# Voriconazole Paediatric Dose: an Example

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Global Pharmacometrics

# Outline of Presentation

- Current voriconazole (Vfend®) adult dosing
- Derivation of paediatric doses
  - data gathered
  - analyses performed
  - interpretations drawn
  - mechanistic implications
- Current voriconazole (Vfend®) paediatric dosing within EU

# Vfend® Adult Labelling

- Adult dosing for invasive aspergillosis
  - 6 mg/kg IV q12h for first 24h as loading dose
  - 4 mg/kg IV q12h as maintenance dose
  - 200 mg PO q12h as maintenance dose
- Adult dosing for candidemia
  - 6 mg/kg IV q12h for first 24h as loading dose
  - 3-4 mg/kg IV q12h as maintenance dose
  - 200 mg PO q12h as maintenance dose
- PO maintenance dosage adjustment possible to 300 or 100 mg q12h
- Voriconazole (Vfend®) is a valuable but complex and challenging compound, from a PK perspective



# Pfizer Paediatric Model Derived Dosing Approach

| **Adult data analysis** | **Ped. data analysis** |
| --- | --- |
| N=11 P1 studies<br>N=236 subjects<br>N=2313 samples<br>Completed in 2000 | N=2 studies<br>N=35 subjects<br>N=355 samples<br>Completed in 2001 |
| **Non linear PK**<br>Intrinsic PK for label<br>CYP2C19 (most influential), gender and age important<br>High Bioavailability<br>Japan bridging | **Linear PK**<br>Intrinsic PK for label<br>Comparable dose to adult 3 mg/kg<br>CYP2C19 (most influential), liver enz. weight important |

# (Predicted) PK Exposures in Paediatrics and Adults

1.33 fold dose inc.

| Medians | 3mg/kg | | 4mg/kg | |
|---|---|---|---|---|
| | *Paed. | **Adults | *Paed. | **Adults |
| $C_{ave}$ (ng/ml) | 889 | 1155 | 1186 | 3217 |
| AUCτ (ng·h /ml) | 10, 670 | 13, 855 | 14, 227 | 38, 605 |

1.33 fold  2.78 fold

*** model based analysis of 35 subjects from SD and MD PK studies**
**** model based analysis of 236 healthy volunteers from SD and MD PK studies**

