	**Yes With exclusivity**	**Yes**	**Yes**
Biologicals (most)	**Yes**	**All**	**All**
Orphan	**Included**	**Excluded**	**Included**
Decision	**FDA**	**FDA**	**EMA (Opinion: PDCO)**

Paediatric workshops

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000416.jsp&mid=WC0b01ac0580925cc6

- **2017**
  - FP7 Small-population research methods projects and regulatory application workshop (29-30 March 2017)
- **2016**
  - European Medicines Agency public workshop on extrapolation of efficacy and safety in medicine development (17-18/05/2016)
  - European Medicines Agency-Industry stakeholders Platform second meeting on paediatric medicines (15/04/2016)
- **2015**
  - European network of paediatric research-European Medicines Agency meeting on rare gastrointestinal and liver diseases (08/12/2015)
  - Expert meeting on paediatric development of fixed-dose combinations for the treatment of the human immunodeficiency virus (HIV) (10/11/2015)
  - European Medicines Agency workshop on extrapolation across age groups (30/09/2015)
  - Applying regulatory science to neonates: launch of the International Neonatal Consortium (INC) (18-19/05/2015)
  - European Medicines Agency-industry stakeholders platform meeting on paediatric medicines (11/05/2015)
  - Collaboration on neonatal issues between researchers and the European Medicines Agency (17/03/2015)
- **2014**
  - Expert meeting on the clinical investigation of medicines for the treatment of paediatric hepatitis C (09/12/2014)
  - Paediatric osteoporosis expert meeting (02/06/2014)
  - Pharmacovigilance in the paediatric population workshop (28/04/2014)
- **2013**
  - Workshop on paediatric investigation plans in type-2 diabetes mellitus (25/02/2013)
- **2012**
  - Paediatric anticoagulation therapy expert meeting (06/11/2012)
  - Joint European Medicines Agency / Food and Drug Administration workshop for paediatric Gaucher disease type I: exploring the way forward (17-18/10/2012)
  - Workshop on endpoints for cystic fibrosis clinical trials (27-28/09/2012)

Scientific guidelines: paediatrics
Quality / Non-clinical / Clinical E & S / etc

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000404.jsp&mid=WC0b01ac0580029572

- Clinical evaluation of medicinal products used in weight control - addendum on weight control in children
- Clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy
- Clinical trials in small populations
- Conduct of pharmacovigilance for medicines used by the paediatric population
- Evaluation of anticancer medicinal products in man - addendum on paediatric oncology
- ICH E11 Clinical investigation of medicinal products in the paediatric population
- Investigation of medicinal products in the term and preterm neonate
- Paediatric addendum on the CHMP guideline on clinical investigation of medicinal products for the treatment of acute heart failure
- Paediatric addendum to the guideline on clinical investigation on medicinal products in the treatment of hypertension
- Paediatric addendum to the guideline on clinical investigation of medicinal products in the treatment of lipid disorders
- Paediatric addendum to the guideline on clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension
- Role of pharmacokinetics in the development of medicinal products in the paediatric population

More information on paediatric medicines

◆ Article 45 assessments

- Nationally authorised medicines: 219
- Centrally authorised medicines: 62

→ ~140 SmPC updates

→ 16 new paediatric indications (including in areas where no paediatric medicines were approved.)

◆ Article 46 assessments

- Nationally authorised medicines: 80
- Centrally authorised medicines: 280

→ ~90 SmPC updates (incl. paed. ind. for leuporelin acetate)

10-year Report to EC on the Paediatric Regulation

Agence nationale de sécurité du médicament et des produits de santé

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- La présente intervention s'inscrit dans un strict respect d'indépendance et d'impartialité de l'ANSM vis-à-vis des autres intervenants.
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