CROSS-PHARMA
PRECLINICAL DEVELOPMENT

ILSI / HESI workshop : The Value of Juvenile Toxicity Studies Introduction and ‘Warm up’

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Washington DC, 5-6 April 2010

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Children Cannot be Viewed Simply as Little Adults

Species selection

Species/ parameter	Rat	Dog	Monkey
Target organ toxicity	Good	Good	Good
Exposure/ toxicokinetics	Fair	Good	Good
Development staging	Good	Good	Good
Human matching	Poor	Poor	Good
Background data	Good	Fair	Poor
CNS functional development	Good	Poor	Poor
Reproductive development	Good	Impractical	Impractical
Statistical analysis	Good	Poor	Poor

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Neonatal / Juvenile Testing - Dosing

DOSE ROUTE	SPECIES			
(EARLIEST DAY PP)	RAT	MOUSE	RABBIT	DOG
ORAL GAVAGE	1	(4-7)	14	1
IV BOLUS	(7) 15	?	?	1
IV INFUSION	21	?	?	56
INHALATION	7	21	?	10
PARENTERAL (IM/SC/IP)	feasible	feasible	feasible	feasible
DERMAL	21	21	35	42

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Rat studies - Why

- Basic species for general toxicity data
- Can synchronise breeding/animal supply
- 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

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Rat studies - why not?

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

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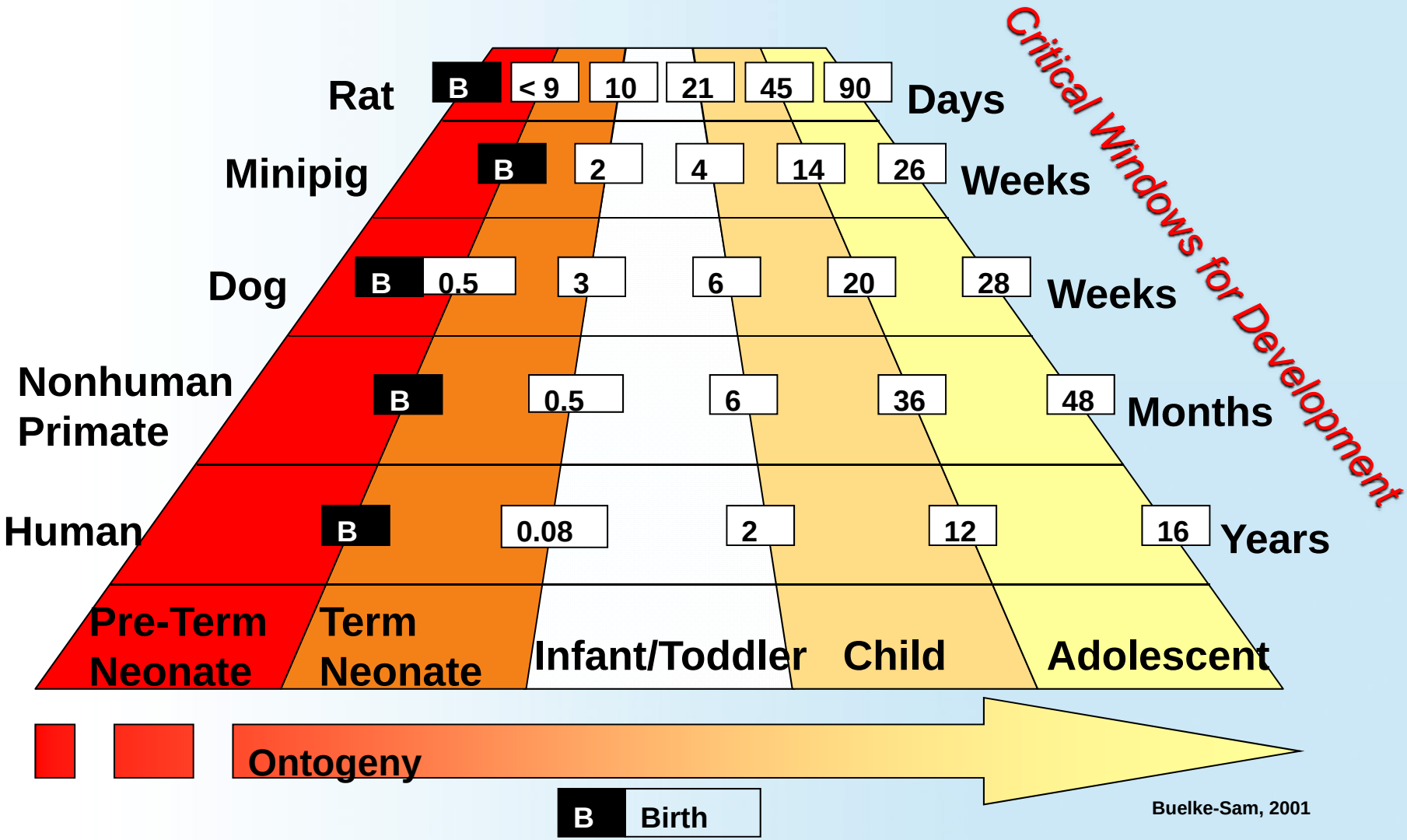
Age selection

- Matching the neonate and infants: can do it with rat, and may manage it with minipig
- Other species, difficult to obtain dams with litters and animals may be disturbed by treatment of the offspring
- Once weaned (approximate equivalent to human age 2+) all species could be used
- If treatment starts after weaning species (rat/dog/minipig) offer advantage of distributing litter mates among the treatment groups
- For primates each baby will be sourced from a different mother