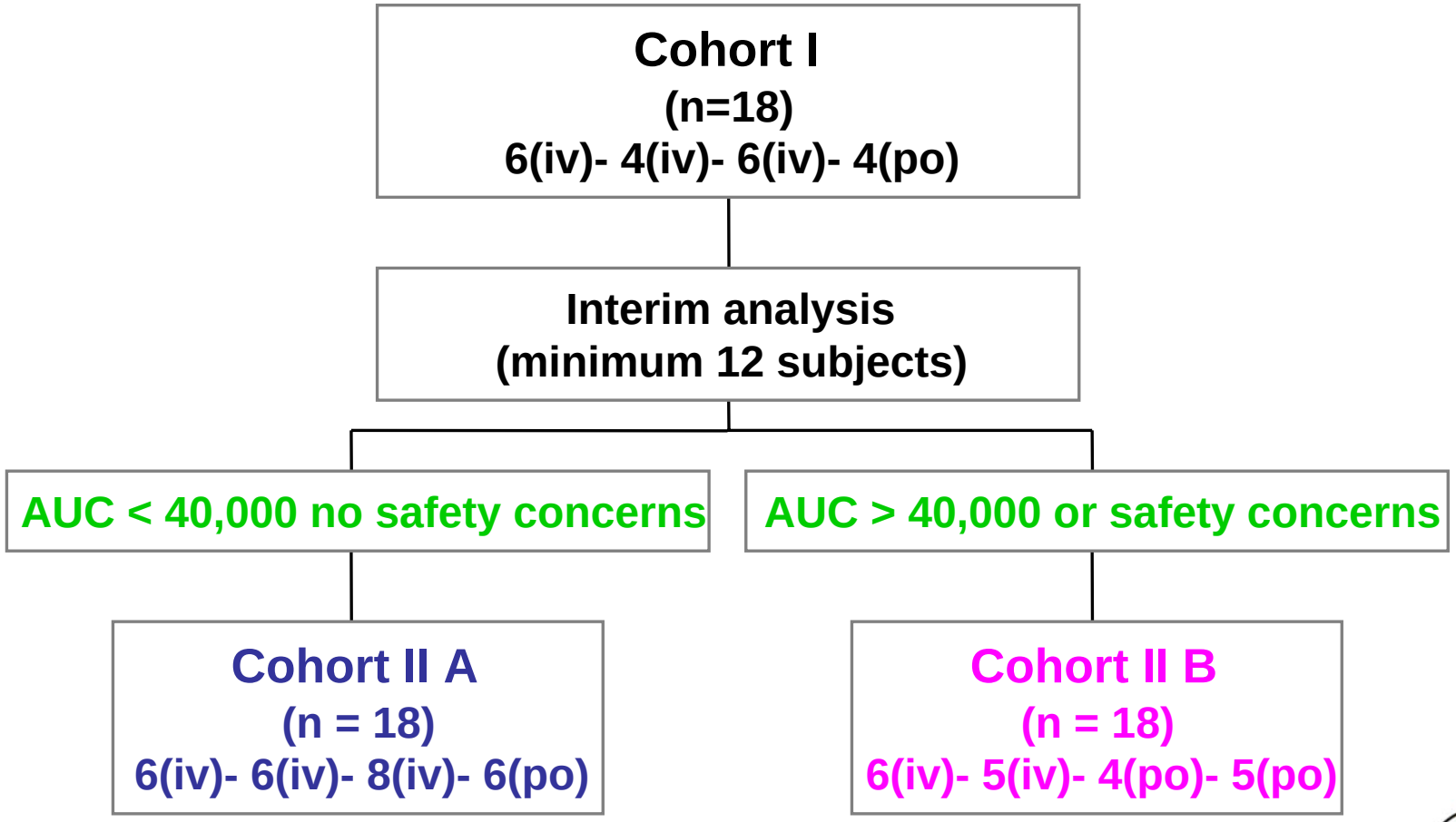
# Some Pharmacokinetic Principles

- Intravenous

$$CL = \frac{Dose}{AUC}$$

CL = clearance, F = bioavailability, AUC = area under the curve

# Dosing Strategy for Subsequent Paediatric Study



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# Model predicted voriconazole AUCtau given nominal dosing schedules (n=47)

| Median AUCtau (ng·h/ml) | | |
|---|---|---|
| Cohort I<br><br>(6, 4, 6, 4)* | Cohort IIA<br><br>(6, 6, 8, 6)* | Cohort IIB<br><br>(6, 5, 4, 5)* |
| 13410 | 24730 | 18060 |
| 24710 | 38540 | 5710 |
| 5710 | 9090 | 7350 |

*Denotes the mg/kg q12h doses Day 1 (iv), days 2-4 (iv), days 5-8 (iv/po) and days 8-12 (po)

