Uncertainty quantification for complex models supporting regulatory decision making

First published: 21/08/2025

Last updated: 21/10/2026

Study Finalised

Administrative details

EU PAS number

EUPAS1000000717

Study ID

1000000717

DARWIN EU® study

No

Study countries

Austria

Germany

Sweden

Study description

Model-informed drug development (MIDD) plays a crucial role in drug development, and evaluation by regulatory agencies. A key component of MIDD is the use of complex mechanistic models, built on an understanding of physiology, drug characteristics, and pharmacology, to make extrapolations. However, these models often result in inadequate assessment of uncertainty due to their complexity and the sources of parameters.

This study aims to enhance drug development and regulatory decision-making by improving uncertainty quantification (UQ) methods for complex models.

The primary objectives are to assess existing UQ methods, conduct simulation studies to evaluate these methods, and develop a toolkit and tutorial for applying the best methods.

The methodology involves a comprehensive literature review to identify and summarize UQ methods, followed by simulation studies to test selected methods on use-cases such as drug-drug interactions and pediatric dosing.

The project will culminate in the development of user-friendly tools and tutorials for implementing UQ methods.

Study status

Finalised

Research institutions and networks

Institutions

Uppsala University

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Medical University of Vienna

Austria

First published: 01/02/2024

Last updated: 26/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility

University Medical Centre Göttingen (UMG)

Germany

First published: 26/11/2025

Last updated: 26/11/2025

Institution | Hospital/Clinic/Other health care facility

Austrian Agency of Health and Food Safety

Contact details

Study institution contact

Andrew Hooker andrew.hooker@uu.se

Study contact

andrew.hooker@uu.se

Primary lead investigator

Andrew Hooker 0000-0002-2676-5912

Primary lead investigator

ORCID number:

0000-0002-2676-5912

Study timelines

Date when funding contract was signed

Actual: 18/04/2025

Study start date

Planned: 15/05/2025

Actual: 15/05/2025

Date of final study report

Planned: 17/10/2026

Actual: 17/10/2026

Sources of funding

- EMA

Study protocol

ROC22_CONFIRMS_Preliminary_Study_Plan.pdf (914.12 KB)

ROC22_CONFIRMS_Deliverable_3.pdf (706.55 KB)

Regulatory

Was the study required by a regulatory body?

Unknown

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study type:

Not applicable

Scope of the study:

Method development or testing

Data collection methods:

Secondary use of data

Study design:

Literature review

Main study objective:

1. To identify and characterize existing UQ methods used in PBPK, QSP, and ML models within the framework of regulatory decision-making in drug development.
2. To explore UQ methodologies from broader disciplines, including statistics, toxicology, engineering, and analytical chemistry, that may be adaptable to these complex modeling approaches.

Study design details

Data analysis plan

Characteristics of articles and proposed methods were described by using descriptive analyses such as line charts and bar charts. The collected categorical variables were summarized by providing absolute and relative frequencies. To enable an overview of the uncertainty quantification methods, model names as they were proposed by the authors were classified into broader classes of models. The main characteristics of these suggested categories are introduced, and examples for the categories were provided. All statistical analyses were performed in R (version 4.5.1).

Summary results

Conclusion and discussion

This review shows a clear gap in the availability of well-established methods for UQ tailored to complex models in drug development and regulatory evaluation, as illustrated in Figure 8. Nonetheless, a diverse range of UQ techniques originating from disciplines such as mathematics and statistics, engineering, analytical chemistry, and toxicology holds substantial potential for application

in this context, as illustrated in Figure 7. Among these, global sensitivity analysis, uncertainty propagation, and Bayesian approaches emerged as the most frequently reported and widely applied methods. The findings underscore the critical importance of adapting adequate UQ methodologies to improve the reliability and robustness of PBPK, QSP, and ML models. By identifying promising
candidate methods from both within and outside drug development, this review lays the groundwork for targeted simulation studies. These next steps will provide a robust evidence base for selecting and refining UQ methods that can meaningfully enhance decision-making in drug development and evaluation.

Documents

Study report

UQ_deliverable2_literature_review_report_final_RWD.pdf (2.37 MB)

ROC22 - EMASA EPAR Review - v1 RWD.pdf (1.45 MB)

ROC22_CONFIRMS_Deliverable_4_FINAL.pdf (2.38 MB)

CONFIRMS_Deliverable4_UU_FINAL.pdf (2.85 MB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data sources (types)

Published literature

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No