EMA EFPIA Workshop
Breakout Session No. 3

Case Study Title: Evaluation of Fixed Dose Combinations in Paediatric Indications - Use of Pharmacokinetic Bridging

DISCUSSION

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The CASE – Clinical Importance?

1. Importance of fixed dose combinations?
   - Yes, often used against bacterial, viral, protozoal infections (e.g., Proguanil/Atovaquone; Sulfamethoxazole/Trimethoprim)
2. Importance of ethnicity?
   - Yes, infectious disease is <u>global</u>
3. Importance of children?
   - Yes, infectious disease is <u>paediatric</u>

The CASE – Relevance of PK?

Yes, the concentration/effect relationship (pharmacodynamics) of the two compounds is the same in adults and children, as well as across different ethnicities

The CASE
Bridging From Adults to Children?

Knowledge of drugs

- **Limited knowledge of the mechanisms**

No, because “bridging” from adults to children without key knowledge of PK concerning developmental pharmacology and ethnicity might fail!
→Generate data within the paediatric population, especially younger ages

The CASE - Limitations

1. Limitations of the case

- Limited number of patients (Asians)
- Failure to hit a relevant population

  (< 2 years of age in Asians,

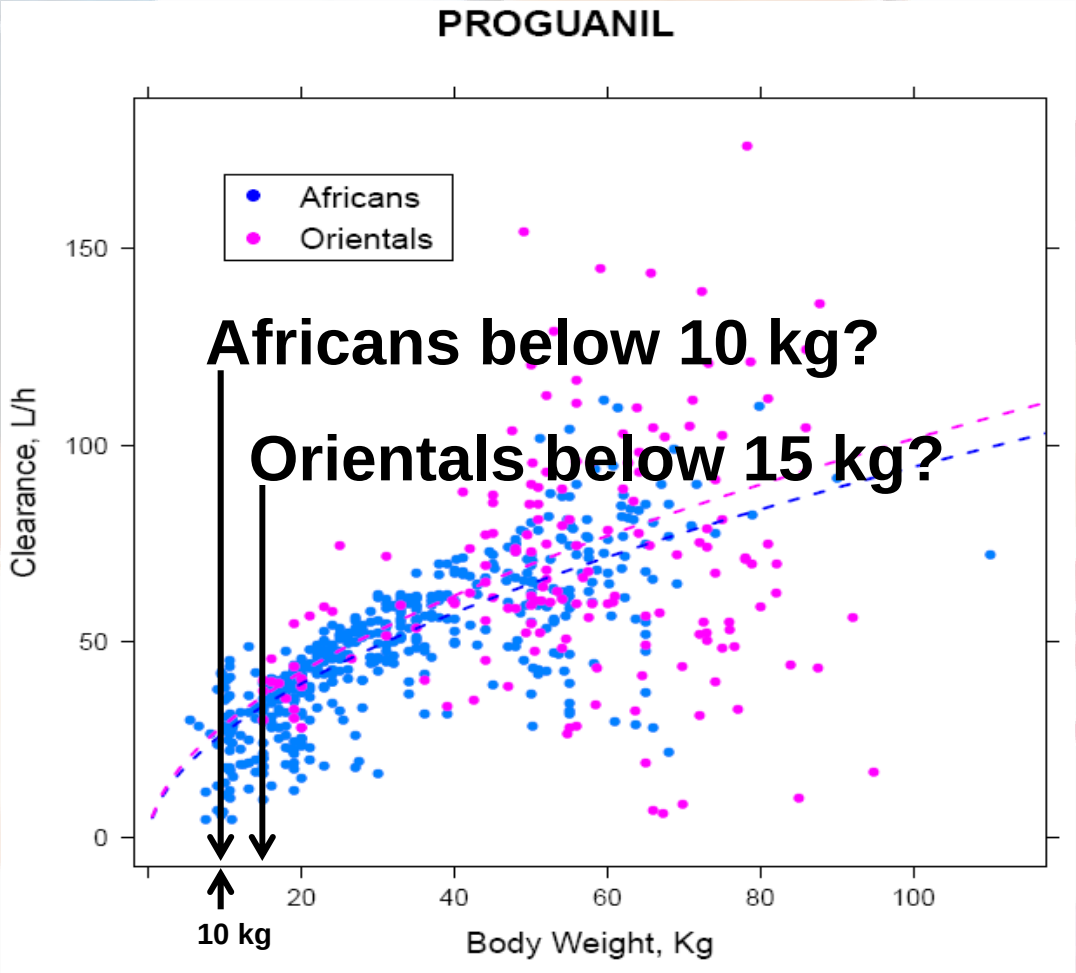
  < 1 year of age in Africans)

The CASE – Limitations

Generated data (Proguanil)	Children (mean/range)	Adults (mean/range)
Afri	402	105
	41	146
	10	46
	26.8 (5.4-68)	62.5 (39-110)
	9.0 (0.3-17)	40.5 (15-79)
	225/222	207/72
ct	1.9 (1-13)	6 (1-19)

What is the age distribution in each subgroup, especially the number of patients who are below 2 and 1 years of age?