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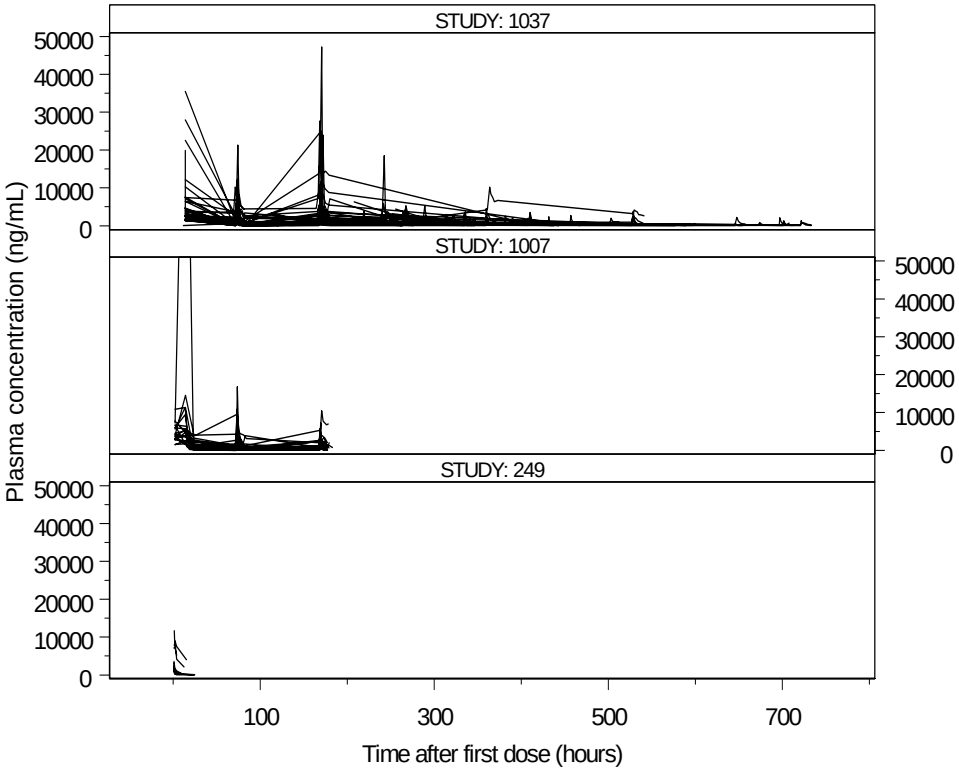
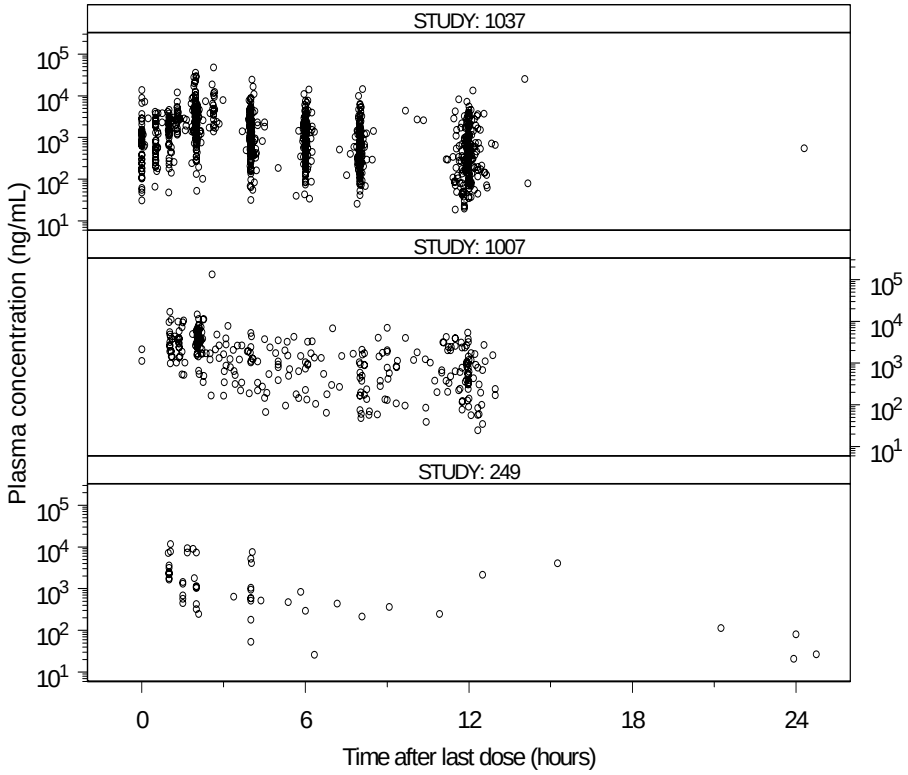
