PIP's Pup's and Problems

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Pediatric Medicine

- Until ~10 years ago, lack of targeted paediatric drug development – extensive "off-label" use.
- Assumes that paediatric patients will exhibit similar disease progression and respond similarly to the intended therapeutic intervention.
- Estimated 50% - 90% of drugs never specifically evaluated for paediatric use.
- How can we be sure that adult/paediatric toxicity profiles are the same?

Guidance

- Juvenile toxicology guidelines free and flexible ?
- Both sets of regulators expect to be consulted regarding exact study design
- Juvenile toxicology studies are also developing
- Regulators asking for
  - - more drugs
  - - more species
  - - more endpoints

Regulatory involvement

- The original proposal was that the conduct of juvenile toxicity studies should be considered on a case-by-case basis.
- The emphasis has changed though. Rather than questioning whether studies need to be conducted, there is now an assumption that these are required unless you can justify why they are not!
- Study design/content must be discussed with, and approved by, the Regulatory Agencies (FDA/EMA).

Industry Perspective

- Juvenile animal studies are not new !
- Now more consideration on whether such work is needed for each specific NME and if yes, use of a robust study design
- Need to avoid production of unnecessary, uninterpretable data
- Juvenile animals may be more appropriate for predicting postnatal developmental toxicities in children when…….
  - Safety data is unavailable from toxicity testing or the clinic
  - Preclinical studies indicate target organ / system toxicity
  - Where there are possible effects on growth / development
  - Where there is a particular concern for long term exposure in relation to human developmental stages

CHMP perspective - when studies may be required

- For new, unique chemical classes or unique combination products, juvenile studies may be requested
- Suspect adverse reproductive effects, especially if little or no drug transfer in milk
- Suspect juvenile susceptibility, *e.g.*, (arthropathy, ototoxicity).
- Specific toxicity observed in "old" animals, *e.g.* neurotoxicity.

None of this is available when you write your PIP !!

When juvenile studies are justified

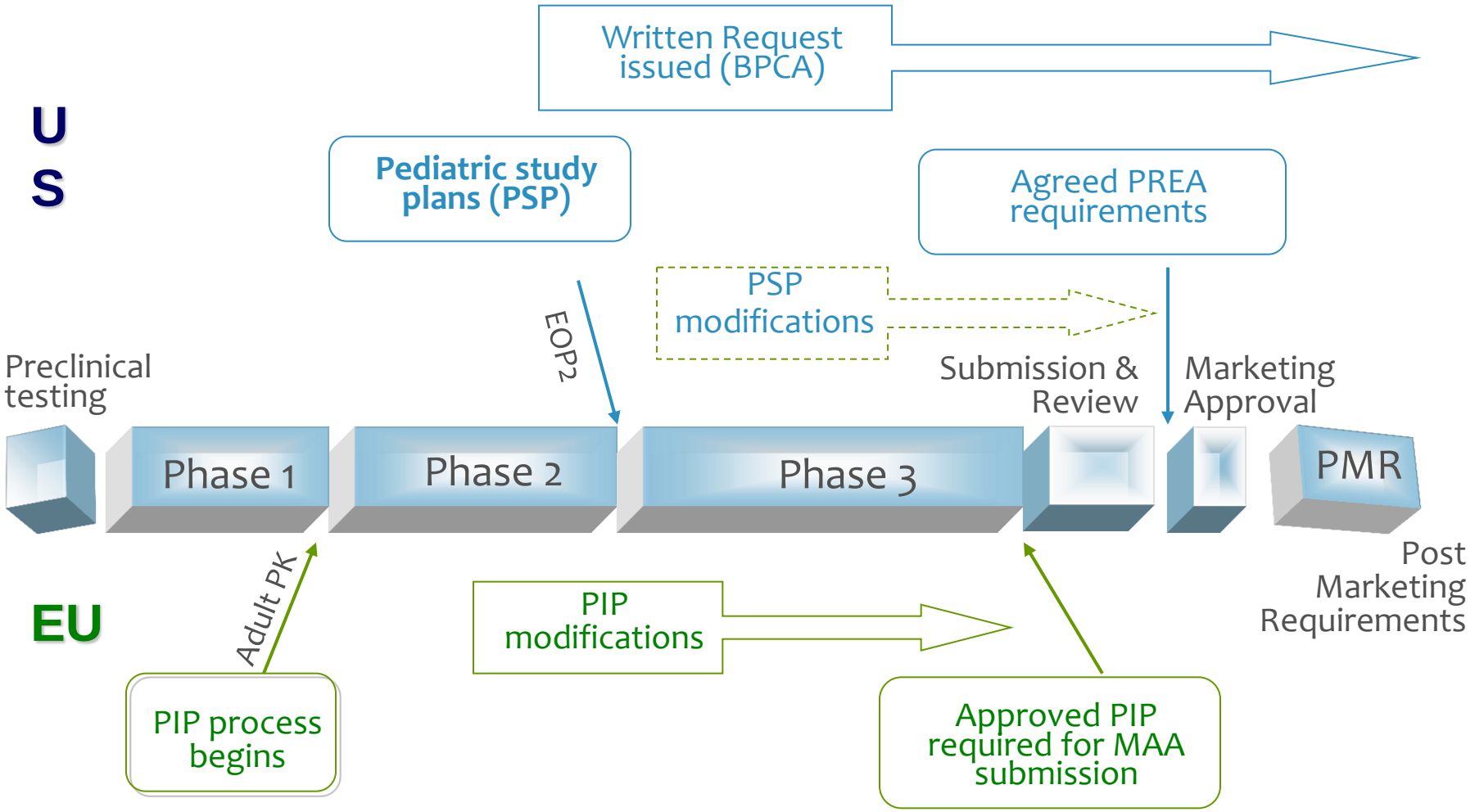
Non-clinical findings suggestive of :