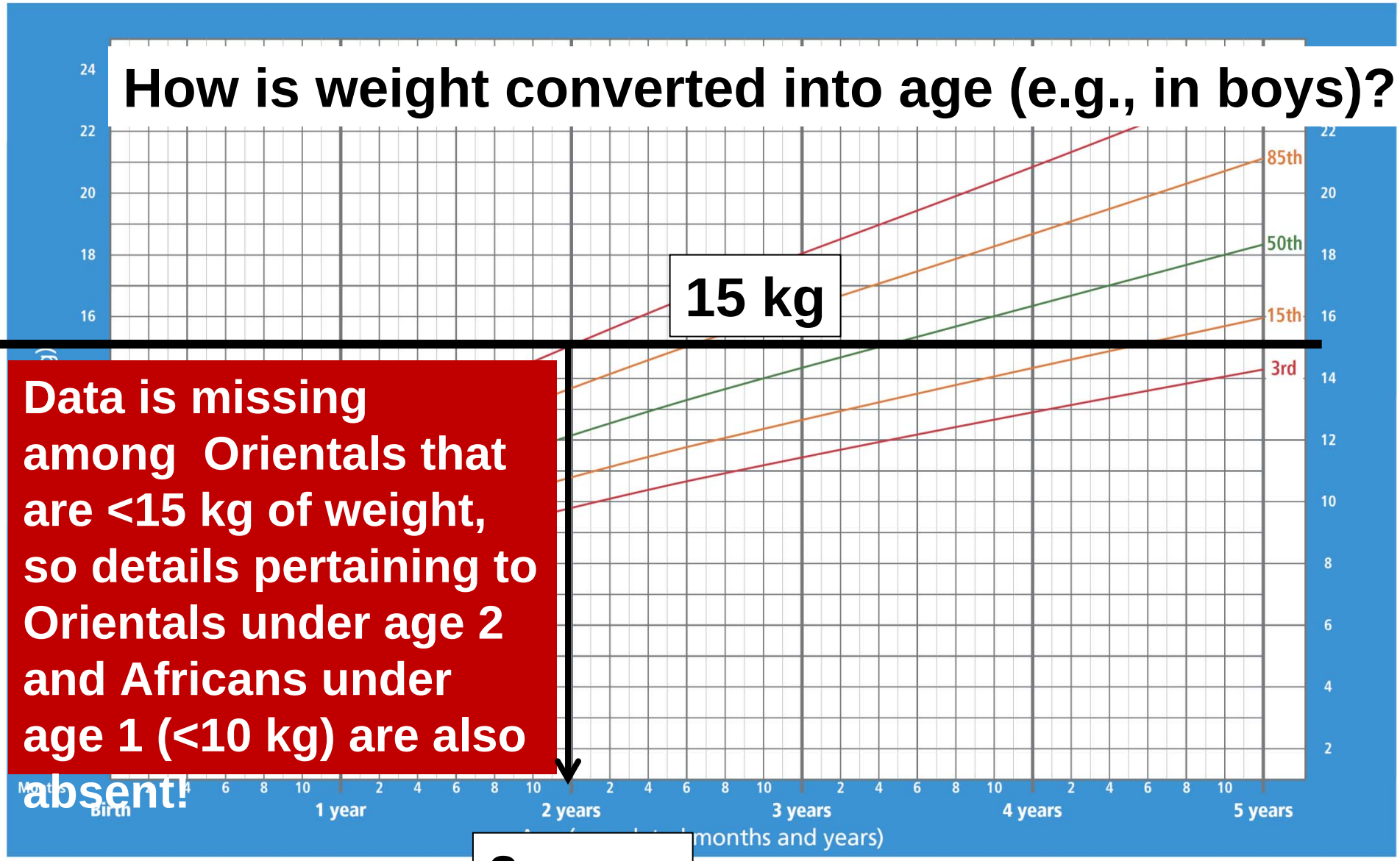
The CASE – Limitations



Weight-for-age BOYS

Birth to 5 years (percentiles)

