Uncertainty quantification

EMA workshop on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and simulation

Session III

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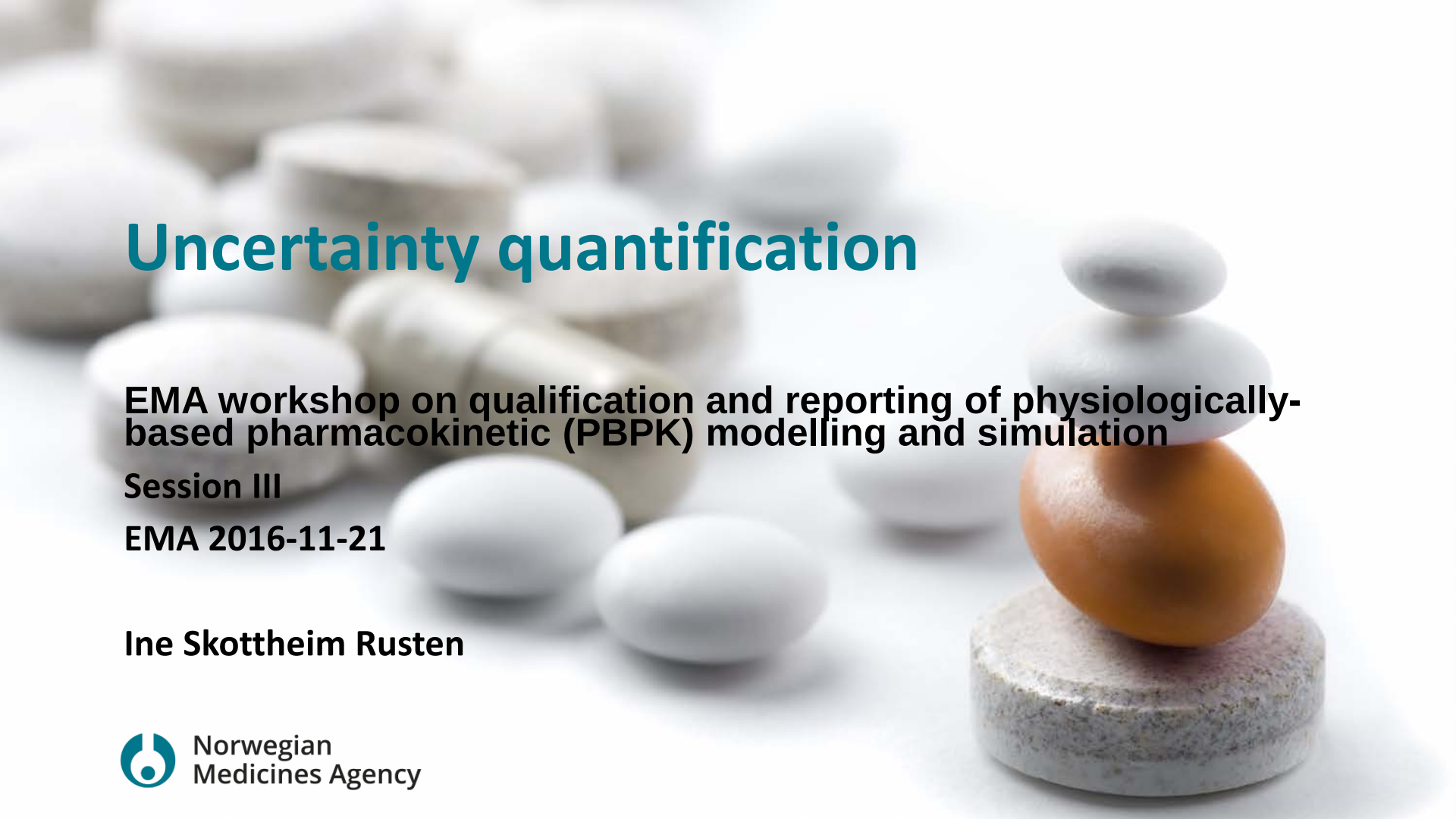

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Uncertainty quantification

How do the various sources of uncertainty

feed into uncertainty in the model prediction for the outcome(s) of interest?

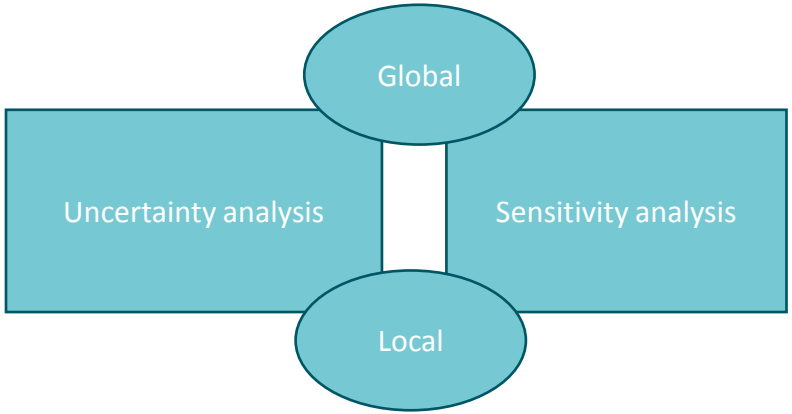
Alleatory

- variability, stochastic uncertainty or irreducible uncertainty
- the physical variability present in the system being analysed or its environment
- normally characterized using probabilistic approaches

Epistemic

- reducible uncertainty
- potential deficiency due to lack of knowledge, can arise from inputs, assumptions, approximations etc
- not necessarily well characterized by probabilistic approaches

Aims and approaches



When to perform?

- Based on suspicion – ie lack of fit?
- Depending on the purpose of use and the regulatory impact?
- As standard?

