Review of regulatory procedures where uncertainty quantification of mechanistic models was of concern – scoping review of EMA Public Assessment Reports and Scientific Advice Procedures

Study Report Version 1.0

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Abstract

Introduction: Modelling and simulation approaches play a crucial role in drug development, supporting decisions such as dose selection, extrapolation between populations, and prediction of clinical outcomes. However, assessment of these models and interpretation of their results depends on the clear quantification and communication of uncertainty. This scoping review aims to systematically identify and map existing methods proposed, suggested, or discussed in regulatory procedures for quantifying uncertainties in modelling approaches employed during drug development.

Objectives: Identify EMA marketing authorization procedures and scientific advice final letters where uncertainty quantification of mechanistic models was of concern in order to identify the specific methods used in a drug development context, identify relevant parameter ranges for future simulation studies, derive representative case studies, and develop an overview of regulatory recommendations.

Eligibility criteria: We included marketing authorization procedures granted and EMA scientific advice final letters issued before June 1st, 2025. Procedures include initial authorizations as well as variations such as extensions of the use of already authorized medicines to other therapeutic areas. We included procedures for which the European Public Assessment Report (EPAR) or the EMA Scientific Advice Final Letter (EMA-SA FAL) discusses uncertainty quantification (UQ) in relation to mechanistic models used to address scientific questions within the drug development programme. The scope of the review was limited to procedures that included a regulatory assessment of at least one mechanistic model (which could be a PBPK or a QSP model) and excluded procedures discussing model uncertainty in relation to e.g. statistical methods for estimation of dose response from dedicated dose-finding studies. Procedures, especially scientific advice

letters, where uncertainty quantification was mentioned by the applicant but not addressed in the regulatory assessment were excluded.

Methods: EPARs available in the database at paediatricdata.eu and EMA-SA FALs available in AGES' in-house regulatory search system were searched for paragraphs matching a predefined list of keywords related to the UQ of mechanistic models. Results were manually screened to exclude unrelated matches. . For the remaining matches, full texts of the corresponding EPARs and EMA-SA FALs were obtained and information items related to UQ for mechanistic models, such as the methods used to quantify uncertainty, model specifications, and parameter estimates relevant for future simulation scenarios, were extracted. Before the final extraction process was finalised, a pilot review of ten procedures was conducted to obtain an overview of the typical level of detail in the provided model and method descriptions and the depth of the relevant regulatory discussion, and to identify common items suitable for systematic extraction.

Results: A total of 357 procedures (70 EPARs and 287 EMA-SA FALs) were identified in the database search and selected for further screening. During screening, 209 procedures were excluded for failing to meet eligibility criteria, resulting in 148 procedures that were selected for further data extraction (32 EPARS and 116 EMA-SA FALs) During data extraction, a further 61 procedures were excluded as eligibility could not be confirmed upon detailed review of the corresponding full-text documents. In the end, information items were extracted from 87 procedures (30 EPARS and 57 EMA-SA FALs) discussing a total of 108 models. The most commonly occurring therapeutic areas (medical speciality) amongst the eligible procedures were oncology and neurology (~35%), and a large proportion of the procedures concerned the development of monoclonal antibodies. However, many therapeutic areas and substance classes were covered by fewer than 2 procedures included for review.

For each procedure, information on any mechanistic model or models with a discussion on UQ meeting the inclusion criteria was extracted. The majority of the extracted models were popPK models, followed by popPK/PD models, and in terms of model specifications 2-compartmental models made up about one third. More than half of the models were primarily used to address questions regarding posology.

In terms of methods used for uncertainty quantification, prediction intervals and relative standard errors (RSE) were mentioned most often. Visual predictive checks (VPC) and prediction corrected visual predictive checks (pcVPC). Overall, the regulatory discussion typically focused on whether the uncertainty of mechanistic models was adequately captured by the UQ method and the implications for how the drug development should proceed rather than the UQ method itself .

Introduction

We performed a review of regulatory procedures to identify EMA marketing authorization procedures and scientific advice procedures where uncertainty quantification (UQ) of mechanistic models was of concern. Specifically, we investigated which methods were used or proposed to evaluate the uncertainty of estimates from mechanistic models to inform scientific questions relevant to the development of medicinal products, and how the overall adequacy of the models was subsequently assessed.