World Health Organization



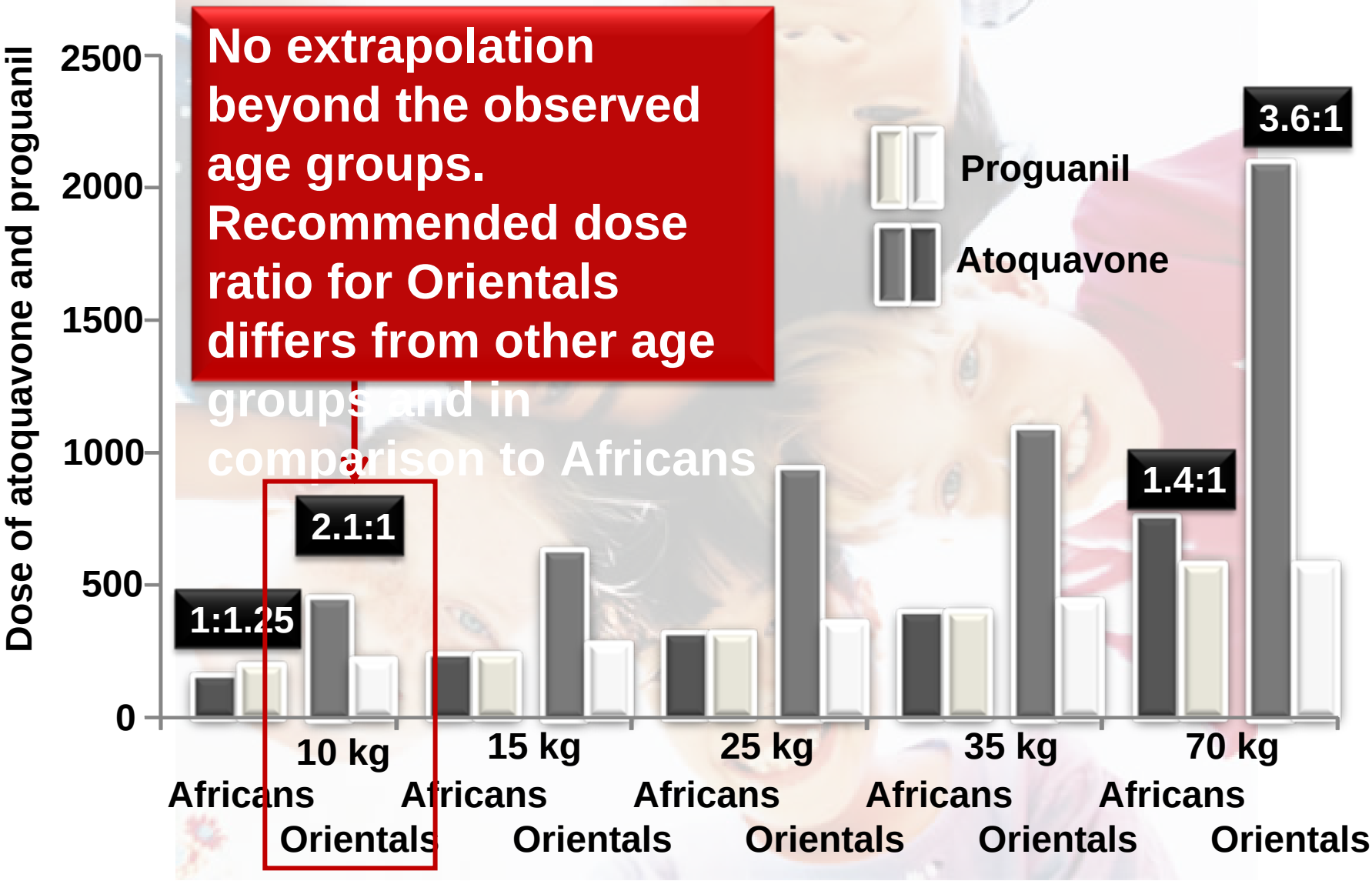
WHO Child Growth Standards

The CASE – Expected Standards

2. Expected standards when using particular modeling approach

- Transparancy regarding the included age group
- No extrapolations beyond the observed age groups

The CASE – Expected Standards



The CASE – Further Scientific Worl

3. Additional research is needed

- Standardize modelling and simulation analyses to build a platform for the aggregation of knowledge that serves the paediatric populatio
- Collaboration with PDCO is warranted

The CASE – Further Scientific Work

¾ Allometry alone
explains 67% of CL variability

¾ Allometry + maturation
explains 80% of CL variability

1. Do not skip the specificities and differences of the younger age subsets in which allometric extrapolation does not work (avoid oversimplification).
2. Standardize modelling and simulation analyses to build a platform for the aggregation of data that serves the paediatric population!

*CL = CL(std) x F(size:allometry) x F(maturation) x F(o

*Tod M, Jullien V, Pons G. Clin Pharmacokinet 2008; 47: 231–243.

Anderson B, Holford N Ped Anesth 2011;21:222–237