Industry Perspective : Preclinical Pediatric Drug Development in a Global Context

Shaun Maguire
Safety Assessment
GSK R&D, Ware UK

Industry has had to Integrate Paediatric Development into their plans

target | Target to Lead | Selecting a Candidate | First time to man | Efficacy in adults | Full development | File & Launch | Manage Lifecycle

- Huge challenge to industry increased commitment
- Accelerated early development in children required a shift in development activities to earlier stages : including preclinical activities
- Companies needed to build up early paediatric development experience in many areas
- Resources

Paediatric development is no longer an add on but an integral part of the drug-development process

Paediatric Drug Development
Regulatory Drivers

BPCA/PREA

2007

2007 : EU Paediatric Regulations

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 12 December 2006
on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004
(Text with EEA relevance)

2007 : US Paediatric Regulations
FDAAA BPCA/PREA renewal

2008

Guidance for Industry
Nonclinical Safety Evaluation of Pediatric Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2006
Pharmacology and Toxicology

European Medicines Agency

London, 24 January 2008
Doc. Ref. EMEA/CHMP/SWP/169215/2005

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP)

GUIDELINE ON THE NEED FOR NON-CLINICAL TESTING IN JUVENILE ANIMALS OF PHARMACEUTICALS FOR PAEDIATRIC INDICATIONS

2009 : M3 revision (R2)

2009

ICH

ICH Topic M 3 (R2)
Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Step 4

NOTE FOR GUIDANCE ON NON-CLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS
(CPMP/ICH/286/95)

EU / US Non Clinical Guidelines Similarities

- **Similarities**
  - Highlight **similar areas of concern** / late developing organ systems
  - **Species** : one can (US) will (EU) be acceptable
  - **Duration** : cover relevant postnatal period
  - **Timing** : before initiation of (long term) paediatric trials
  - **Endpoints** : general concordance

EU / US Non Clinical Guidelines Similarities

- **Differences**
  - **Dose level selection**
    - 'Identifiable toxicity' (MTD 'like'?) at high dose (US) while 'frank' toxicity' should not occur (EU)
    - Confounding / secondary effects of 'Frank toxicity'
    - Impact on design/interpretation of Juvenile Studies – default to more 'stringent' regulatory request?
- EU guideline more emphasis on 'case/case' approach while US reads more of a necessary requirement?
  - Industry experience 'drift' from case/case rationale to more of a tick box approach?

ICH Topic M 3 (R2)
Non-Clinical Safety Studies for the Conduct of
Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Step 4

NOTE FOR GUIDANCE ON NON-CLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS
(CPMP/ICH/286/95)

1.1 Objectives of the Guideline

The purpose of this document is to recommend international standards for, and promote harmonisation of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

Harmonisation of the guidance for nonclinical safety studies will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions.

12. CLINICAL TRIALS IN PEDIATRIC POPULATIONS

Generally, juvenile animal toxicity studies are not considered important for short-term PK studies (e.g., 1 to 3 doses) in pediatric populations.

Depending on the therapeutic indication, age of the pediatric population, and safety data from adult animal and human exposure, the appropriateness of obtaining juvenile animal study results before initiation of short-duration multiple-dose efficacy and safety trials should be considered.

For long-term clinical trials in pediatric populations when an assessment of juvenile animal toxicity is recommended, the nonclinical studies should be completed before the initiation of the trials.

There can be cases where a pediatric population is the primary population and existing animal studies have identified potential developmental concerns for target organs (toxicology or pharmacology). In some of these cases long-term juvenile animal toxicity testing can be appropriate. A chronic study initiated in the appropriate age and species with the relevant end