Based on this review, we will define relevant parameter ranges to inform a simulation study on methods of UQ, derive case studies that illustrate the findings of the simulation study, and outline general regulatory recommendations. To do so, we intend our next step to involve extraction of aggregate data (model parameter estimates and corresponding uncertainty measures) on specific models based on information obtained during full text extraction, such as tables directly giving parameter estimates and uncertainty measures, plots of model predictions, and figures of model schemata.

Objectives

The main objective of this review was to identify documents where UQ methods were used to address uncertainty challenges in mechanistic models such as popPK, PBPK and QSP models. For selected documents we primarily investigated what UQ methods were used and what the key findings and regulatory conclusions were (for example regarding discussion around prediction uncertainties, parameters uncertainties, etc.).

Eligibility criteria

Inclusion criteria

1. Regulatory procedures with a positive opinion (EPAR) or final advice letter (EMA-SA FAL), issued before June 1st, 2025, where uncertainty quantification of mechanistic models was identified as an issue during regulatory assessment.
2. Initial authorization or variation (e.g. extension of the authorised use to another therapeutic area), or Scientific Advice Final Letter.
3. Procedures for which the EPAR or EMA-SA FAL discusses at least one mechanistic model to address some relevant aspect of the drug development programme.
4. Procedures for which the EPAR or EMA-SA FAL discusses at least one method for UQ of a mechanistic model intended to inform regulatory conclusions on aspects of the drug development programme.
5. Procedures that contain a regulatory discussion of the UQ method.

Exclusion criteria

1. Marketing authorization procedures currently under review.

2. EMA-SA procedures currently under assessment (i.e. EMASA FAL not issued, before June 1st, 2025).
3. Marketing authorization procedures withdrawn by the Applicant or with a negative opinion.
4. Procedures that do not discuss at least one mechanistic model.
5. Procedures that do not discuss UQ.
6. Procedures where the discussion of UQ does not refer to a mechanistic model (e.g. confidence intervals for parameters estimated in a dose-finding clinical trial or population pharmacokinetic analyses).
7. Procedures where UQ is mentioned by the Applicant but not discussed in the regulatory assessment.

Methods

Search strategy

A comprehensive search of EMA Public Assessment Reports (EPARs) was conducted in the electronic database provided at paediatricdata.eu. In addition, the AGES database of EMA-SA FALs was searched to identify related scientific advice procedures. Search terms were prespecified and included terms such as “uncertainty quantification” (see below) in different types of spelling. Searches were restricted to procedures with a positive opinion and EMA SAs where the FAL had been issued by CHMP before June 1st, 2025.

The following structured search terms were used:

Category	Terms Included
Modelling-related Terms	“in silico”, “in-silico”, “mechanistic model”, “M&S”, “modeling & simulation”, “modeling and simulation”, “PBBM” , “PBPK”, “pharmacometric”, “physiologically based biopharmaceutic”, popPK , “population pharmacokinetics”, “population PK” , “QST”, “quantitative systems toxicology” , “quantitative systems pharmacology”, “QSP”
Uncertainty-related Terms	“uncertainty quantification”, “uncertainty evaluation”, “model uncertainty”, “parameter uncertainty”, “structural uncertainty”, “evaluation of uncertainty”, “credible interval” , “prediction interval”, “probabilistic sensitivity analysis”

Searches combined both categories using the AND operator to increase the likelihood that potential matches meet inclusion criterion 3 and exclusion criteria 4 and 5.

An initial limited search of paediatricdata.eu and the AGES database was undertaken on July 14th, 2025 to evaluate the feasibility of a search strategy based on full text queries.

The final search strategy, including all search terms and conditions for selection, was adapted slightly, taking into account

- low-specificity search terms returning large numbers of irrelevant results (e.g. ‘confidence interval’) due to frequent use of the term outside the modelling context,
- the results of a pilot review (see Section on Data extraction),
- and the suggestions EMA provided during a project meeting on July 17th, 2025 , where results from the pilot search were presented (e.g. ‘QSP’, ‘PBPK’).

The final search was performed on July 23rd, 2025, once again on the following two databases:

- paediatricdata.eu – Full-Text search of EMA EPARs: https://paediatricdata.eu/shiny/users/ralfherold/emaepars/
- AGES internal database of EMA Scientific Advice letters.

Both support combinations of search terms using logical operators, and the final search was performed for all combinations of individual terms from the modelling-related and uncertainty-related terms combined using the “AND” operator.