Comparative Age Categories based on Repro and CNS Development



Buelke-Sam, 2001

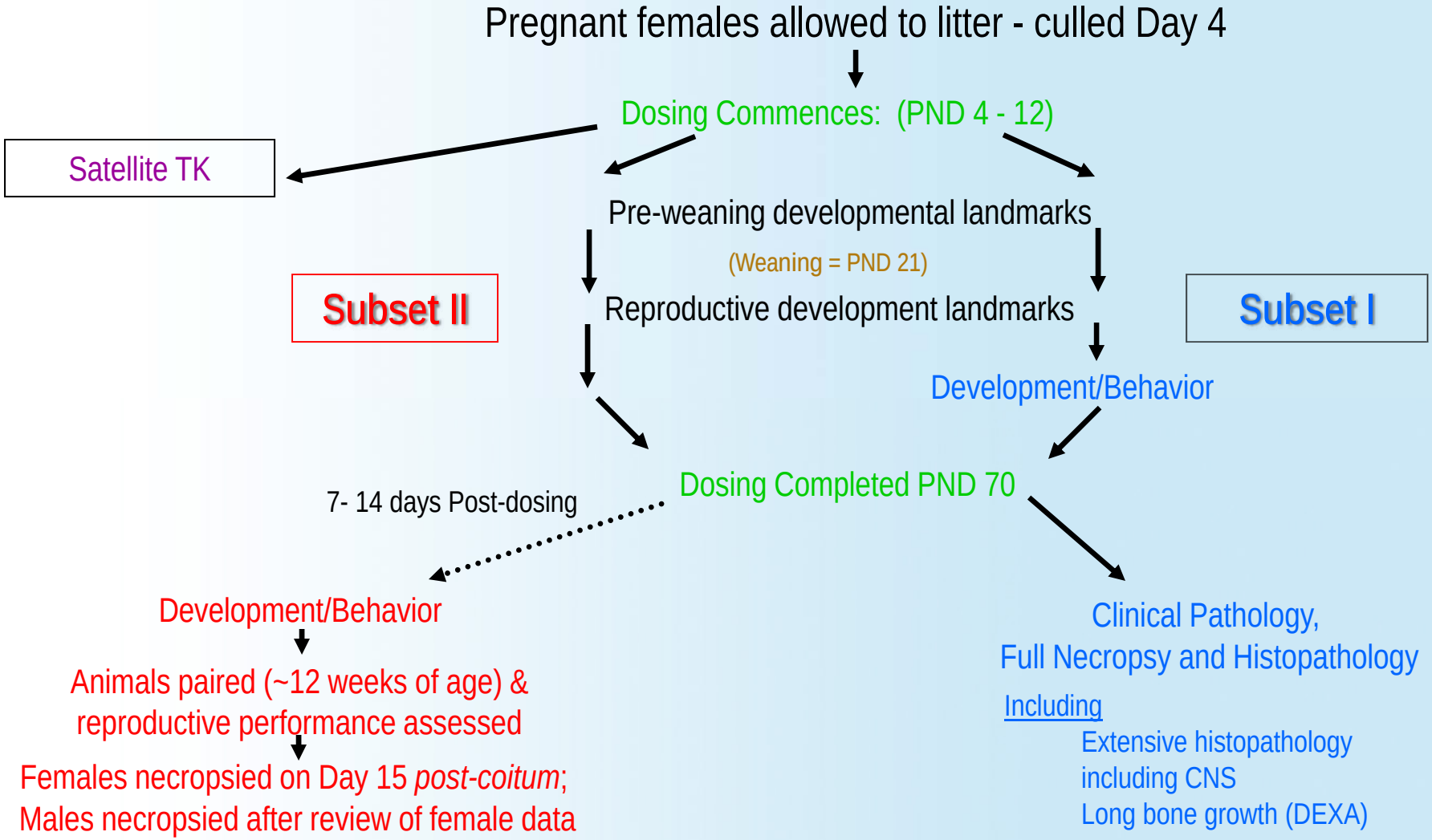
Rat organ system development
(*Rat age - days post partum*)

Brain	10
Kidney	?(anatomical at 5 - 7,*functional at 13-15*)
Liver	? (metabolic capabilities)
Lungs	14 Days (anatomical)
Reproductive	Puberty at 32 and 48 days (F+M)
Immune	'competence' 0 to 30 days (memory 30 - 60 days)
Skeletal	?(epiphyseal closure 15-17 weeks)
Cardiovascular	? (day 3 equals 3 weeks human)

Structural and functional development of human systems

Nervous system:	up to adulthood.
Pulmonary system:	up to 2 yrs.
Reproductive system:	up to adulthood.
Renal system:	up to 1 yr of age.
GI system:	up to 1 to 2 yrs.
Immune system:	up to 2 to 4 yrs.
Liver:	depending on the endpoint differences in functioning of drug-metabolising enzymes, transporters, etc. during the first months - years

Typical Pre-weaning Juvenile Toxicity Study Design



Study Metrics

- Typically 3 treatment groups + 1 Control.
- Group size:
  - Subset I - 12 males and 12 females / group.
  - Subset II - 20 males and 20 females / group.
  - TK Satellites - typically 12 males and 12 females / group.
  - TOTAL – approximately 350 animals not including the original parental females.
- Duration:
  - In-life approximately 20 weeks.
  - Reporting 12-20 weeks (*depending on parameters included)*.
- Cost - *One arm and one leg* = 200-300k (*depending on parameters included.*)

Duration of Treatment

- To cover the stages for planned human use
- To link up with the age at which general toxicity studies performed
- Will treatment be continuous throughout life ?
- Will a recovery period be necessary ?