Global Paediatric Development
EU/EMA : Regulations : Timings

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 December 2006

on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

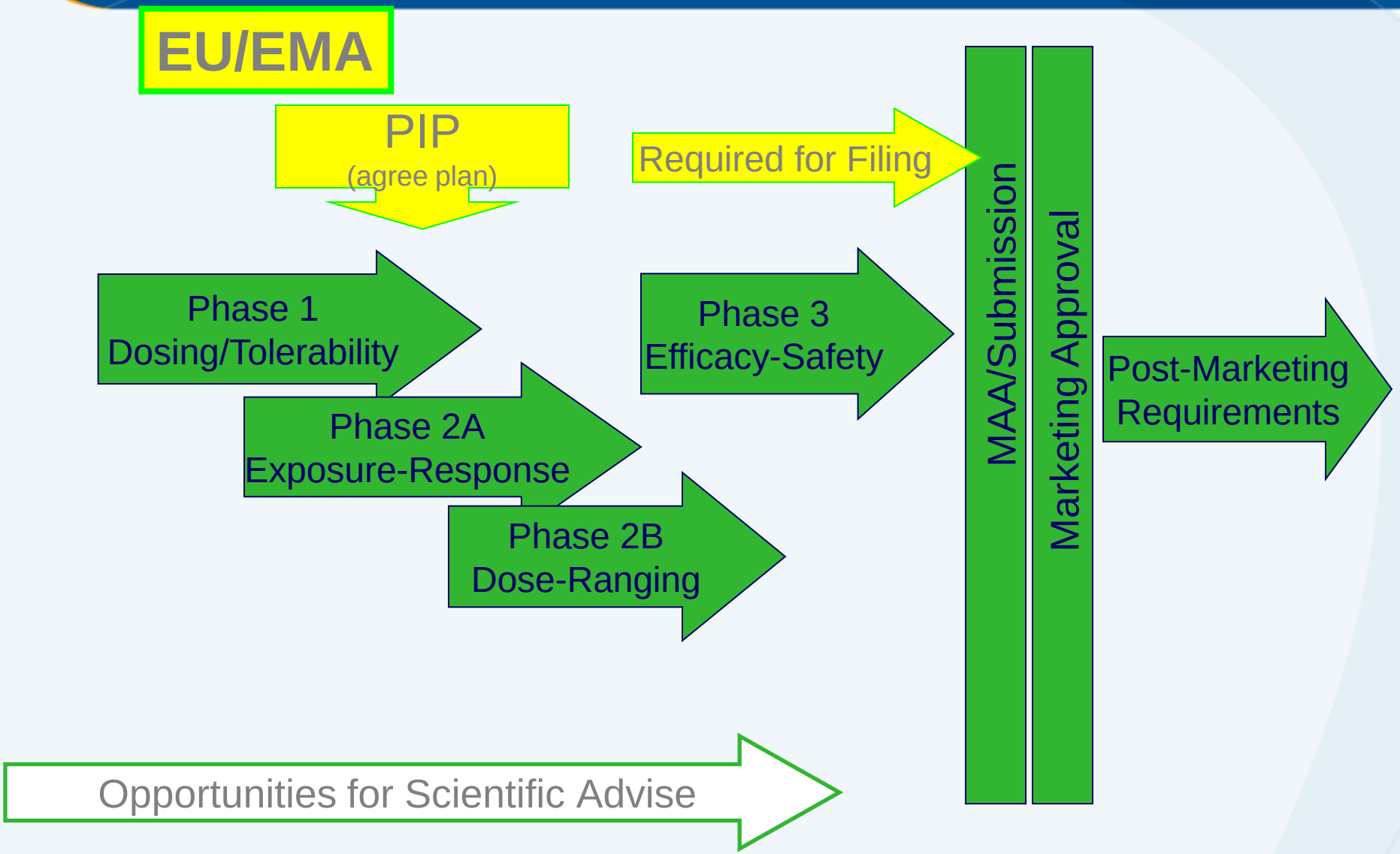
(Text with EEA relevance)

(OJ L 378, 27.12.2006, p. 1)

Article 16

1. In the case of the applications for marketing authorisation referred to in Articles 7 and 8 or the applications for waiver referred to in Articles 11 and 12, the paediatric investigation plan or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, not later than upon completion of the human pharmaco-kinetic studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC, so as to ensure that an opinion on use in the paediatric population of the medicinal product concerned can be given at the time of the assessment of the marketing authorisation or other application concerned.