- Target organ / general toxicity relevant for developing systems
- Possible effect on growth / development in intended age group
- Pharmacological driven effect on developing organs - Mode of action (MOA)
- To address a specific concern
- To study reversibility, aggravation of expected findings, definition of safety margins, …
- To identify age groups in which the drug should not be used or where special warnings are needed.

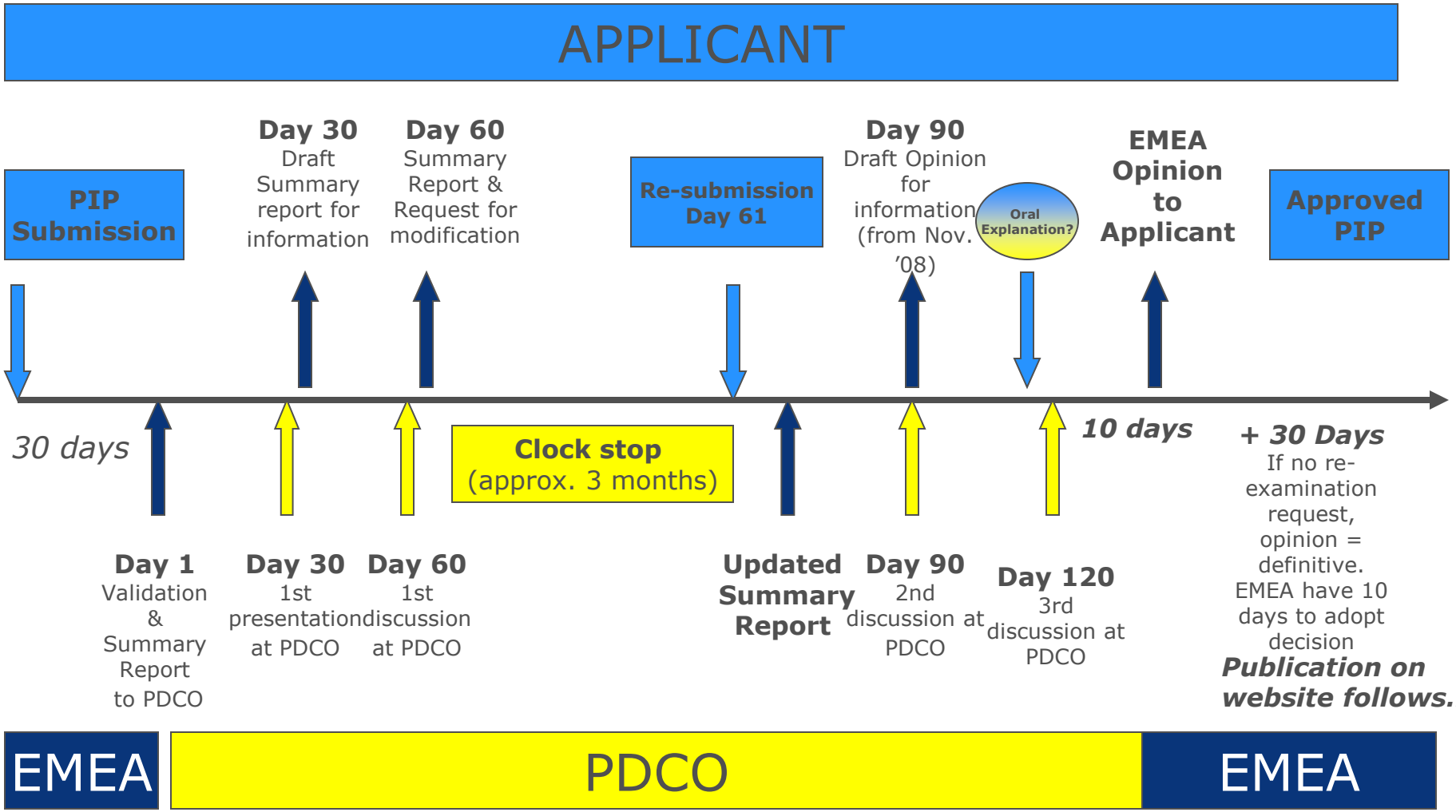
Does this fit with the search for unexpected findings ??

