

UNLOCKING DIVERSITY: Towards a Comprehensive Framework for Physiologically Based Pharmacokinetic Population Qualification in Sub-Saharan Africa

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1. Introduction

Physiologically based pharmacokinetic (PBPK) models play a crucial role in simulation software for representing diverse populations. However, the categorization of individuals into distinct populations raises important hypotheses regarding the criteria employed in this classification. What guidelines/regulations are provided by the European Medicines Agency (EMA) and Food and Drug Administration (FDA)? This study investigates the diversity of CYP450 phenotypes across African countries, aiming to assess the feasibility of considering Sub-Saharan Africa (SSA), and even subregions thereof, as a single population.

2. Characterization of a population

Guidelines of the EMA and FDA provided following information: in the qualification of populations within PBPK models, the process involves the establishment of system-dependent parameters, followed by the prospective prediction of PK parameters within the target population for verification.

4. Prediction and comparison of PK parameters across SSA

Table 2: Example of PK parameters in African populations from specific regions (SSA, Central, East, South and West) using efavirenz, a probe substrate for CYP2B6 and the 90% confidence intervals.

	PK parameters	Geometric mean	Confidence Interval	
SUB-SAHARAN AFRICA	C _{Max} (mg/L)	6.24	6.05	6.43
	T _{Max} (h)	3.20	3.19	3.22
	AUC (mg/L.h)	110	107	114
	C _{Min} (mg/L)	3.44	3.30	3.58
	CL (L/h)	5.44	5.26	5.61
CENTRAL	C _{Max} (mg/L)	5.64	5.48	5.80
	T _{Max} (h)	3.16	3.14	3.18
	AUC (mg/L.h)	96.6	93.7	99.6
	C _{Min} (mg/L)	2.90	2.78	3.02
	CL (L/h)	6.21	6.02	6.41
EAST	C _{Max} (mg/L)	5.59	5.44	5.75
	T _{Max} (h)	3.16	3.14	3.18
	AUC (mg/L.h)	95.6	92.8	98.6
	C _{Min} (mg/L)	2.87	2.76	2.99
	CL (L/h)	6.27	6.09	6.47
SOUTH	C _{Max} (mg/L)	6.29	6.10	6.47
	T _{Max} (h)	3.20	3.18	3.22
	AUC (mg/L.h)	111	108	115
	C _{Min} (mg/L)	3.45	3.31	3.59
	CL (L/h)	5.40	5.23	5.58
WEST	C _{Max} (mg/L)	5.91	5.74	6.09
	T _{Max} (h)	3.17	3.16	3.19
	AUC (mg/L.h)	102	99.2	106
	C _{Min} (mg/L)	3.11	2.98	3.24
	CL (L/h)	5.86	5.68	6.05

3. CYP450 activity phenotype data

Table 1: Phenotype relative frequency data for CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A5 across five regions in Africa (Sub-Saharan Africa, Central, East, South and West) obtained from literature.

	SSA		Central		East		South		West	
	PM	EM	PM	EM	PM	EM	PM	EM	PM	EM
CYP2B6	0.44	0.56	0.15	0.85	0.14	0.86	0.46	0.54	0.23	0.77
CYP2C9	0.14	0.86	0.02	0.98	0.04	0.96	0.15	0.85	0.02	0.98
CYP2C19	0.12	0.88	0.04	0.96	0.18	0.82	0.12	0.88	0.05	0.95
CYP2D6	0.26	0.74	0.05	0.95	0.27	0.73	0.30	0.70	0.03	0.97
CYP3A5	0.27	0.73	0.18	0.82	0.18	0.82	0.73	0.27	0.18	0.82

5. Statistical significance between the regions

A pairwise proportion test, corrected for multiple testing with a Bonferroni correction, was performed on the frequency data per CYP450 enzyme between the five regions (SSA, Central, East, South and West Africa) using R studio. The statistical testing revealed significant differences for CYP2B6 between SSA and West ($p = 7.2e^{-11}$), SSA and East ($p < 2e^{-16}$), West and East ($p = 0.0061$), West and South ($p = 6.9e^{-11}$) and South and East ($p < 2e^{-16}$). For CYP2C19 there was a statistical difference between West and East ($p = 0.0075$). For CYP2D6 a statistical difference was observed for SSA and Central ($p = 5.7e^{-5}$), East and Central ($p = 9.1e^{-5}$) and for South and Central ($p = 2.8e^{-6}$). For CYP2C9 and CYP3A5, no significant differences were observed.

6. Conclusion

PBPK population development is not regulated, only guided by the EMA and FDA. Phenotype data on CYP450 enzymes can be collected for subregions within an already existing population. Statistical analysis can be performed to check for significant differences. Numerous studies have substantiated the presence of inter-ethnic diversity within SSA. This study justifies the subdivision of SSA into Central, East, South and West Africa. Ideally, subpopulations are verified using available *in vivo* data. Further research is imperative to investigate if further subdivisions in these regions should be considered.