

BOS3 Regulatory Discussant Case 1

Terry Shepard MHRA



Topic 1



Impact of the M&S exercise on benefit-risk decision and level of regulatory scrutiny?



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Use of literature models

If literature models are used for high impact regulatory decisions, then it is important to provide a critical assessment, justification and appropriate documentation

Topic 3



What do PBPK models offer for extrapolation of PK across populations?



How do populations vary?



How do populations vary? Children versus adults.



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The degree of complexity of the PBPK model can vary according to the need.



What do PBPK models offer for extrapolation of PK across populations?

Particularly useful where ethics/practicalities limit the availability of data (make best use of every datum).

Sparse data on drug is made more useful by "borrowing" information from biology and other drugs.

Predict variability in PK beyond observed limits and to anticipate individuals whose attributes combine to give extreme PK risk.



What do PBPK models offer for extrapolation of PK across populations?

Complementary to other approaches:

Identification of covariates for incorporation into POPPK modelling.

Tool for quantifying impact of ADME assumptions (sensitivity analysis).

Assumption	Probability to violate	Consequence
PKproperties	Definitely Likely Unlikely Improbable	Minor Major Unknown





Many factors are highly correlated (e.g. age, disease, polypharmacy). Often too complex to predict intuitively or empirically. Need a mechanistic model.



What do PBPK models offer for extrapolation of PK across populations?

Provides an opportunity to learn about drug or system.

Predict/learn/confirm cycle adds confidence to regulatory decisions based on small populations.