cf. "*Purpose is to identify age-related toxicity (i.e. unique developmental effects as well as differences in sensitivity)"*

Pediatric Planning in the Drug Development Process



PIP evaluation timeline



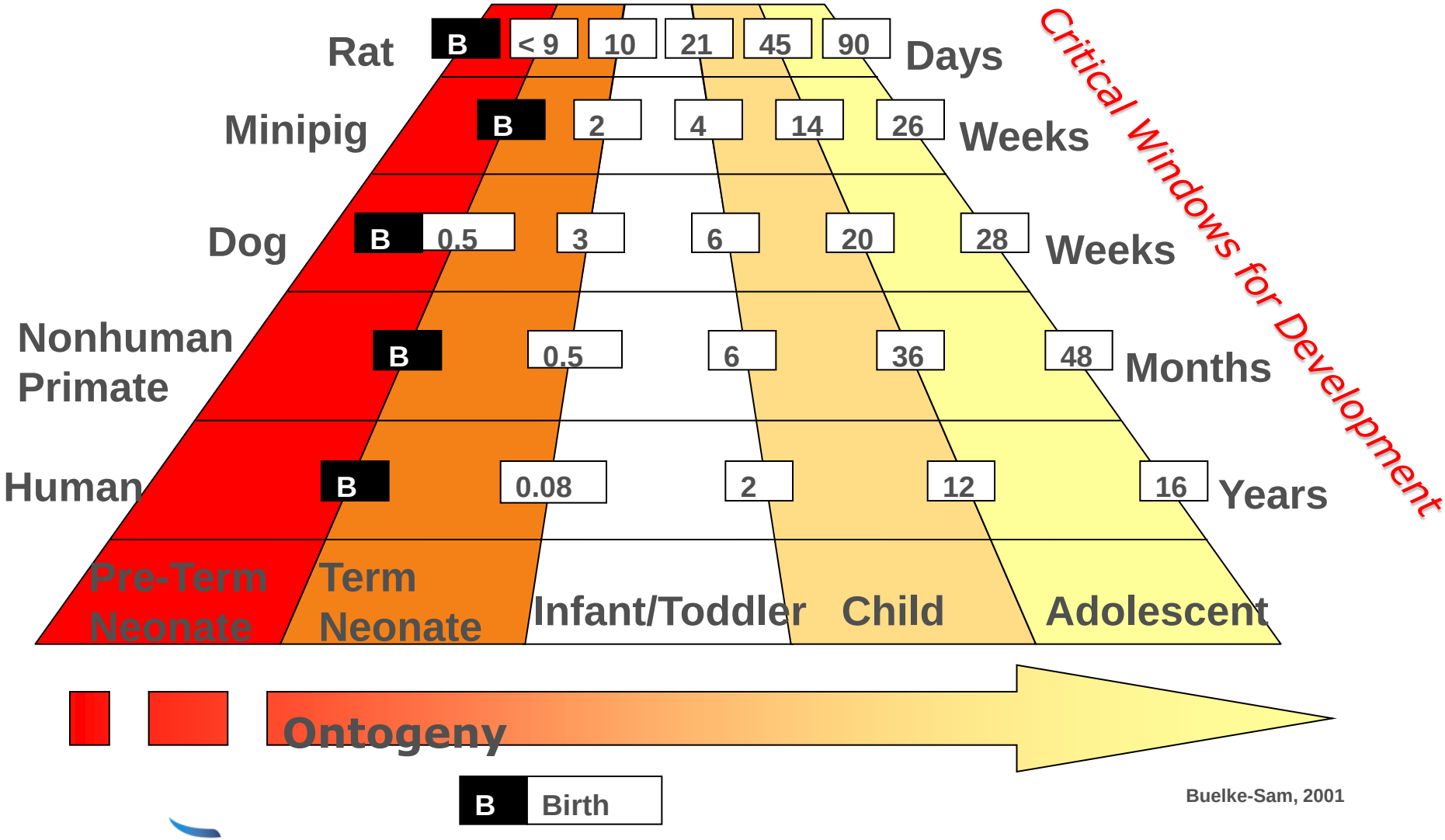
PIPs: Nonclinical section

- Justify the non-clinical development strategy
- Justification of the juvenile toxicity study designs: species, age, duration of treatment
- Justify why juvenile studies are not warranted
- Specify which studies (including non juvenile studies) should be completed before dosing children

Age Categories

- Preterm Newborn Infant (< 36 w gestational age)
  - Unique pathophysiology
  - Difficult to extrapolate from adults or older patients
- Newborn Infant (< 1m)
  - As above
  - Blood brain barrier immature
  - Altered pharmacodynamics
  - Less predictable absorption
- Infants and Toddlers (1m-2y)
  - CNS, immune system, growth still developing
  - Altered pharmacodynamics
- Children (2y - 12 y)
  Adolescents (>12 y)
  - Growth phase
  - Developing reproductive system
  - Increasing issues with compliance