Search results for individual search terms were cleaned, processed, and collated for further processing using the statistical software R. Duplicates were removed and EPARs and EMA-SA FALs were filtered to match predefined combinations of search terms.

Study/Source of evidence selection

Text paragraphs from EPARs and EMA-SA FALs that matched the search terms were screened against the inclusion criteria in the first step of the detailed review; this was done by individual reviews using a screening form especially developed and evaluated for usability during the pilot screening (see section on Data extraction). The final screening form was implemented using Microsoft Forms (see Supplementary Document 1). Procedures intended for detailed extraction were divided between three reviewers who were assigned a partially pre-filled (document id, document link) form for individual completion per procedure.

Considering the large number of search results (357), screening was performed by individual assessors only as duplicate screening would not have been feasible (this is in line with the protocol). Reviewers met regularly to discuss progress, align on specific application of eligibility criteria, and resolve controversial cases.

In most cases, full text EPARs and EMA-SA FALs indeed required detailed assessment against the eligibility criteria since the search matches and document context reported by the employed search engines were not sufficient to determine inclusion. Reasons for exclusion of procedures at this stage were recorded in the screening form, together with additional information on the location of relevant content related to UQ (section, question, page number) and free-form notes to facilitate subsequent extraction.

Data extraction

In a first step, only data from 6 EMA-SA FALs and 4 EPARs were reviewed with the aim to obtain information on items including:

- Drug development question addressed
- Type of model and specification
- Uncertainty quantification methods proposed or applied
- Recommendations provided by the EMA regarding uncertainty quantification
- Estimates of model parameters
- Estimates of uncertainty measures

using a pilot extraction form. Based on this, the final extraction form was developed (see Appendix A for the table of items, Supplementary Document 2 for the form). The data extracted includes specific details about the procedure, product, indication, substance class, eligibility criteria, extent of the discussion of the UQ method, modelling context and type of mechanistic model, UQ methods proposed by the Applicant or the regulatory agency, regulatory recommendations concerning UQ, and key aggregate model parameter and uncertainty measure estimates.

Data from EPARs and EMA-SA FALs included after screening were extracted by individual reviewers using full text documents of EMA-SA FALs and EPARS. For more recent EMA-SAs, the full text briefing documents were obtained in order to review Applicant positions and additional background material (e.g. to extract model specifications and model parameter estimates that were not reproduced in the CHMP answer).

Due to the large number of procedures included for extraction (148), independent extraction by two reviewers was not considered feasible and documents were assigned to individual reviewers. Extraction was preferentially assigned to a different reviewer than the screening reviewer. Reviewers met regularly during the extraction process to align extraction practices and discuss controversial cases. Due to an error in the assignment software, a number of documents were randomly assigned to two or three reviewers for extraction. In total, 28 documents were reviewed by two reviewers, and 5 by three. Agreement on procedure inclusion was high (~70%), and information extracted independently aligned to a large degree. In case of disagreement, eligibility was reviewed and resolved by the first author.

The number of models discussed in the procedure was limited to those where uncertainty quantification was specifically mentioned. Other models reported or discussed in the same procedure that did not involve a discussion related to UQ were therefore not counted. Discussions related to uncertainty quantification of models built in a hierarchical manner (e.g. an exposure-response model based on an elsewhere discussed popPK model) were counted as a single model if the discussion concerned uncertainty propagated from a separate and dependent model (e.g. ‘precision of E-R model predictions is questioned due to limitations discussed in relation to the popPK

model'). However, if the popPK model was further extended by adding additional mechanistic layers (e.g., non-linear drug effect model and/or an indirect response model) and a discussion in relation to UQ was identified it was counted as an additional model.

For EMA-SA FALs, the non-proprietary and invented names could not be extracted consistently. At the stage of the SA procedure, products are often referred to by non-descriptive IDs. Considering the confidentiality of the procedures, these data were used for internal tracking and quality control purposes (i.e. identification of duplicate or mislabeled extractions) and not reported.

Products were categorized into several substance classes at extraction. Corresponding classes were primarily derived from information in the EPAR (e.g. "Section 2.2. About the product") and EMA SA FAL (e.g. the corresponding paragraph of the cover letter) at extraction. In cases where these descriptions did not contain the broader therapeutic substance class, AI queries and web searches in the NCI thesaurus and wikipedia were performed to facilitate categorization.