Global Paediatric Development
EU/EMA : Regulatory Interactions



Comments from EMEA at recent EFPIA discussions

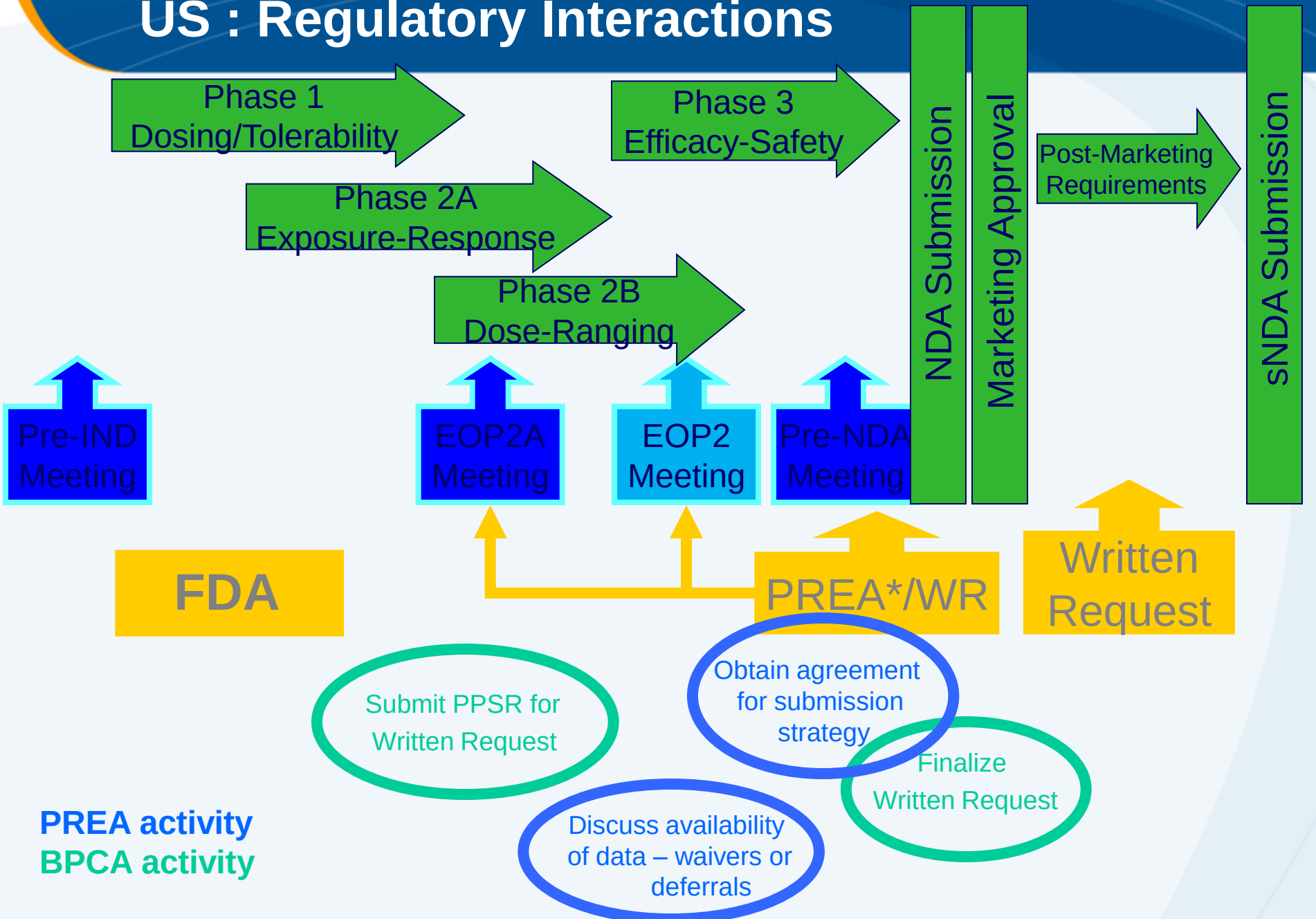
PIP timings

…PIP should be submitted close to the end of Phase 1, however acknowledged that at this stage often limited data…deferral until sufficient data available?….

EFPIA asked about the advantage for the Agency to receive the PIP during early stage of the development.

….The advantage is both for the Agency and for the company. … companies should consider that the EMA sees applications not in isolation but often has knowledge of similar indications leading to questions that may seem inappropriate