Comparative age categories based on repro and CNS development



Buelke-Sam, 2001

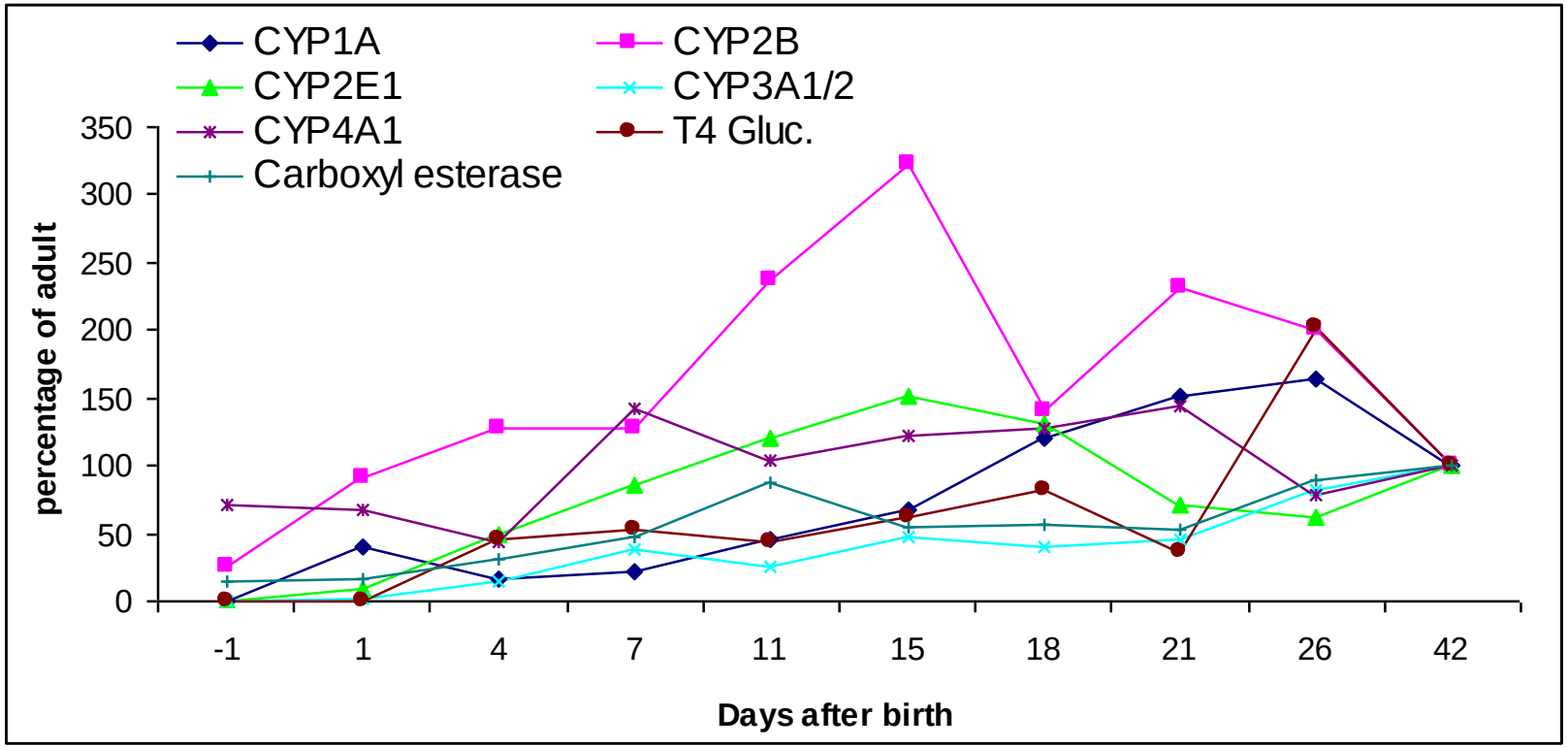
Guidance

- Rat as default animal for broad cover all aspects of juvenile development
- Dog (or monkey) may be required to assess specific findings suggested by findings in adult animals
- Minipig may increase in importance as becomes more widely used as second tox species

Guidance

- All aspects of ADME show major difference between the baby and the adult and responses vary between species according to relative maturity
- This means that alterations in drug effect with age may be due to pharmacokinetic changes and change in exposure with age
- Absorption rate more influenced than extent.
- Changes in body composition may result in alterations in distribution;
- Major changes in metabolism and renal excretion

Ontogeny of enzymes in Rat



Guidance

- Relevance and Impact of altered PK at young age
- dose adjustments in children are needed
  - to avoid toxicity
  - to achieve efficacy
- unexpected exposure/behaviour of drug and/or metabolites in animal studies
- It is most useful to understand mechanisms underlying differences in PK

Guidance

- We now realise how different adult and baby responses can be to drugs
- Large numbers of drugs given to babies when we do not know the response

Do you need juvenile studies - key factors

Clinical aspects:

- Adult human PD/PK data
- Age of intended patient population
- Duration of treatment
- Type of the disease

Nonclinical aspects :

- Animal data, known target organ toxicity, MOA, developing organ exposure
- Data from pre- and postnatal developmental toxicity study (incl. exposure)
- Juvenile animal data from a compound from same class

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

Drivers of timing of paediatric program :

- Intended disease target ? Therapeutic class ?
- Unique paediatric indication ? Seriousness and prevalence of the condition ? Alternative treatments ? …
- Need for a paediatric formulation ?