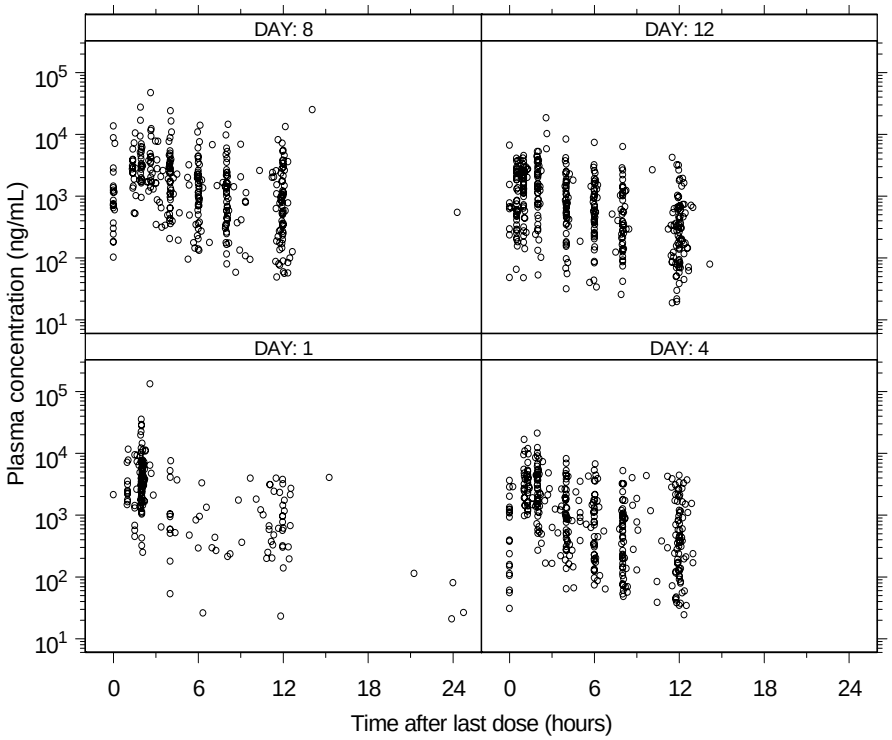
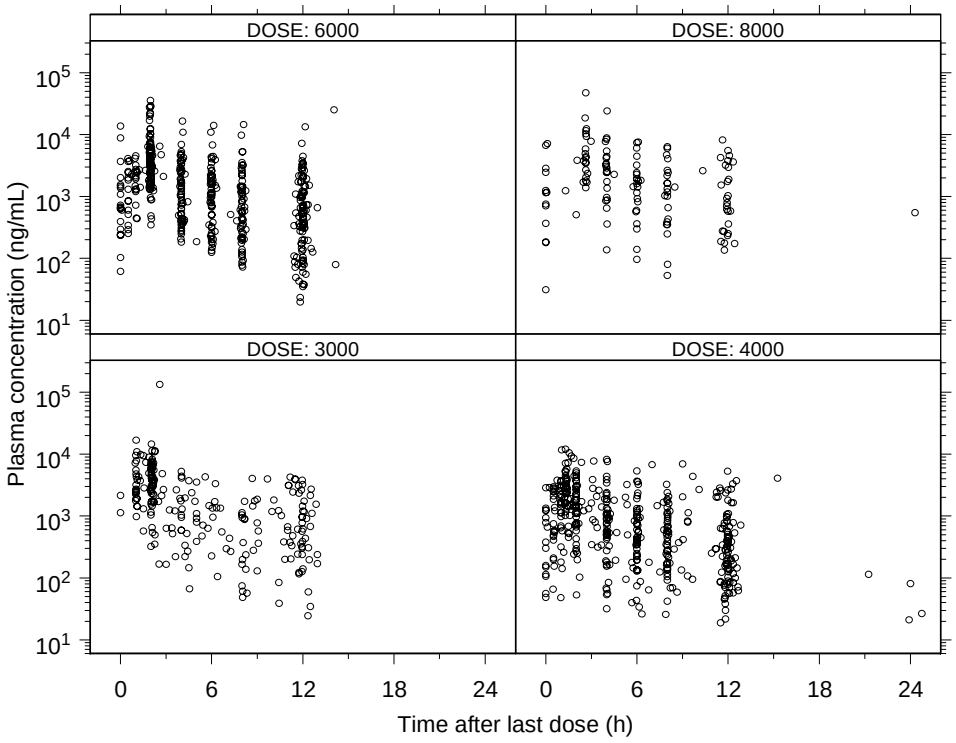
# Analysis Concentration Data (1)