Global Paediatric Development
US : Regulatory Interactions

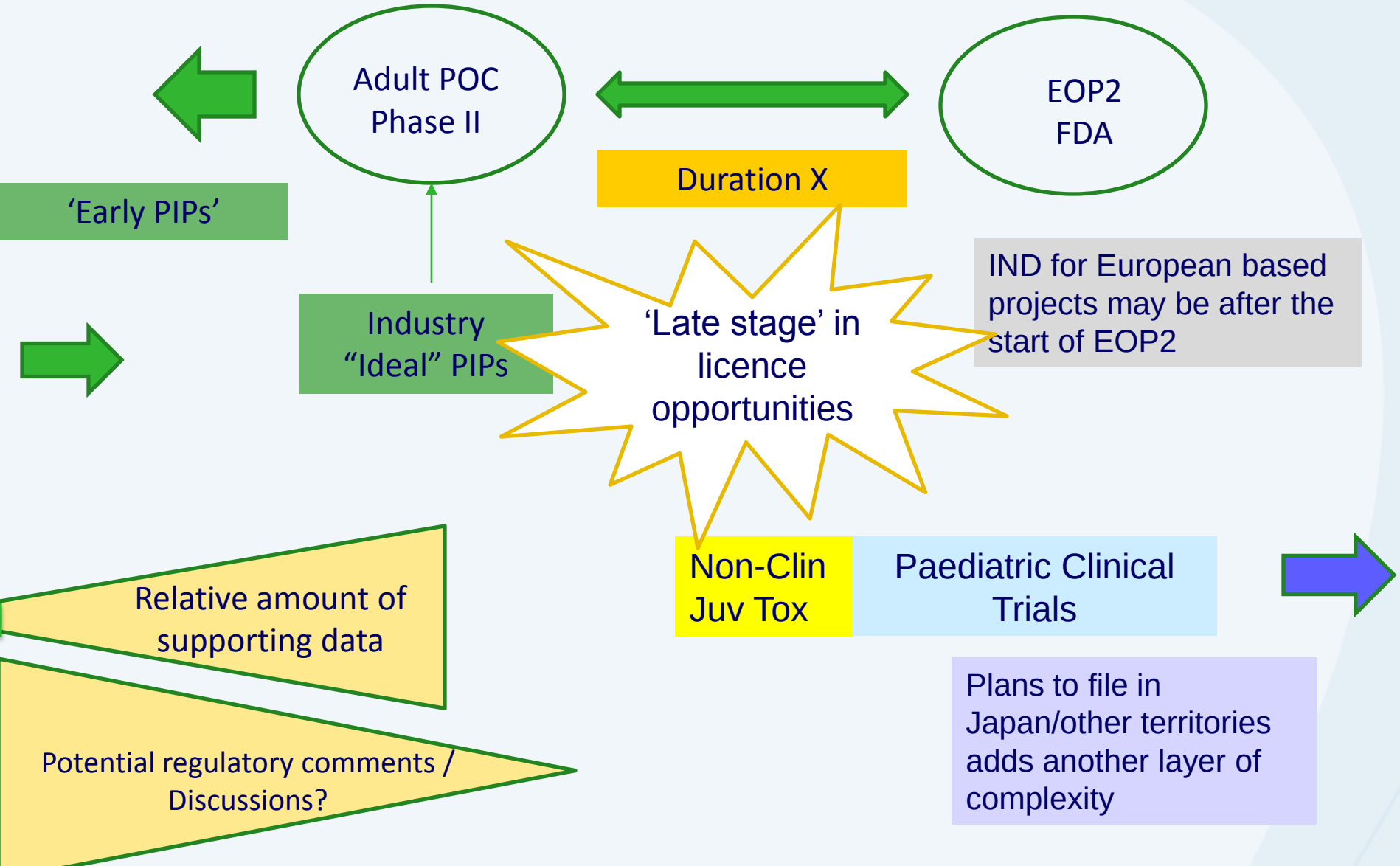


Global Paediatric Development
Regulatory Submissions: Challenges

Can a single approach to all territories be achieved ?

How can these different regulatory expectations be managed?

Global Paediatric Development Regulatory Submissions: Challenges



Challenge of regulatory concordance Example i

- **EMEA/PDCO position in PIP (D.III.a - *Strategy in relation to non-clinical aspects) (for proposed support of adolescents aged 13-17)***
  - ***Rapporteur*** *Comment:* We ***strongly disagree*** with the company's opinion that a juvenile toxicity study is not needed. A full juvenile toxicity study should be performed in line with EMEA/CHMP/SWP/169215/2005
  - A rat study is needed: PND 21 up to ***adulthood (D91)*** with special attention to behaviour/CNS effects. Morris water maze, Avoidance Learning and Prepulse Inhibition should be included
  - Resulted in a large and expensive study
- **FDA Preliminary Responses, End-of-Phase II Face to Face Meeting – 1 year+ after PIP**
  - We would like to point out that the Division ***does not require juvenile animal toxicity*** studies to support a clinical development program in adolescents (ages 13-17). However, the proposed studies ***(already mandated by the PIP)*** generally appear to be adequate for this age group.