Drivers of timing of juvenile toxicity :

- Duration of treatment ?
- Paediatric susceptibility concerns ?
- Regulatory position
- Toxicology findings in adult animals
- Safety Issues from adult program

Questions to Help Guide the Preclinical Pediatric Program

- Indication/Therapeutic area
- Intended age of use
- Duration of treatment
- Clinical concerns identified during adult use
- What excipients will be used in the formulation
- Will there need to be a “novel” formulation
- Anticipated safety issues/concerns specific for intended pediatric population

Study design parameters

- Age of animals at start of dosing
- Duration of dosing period
- Route of administration
- Selection of species (appropriate for evaluating toxicity endpoints relevant for intended pediatric population)
- Dose selection (exaggerated toxicity not desirable, aim is to detect increased sensitivity of young vs adults)
- Inclusion of PK essential
- Endpoints (flexible - tailor-made study design)
- Preliminary study essential
- Numbers per sex per group not standard

Guidance

- Dose selection contrast policy between USA and the rest : USA want overt toxicity
- Don’t push the dose level too high - overcomplicates the issue
- Very focussed on toxicokinetics to measure exposure
- Animal numbers per end point critical to assessing significance
- The more variable each measurement the more animals required
- FDA not very 3R orientated - problem for Europeans to use animals most efficiently - assess multi-points per animal

Guidance

- Data interpretation depends on accuracy that each point can be defined
- Multiple end points mean some will be statistically significant - need to identify biologically significance combination of findings - weight of evidence - expert judgement
- linkages by mechanism of action/function/ correlation with dose
- Link adult animal >> juvenile animal

How Old Are You ?

Adult rats … asking Google, Medline etc.

Ace Animals, Inc.:

- Sprague Dawley adult body wt: 250+ for female, 450+ for male = PND105+
- Breeding onset is between 65-100 days of age in both females and males

Harlan

- Sprague-Dawley adult = 56 days

Charles River

- – France, adult = 60 days – Germany, Adult = 70 days

Mahidol University laboratory animal centre:

- Wistar and Sprague Dawley: adult body wt male 250–300 g, female 180-220 g

Publications, e.g. in Society for Experimental Biology and Medicine:

- 'Thus, we consider 4 ± 0.5-month-old rats (367 ± 10 g body wt) as young adult subjects that have reached a mature stage of life.'
- adult body wt male 300–400 g, female 250-300 g (Baker et al, 1979):

→ no common definition of the age or BW of an adult rat

→ Generally: adolescent rat PND 28-42; adult rat PND 70

Selection of species

- Must be appropriate for evaluating tox endpoints relevant for intended pediatric population
- Rats and dogs are traditionally the species of first choice.
- Testing in one appropriate species using both sexes will normally be sufficient (but not always!).

Rat studies – Why / Why not

PRO's

- Basic species for general toxicity data
- Can treat offspring from an early age
- Can use large numbers of animals for statistical assessment
- Can apply functional/behavioural tests
- Can assess reproductive function

CON's

- May not respond to compounds in similar way to man and may produce differences in drug metabolism
- Small size
  - may compromise some routes of dose administration
  - makes toxicokinetic sampling difficult
  - makes clinical pathology sampling difficult

Are studies supportive of clinical development?

Positives

- Identification of potential safety/PK issues
- Assessment of effects that cannot be adequately studied in pediatric trials
- Selection of (additional) clinical endpoints - study design
- Elucidation of mechanism of toxicity
- Additional information on label (e.g. contra-indicated in < 1 yr.)

Negatives

- Potentially wrong conclusions
- Can hold up clinical development

Conclusions 1

- Juvenile toxicity studies are becoming a much more important part of the drug development programme
- Start planning very early
- Consider all possible end points and develop your plans to select only important end points
- Discuss with regulators

Conclusions 2

- Be very careful with setting your planned time point for starting needs to be relevant to human treatment
- The younger the child you must treat the more differences you are likely to encounter between adult and child and the more complicated things are likely to become

Conclusions 3

- Research the potential metabolism of the test material and similar materials so that you have a chance of predicting what might happen in the juvenile animal cf the adult
- Keep up to date with the developing approaches e.g. JJ Symposium in Beerse.