Processing of extracted information

Data extraction was performed using the aforementioned MS Forms based online questionnaire (see Supplementary Document 2) that collects extracted data in a spreadsheet. Spreadsheet data were cleaned to remove extraction form test entries, and then imported and further processed using R.

Therapeutic indications were manually mapped to broader categories of medical speciality. A first classification was obtained using MS Co-Pilot (using extracted indications only). Each classification was then manually checked for plausibility. Unclear cases were reviewed, compared to corresponding information on wikipedia.org, and, if necessary, corrected. Reported categories were changed to uniform terminology (e.g. "mab" was mapped to "monoclonal antibody") and further simplified (e.g. "humanized monoclonal antibody" was mapped to "monoclonal antibody").

Extracted modelling context ("Drug development question asked"), model type ("Type of Model"), and model specification were simplified and manually mapped to a small set of unique categories (e.g. questions related to dosing and duration of treatment were mapped to "posology", "popPK and PD" to "popPK/PD", "two compartmental model with first order absorption" to "2-compartmental model"). UQ Methods discussed ("Uncertainty Quantification Method Proposed/Applied") were similarly manually mapped to consistent categories.

Data analysis

Descriptive statistics to summarize data extracted from EPARs and EMA-SA FALs were used. We provide an overview of the number of procedures, therapeutic areas, and specific indications involved. We qualitatively and quantitatively summarize the types of

modelling approaches utilized, the specific drug development questions addressed (e.g., dose selection, extrapolation), and the methods proposed, discussed, or recommended by EMA for quantifying uncertainty.

Relevant outcome measures, including model parameters, confidence or credible intervals, and sensitivity analyses, were mainly collected through screenshots of relevant tables and figures. Corresponding results are available for further extraction and processing to inform the design of the simulation study.

Results

Study selection

EPAR search

At the time the final search was performed (July 24th, 2025) the database a paediatricdata.eu held records on 1897 procedures and 6425 full-text reports for procedures with an authorization date up to June 1st, 2025 (corresponding to the May Meeting of the European Medicines Agencies, Committee for Medicinal Products for Human Use).

The combined keyword search returned 70 documents in the database. Returned paragraphs and links to full-text documents were grouped by procedure and screened by individual reviewers (see above). Following this screening step 32 out of 70 procedures were selected for full-text review and extraction.

In total, 32 procedures were reviewed in detail. During review inclusion was confirmed for 30 procedures. For 8 of the included procedures the EPAR included discussions on uncertainty quantification for more than one model. Consequently, information about a total of 38 models were extracted for the review.

EMA-SA FAL search

At the time the final search was performed (July 24th, 2025) the AGES internal database of Final Advice letters held records on 12498 full-text reports related to scientific advice. Note, that this may include duplicates, and appendices and other related documents for certain procedures.

The combined keyword search returned 287 documents in the database. Returned paragraphs and links to full-text documents were grouped by procedure and screened by individual reviewers (see above). Following this screening step 116 out of 287 procedures were selected for full-text review and extraction.

In total, 116 EMA-SA procedures have been reviewed in detail. During review inclusion was confirmed for 57 procedures. For 13 of the included procedures the EMA-SA Final Letter included discussions on uncertainty quantification for more than one model. Consequently, information about a total of 70 models were extracted for the review.

Figure 1 provides the PRISM Flowchart for the inclusion process across both databases.