Challenge of regulatory concordance
Example ii : Respiratory combination product
CHMP vs PDCO vs FDA

- CHMP Scientific advise sort on Juvenile toxicity study design and rationale to support 5-11 yr old
  - Proposal
  - 3m Juvenile dog study (from 8w of age) to support phase III
  - 3m study would allow comparison with the adult combination 'bridging study' (3m study in dog)
  - Full programme of work in adult animals with stand alone products.
  - No new/enhanced toxicities in adult combination studies.
  - Prelim 2 week Juvenile tox work in the Rat and Dog showed no new toxicities – expected targets

Example 4
CHMP vs PDCO vs FDA
Respiratory combination product

- CHMP Advise :
  - No definitive Juvenile toxicology requirement prior to conduct of Phase II studies
  - 3m combination juvenile dog study sufficient to support Phase III
  - Design considered ‘reasonable’

Example 4
CHMP vs EMEA/PDCO vs FDA
Respiratory combination product

- PIP/PDCO comment at Day 60
  - *….acknowledged that CHMP scientific advise considered the proposed single 3m combination juvenile dog study to be sufficient but….*
  - *But …not clear why applicant has chosen 3m for the planned study….to adequately address the long term effects the animals should be treated up to reaching adulthood. Clarify choice of dog…suggest use of rabbit*
  - PIP response submitted – again reinforcing rationale re 3m dog study – choice of species
  - Day 90 – PDCO agreed with proposal for dog 3m study

Example 4
CHMP vs PDCO vs FDA
Respiratory combination product

- FDA
  - Advise at Phase II meeting
  - Juvenile study would be required before filing
  - 3m dog study design looked reasonable – but at this stage would not comment on specific study design

- Difficult for the project to manage these different regulatory expectations / timings
- Uncertainties re regulatory acceptance of study (complex / expensive / non rodent study)

Potential Issues
PDCO requests

- **Studies outside proposed indication**
  - Cases where the scope of submitted PIP has been extended; PDCO requests for studies outside the intended indication
  - Resource implications / Non clinical support
- **Changes in proposed age groups**
  - Age range in PIP submission extended (waiver not accepted)
  - PIP submission built around proposed clinical plans (inc. non clinical support / rationale)

Future Developments

Optimised non-clinical investigations

Co-operation within Industry and with the Regulators

Nonclinical support using juvenile animals
More “thinking toolbox” and less “box ticking”

- IF, when, what
- Study Designs
- Reduction, Refinement, Replacement
- Interpretation and Risk communication

Probability of Requiring Juvenile Animal Studies

Class history of effects on developing systems

Age ≤ 2

Target organs are late developing

Age ≤ 4

Exposure in young animals differs from adult

Metabolism/activation is age dependent

Chronic therapy

Age ≤ 11

Subchronic therapy

Acute therapy

Age ≥12

Future Developments – Closer Co-operation within Industry and with the Regulators (EMA and FDA)

- Non clinical study designs / Regulatory interactions
  - Industry Pediatric Forum for Non-Clinical Safety (Europe) established in 2009
  - 20+ pharma companies
    - two F2F meetings : shared experiences, influence
  - Interactions via EFPIA with NCWG/PDCO have occurred (?extend to FDA via PhRMA?)
    - Informal exchange of experiences and issues with PIPs
  - WW input / discussion

efpia
European Federation of Pharmaceutical Industries and Associations

Future Developments – Closer Co-operation within Industry and with the Regulators (EMA and FDA)

- Pediatric Forum for Non-Clinical Safety : Output from EFPIA discussion NCWG/PDCO
  - Discussion re remit / function of NCWG
    - EMA agreed that the concerns/suggestions highlighted by NCWG as part of PIP review will be integrated into the summary report
  - Discussion re review process
  - Timing of PIPs
  - Consistency re Scientific Advice
  - Proposal for ‘best practises’ document

- Other initiatives: ILSI/HESI workshop, Biosafe ‘best practises’

Future Developments – Closer Co-operation within Industry and with the Regulators

- Improve concordance between EU and US
  - *PDCO work in a complex EU environment; Industry not to expect harmonised decisions between EU and US, but co-operation and information sharing is in place*
- Industry encouraged to improve quality of PIPs and to be as transparent as possible

Conclusions

- Industry has been challenged to provide medicines that have been specifically developed for children
- This has meant a major shift in development strategies
  - Development of supporting networks of expertise
  - Critical evaluation of EU and US regulatory processes
- Challenges exisit in dealing with timings of regulatory milestones and the different regulatory expectations
- Future developments to better manage these challenges
  - Industry discussion re developing common practices
  - Closer co-operation is being sought between EU, US and Japan regulatory processes – submission and review.
  - There will always be cases for juvenile animal studies but more “thinking toolbox” and less “box ticking” will improve 3Rs – non justifiable precedents should be set