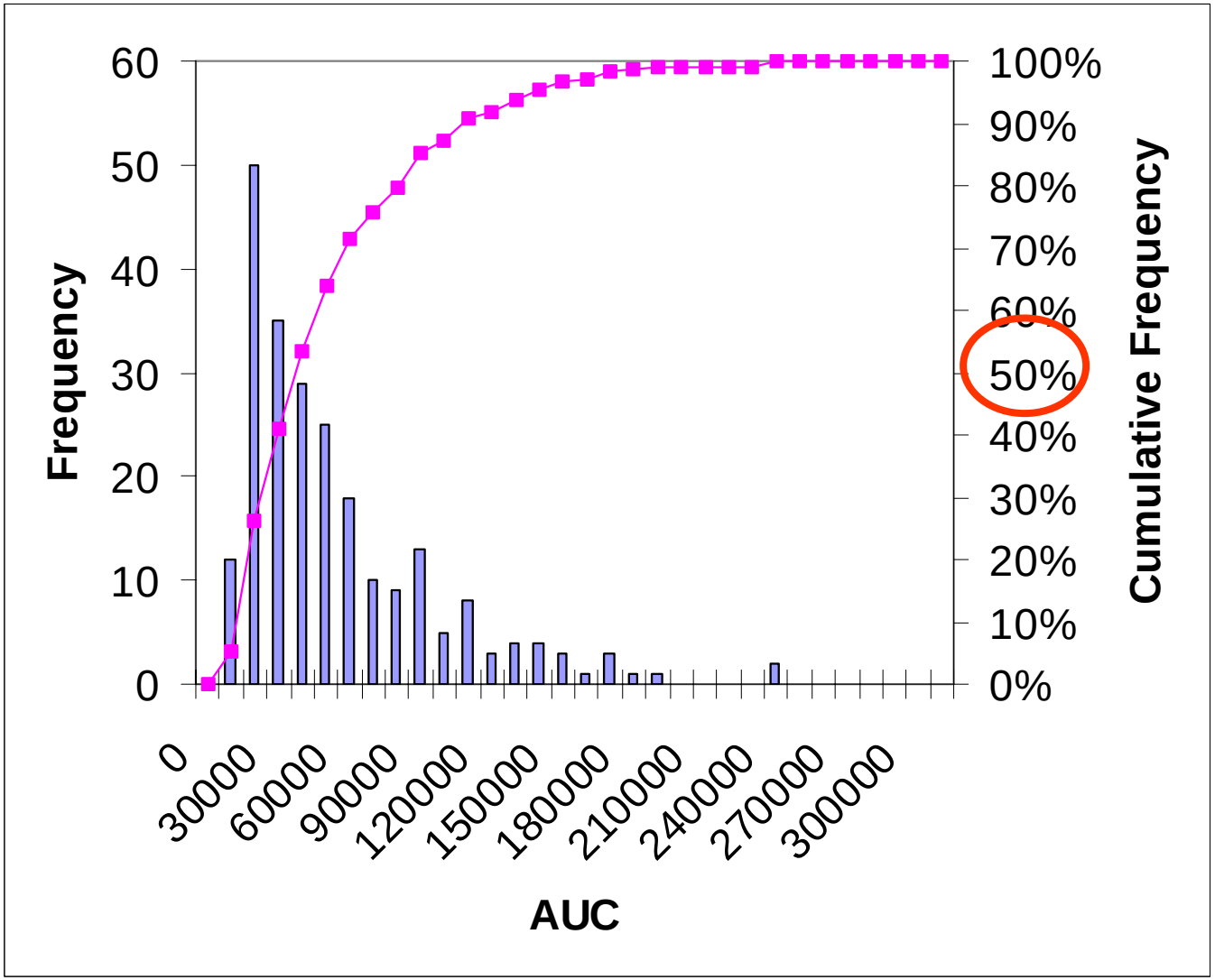



# Analysis Concentration Data (2)



# Adult Reference Distribution – Different Criterion Required?

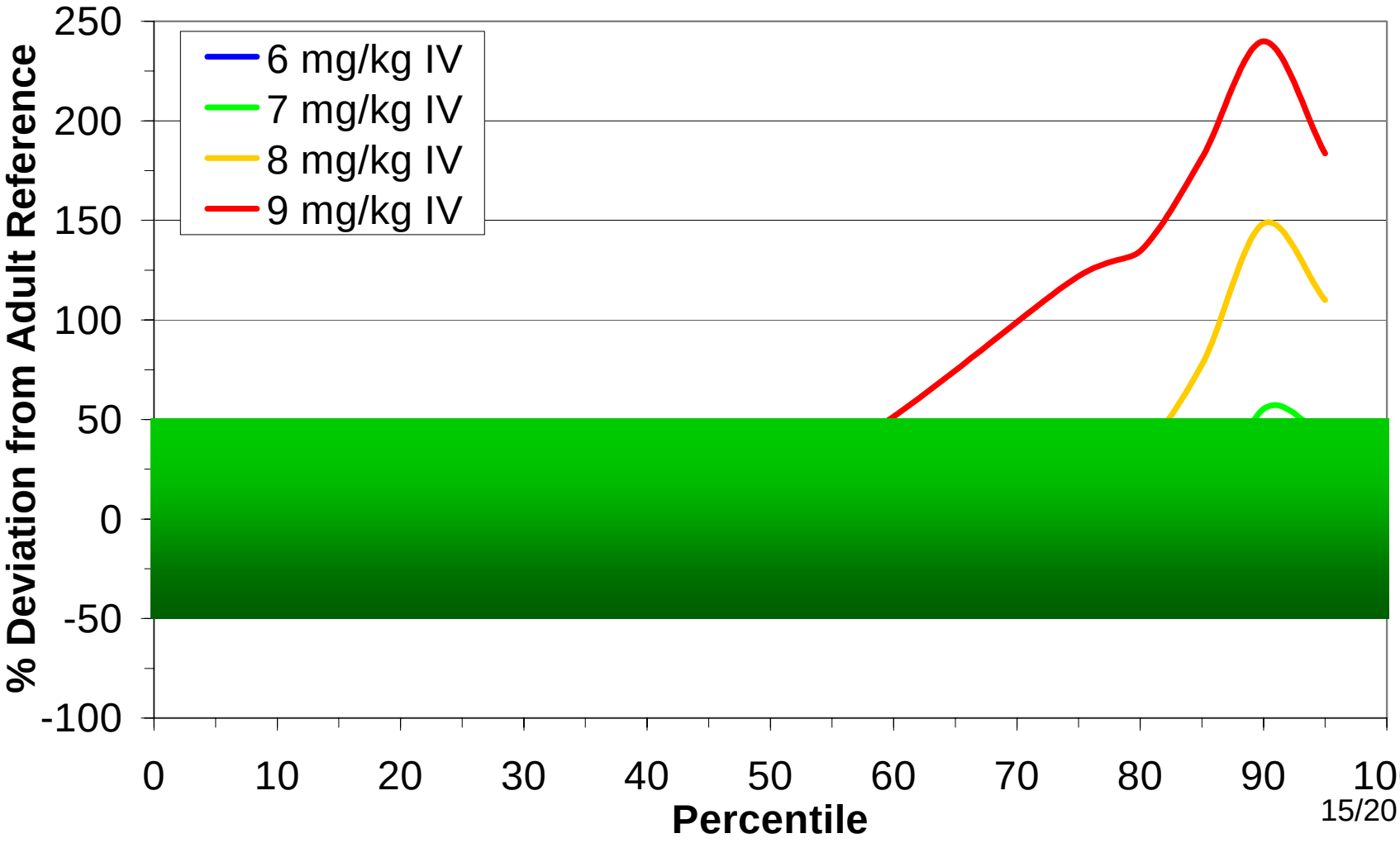


# Criteria Adopted to Assess Dosing Recommendations

- In broadening criteria from median to the entire distribution the dosing recommendations had to balance the following:
  - maintaining concordance with ICH guidelines which seeks comparable AUC in children and adults at the central tendency (median)
  - ***but*** not over or under exposing individuals at other points of the distribution relative to adults
  - ***recognizing*** differing degree of confidence in the predictions of medians compared to tails
- What can be defined as “over” or “under” exposure in this case?
  - sought consistency with the adult label
    - largest magnitude of a change in AUC resulting from co-administration of another compound that ***did not*** warrant a dosage alteration ***41%***
    - smallest magnitude of a change in AUC resulting from co-administration of another compound that ***did*** warrant a subsequent dosage alteration ***70%***
  - led to a “single point” criteria of ***50%*** used to evaluate effects upon AUC distribution
- In the reference adults (n=236) 4 mg/kg IV bid has CV 83% n AUC
  - achieving concordance for across percentiles of the entire paediatric AUC distribution is very challenging