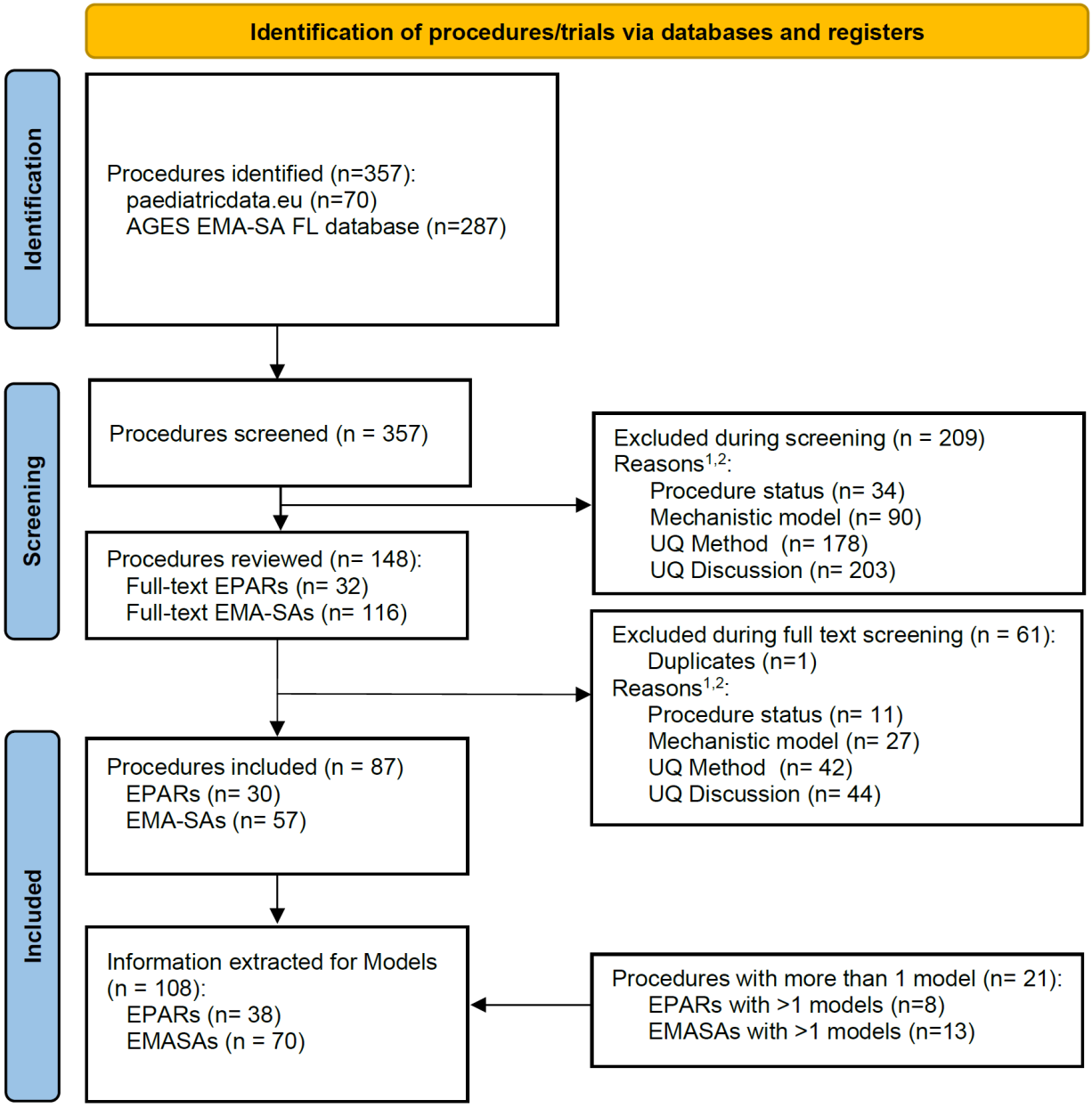

Figure 1: PRISMA 2020 flow diagram – identified and included procedures for the regulatory procedure review.
[1] Reasons for exclusion:
- Procedure status (Inclusion criterion 2, or Exclusion criteria 1, 2, 3 failed),
- Mechanistic model (Inclusion criteria 1, 3, or Exclusion criteria 2, 3 failed),
- UQ Method (Inclusion criterion 4, or Exclusion criterion 5 failed),
- UQ Discussion (Inclusion criterion 5, or Exclusion criteria 6, 7 failed)
[2]Numbers include duplicate mentions per procedure across eligibility criteria

The majority of procedures were excluded due to inclusion criteria 4 and 5 and the corresponding exclusion criteria 5-7. *I.e.:* Include if: “discusses at least one method for

uncertainty quantification of a mechanistic model intended to inform regulatory conclusions on aspects of the drug development programme." and "contains a regulatory discussion of the UQ method." (see Table 1). Corresponding eligibility criteria were applied generously and procedures were included if comments regarding the reported variability (regardless of measure) were noted. However, procedures where regulatory comments were limited to the statement that details on the modelling exercise were missing and assessment of the model was consequently not possible were excluded, even if they alluded to some form of uncertainty.