- Explore the model properties
- Explore the appropriateness of the model

- How much do the outcome(s) of interest depend on a spesific parameter or submodel?
- How much do the outcome(s) of interest vary according to uncertainty in the parameters, assumptions or other model aspects?

Uncertainty analysis

Scenario analysis to identify sources of uncertainty

The need depends on the purpose of use and the regulatory impact

- relevant for consideration
  - parameters
  - assumptions
  - model structures; ie processes and associated mathematical choices
  - computational methods, approximations

- define the perceived boundaries
  - of parameters
  - or alternative setups (processes/mathematical and computational choices)

Case example I - drug model

Ibrutinib is an anticancer drug, CYP3A4 substrate (minimal 2D6)

Model: PBPK

Purpose of use: information in SmPC on CYP3A strong, medium and mild inhibition

Regulatory impact: high

Qualification: within procedure

UQ: regulatory request for local sensitivity analysis based on fitting characteristics for absorption phase

- absorption parameters
- fugut

Sensitivity Analysis on the Effect of Ibrutinib fu_{gut} on Simulated AUC and C_{max} of Oral Single Dose of 120 mg Ibrutinib in Healthy Subjects under Fasted Conditions

$F_{u,gut}$	C_{max} (ng/ml)	AUC (ng.h/ml)	Fg
0.07	26.9	87.1	0.55
0.09	24.0	78.4	0.50
0.11	**21.7**	**71.4**	**0.47**
0.13	19.8	66.7	0.41
0.15	18.3	60.9	0.38
0.17	17.0	56.8	0.35

Sensitivity Analysis on the Effect of Ibrutinib fu_{gut} on Simulated C_{max} Ratio and AUC_{ratio} of Ketoconazole-ibrutinib Drug-drug Interaction

$F_{u,gut}$	C_{max} ratio (Substrate)	AUC ratio (Substrate)
0.07	14.9	22.5
0.09	17.1	25.1
0.11	**19.0**	**27.7**
0.13	21.0	30.4
0.15	22.9	33.0
0.17	24.2	35.8

Case example I - drug model

Ibrutinib is an anticancer drug, CYP3A4 substrate (minimal 2D6)

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Table. The effect of reducing the rate of absorption on ibrutinib FG and on the AUC and Cmax ratios obtained upon co-administration with ketoconazole.

	F_G	AUC ratio[a]	Cmax ratio[a]
Observed data	NA	24	29
Original model	0.47	28	19
Scenario 1[b]	0.49	25	19
Scenario 2[c]	0.55	22	17

NA, not applicable; [a]geometric mean ratios; [b]absorption simulated to start in proximal jejunum; [c]absorption simulated to start in ileum.

Case example II – drug model

X is an anticancer drug, CYP3A4 substrate

Model: PBPK

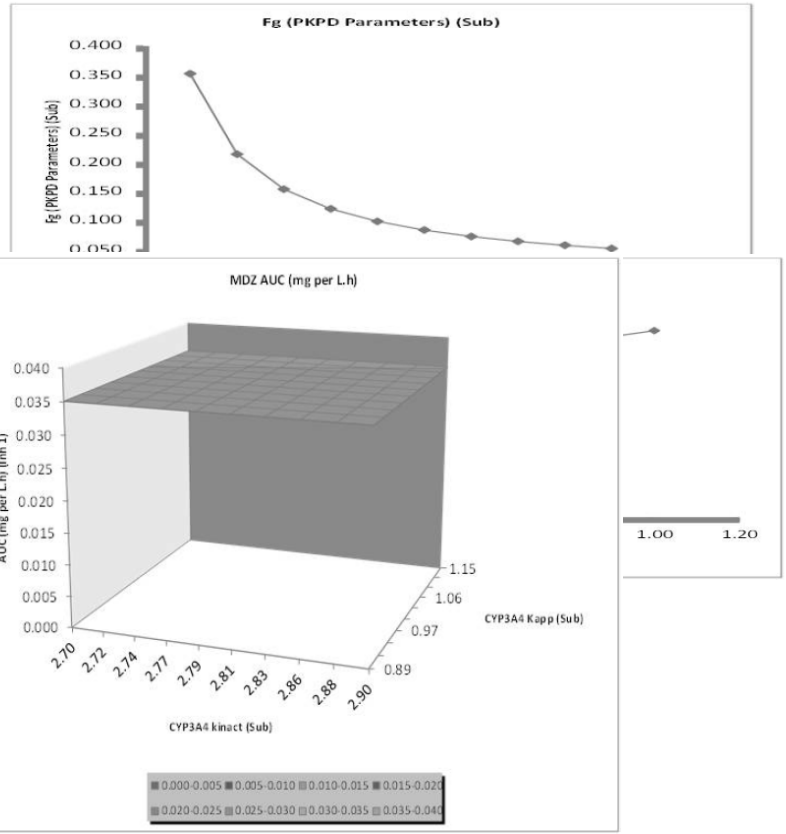
Purpose of use: inform DDI assessment of TDI and mixed inhibition/induction

Regulatory impact: low to moderate

Qualification: within procedure (not considered qualified)

UQ: AUC

- uncertainty analysis
  - rationale not described
- local sensitivity analysis
  - fa, fugut, Qgut on AUC ratio
  - TDI parameters (KI and kinact) and induction parameter EC50 on AUC ratio



Case example III - system model

X is …, Y substrate

Model: PBPK

Purpose of use: inform paediatric dose selection

Regulatory impact: moderate to high

Qualification: within procedure

UQ: for the outcome(s) of interest

- uncertainty analysis
- global sensitivity analysis

Wish list for the uncertainty analysis

- sensitive parameters
- fraction metabolized
- maturation functions
- virtual patient population parameters
- other relevant assumptions
- …

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