# 7 mg/kg IV provides acceptable concordance



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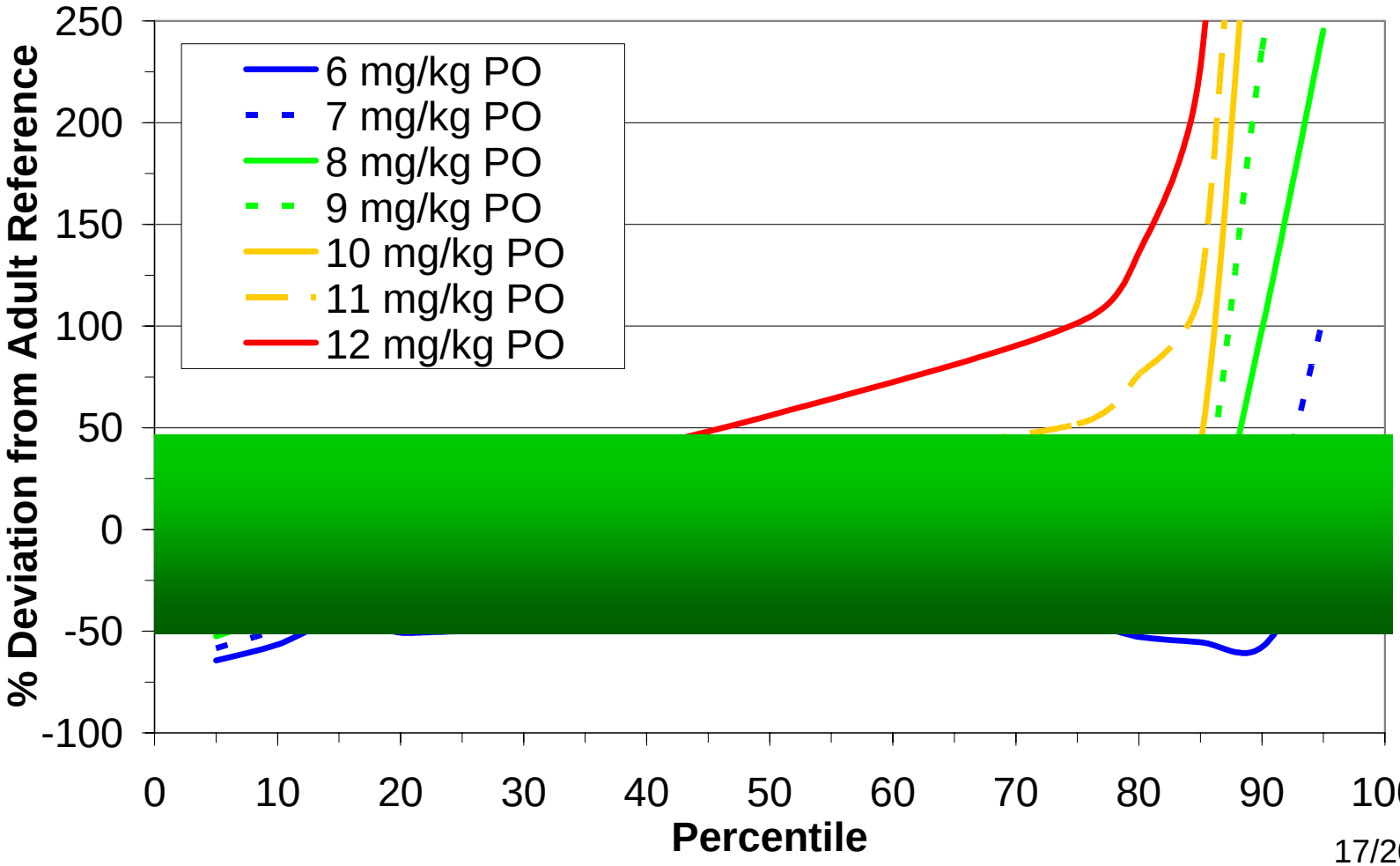
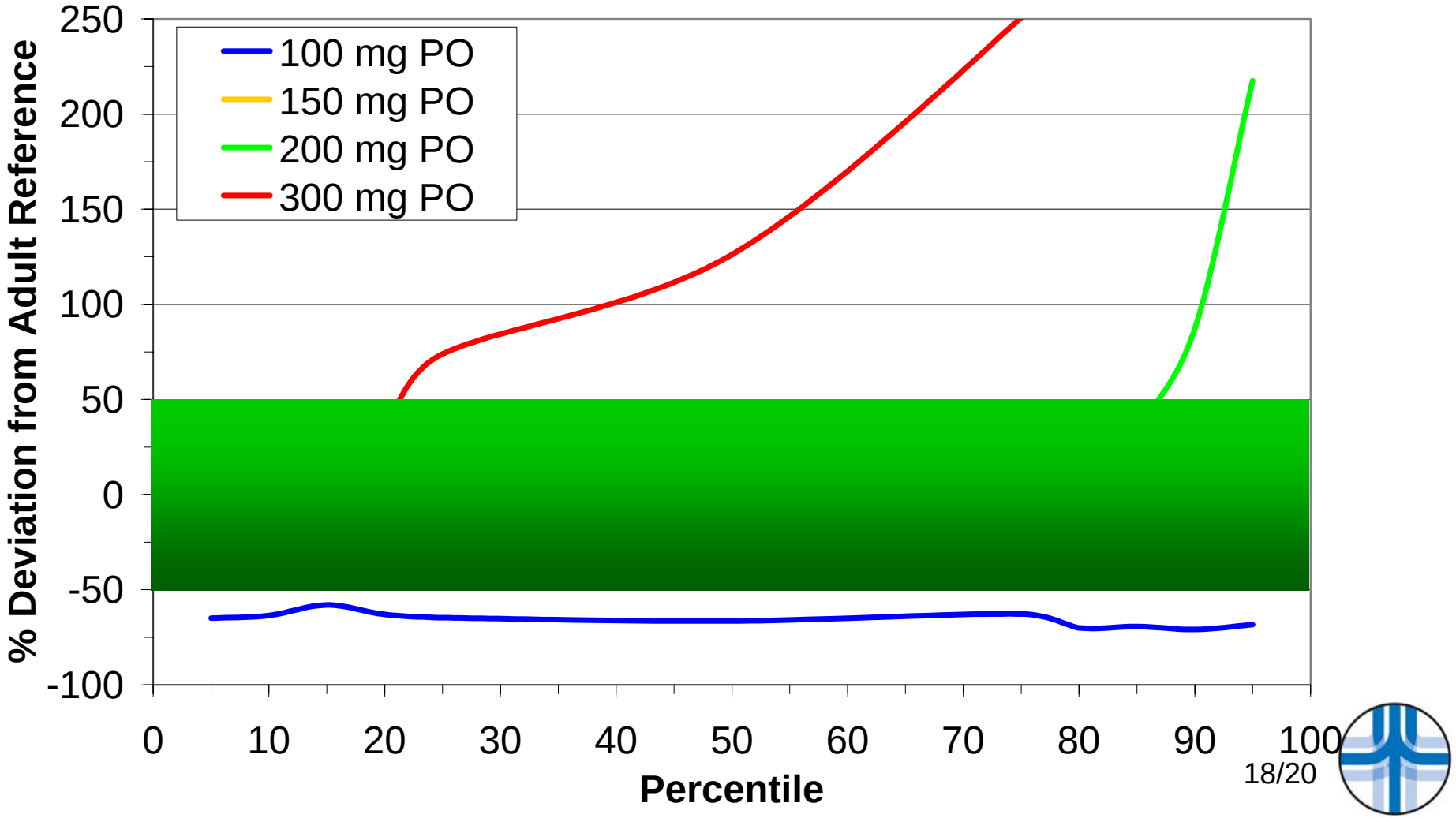
# Oral mg/kg does not provide acceptable concordance



# Fixed mg does provide acceptable concordance



# Oral dose Justification

- An age/weight interaction on bioavailability exists
- Some potential explanations why such an effect may be most pronounced in children, but not adults:
  - Children have a higher Km than adults
    - less saturation of metabolism at similar concentrations compared to adults
  - The hepatic blood flow (per kg bodyweight) is higher in children than in adults
    - for the same mg/kg oral dose, the concentration entering the liver from the absorption site will be lower in children
- 200mg bid oral dosage applicable across the entire weight range
  - For higher body weight subjects, with high bioavailability (consistent with adults), an oral dose of 200mg bid is equivalent to adults
  - For lower body weights subjects, with low bioavailability (inconsistent with adults), the 200mg bid dose provides a higher “effective mg/kg dose” compensating for the low bioavailability in these individuals



# Vfend® Paediatric Dosing Recommendations

- From previous analysis of voriconazole paediatric data 4mg/kg q12h IV comparable to 3mg/kg q12h IV in adults
  - Higher IV maintenance dose due to higher elimination capacity in paediatric patients (greater liver mass to body mass ratio)
- 7mg/kg q12h IV comparable to 4mg/kg q12h IV in adults
  - Larger dose differential due to different degree of non-linearity in voriconazole pharmacokinetics
- 200mg q12 h PO comparable to 200mg q12 h PO in adults
  - For oral administration in paediatrics, an additional consideration (lower oral bioavailability)