Eligibility Criteria	**Numbers failed**
Inclusion Criteria	
1. Regulatory procedures with a positive opinion (EPAR) or final advice letter (EMA-SA) (issued before June 1st, 2025) where uncertainty quantification of mechanistic models was identified as an issue during regulatory assessment.	36
2. Initial authorization, variation e.g. extending the authorised use to another therapeutic area, or Scientific Advice Final Letter.	43
3. Procedures for which the EPAR or EMA-SA FAL discusses at least one mechanistic model to address some relevant aspect of the drug development programme.	103
4. Procedures for which the EPAR or EMA-SA FAL discusses at least one method for uncertainty quantification of a mechanistic model intended to inform regulatory conclusions on aspects of the drug development programme.	200
5. Procedures that contain a regulatory discussion of the UQ method.	226
Exclusion criteria	
1. Marketing authorization procedures currently under review.	0
2. EMA-SA procedures currently under assessment (i.e. EMASA FAL not issued before June 1st, 2025).	1
3. Marketing authorization procedures withdrawn by the Applicant or with a negative opinion.	6
4. Procedures that do not discuss at least one mechanistic model.	79
5. Procedures that do not discuss UQ.	164
6. Procedures where the discussion of UQ does not refer to a mechanistic model (e.g. confidence intervals for parameters estimated in a dose-finding clinical trial or population pharmacokinetic analyses).	54
7. Procedures where UQ is mentioned by the Applicant but not discussed in the regulatory assessment.	73

Table 1: Number of procedures by eligibility criterion failed, individual procedures may fail more than one criterion simultaneously (n=357)

Included procedures by substance class and indication

The majority of included procedures fell into the fields of oncology and neurology, which combined made up about 35% (see Figure 2). Medical specialities occurring in two or fewer procedures were grouped together under the category “Other/ Unclassified”.

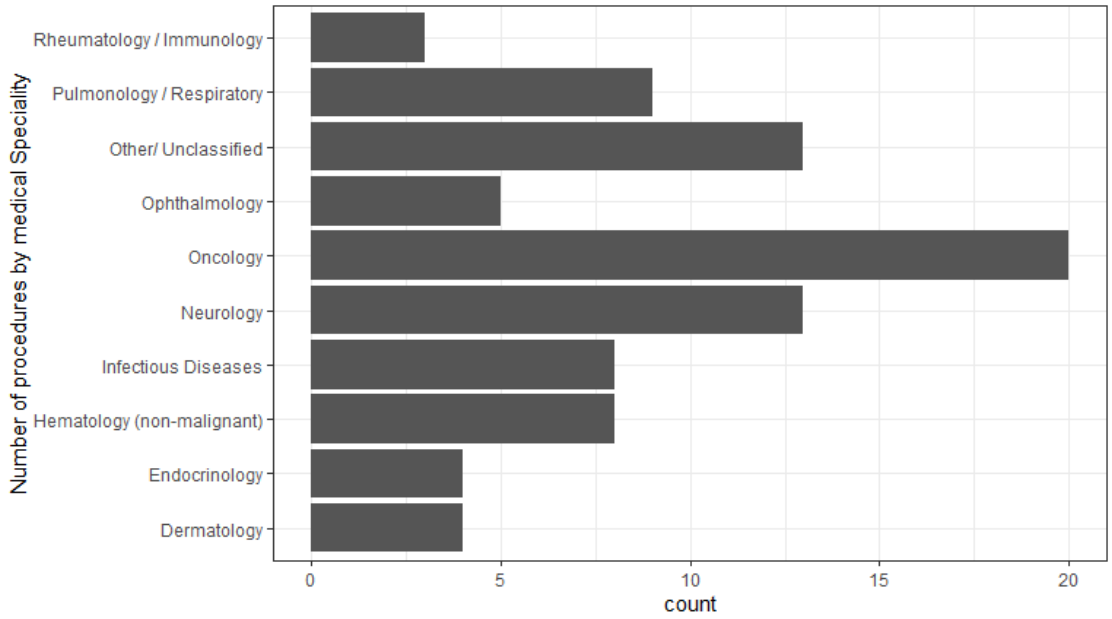

Figure 2: Number of procedures by medical specialty (n= 87); Other/Unclassified: unclassified indications, medical specialities occurring in two or fewer procedures

The largest proportion of products was represented by monoclonal antibodies and kinase inhibitors, together making up about half of the included products (see Figure 3). Substance classes appearing in two or fewer procedures were grouped as ‘Other/ Unclassified’.

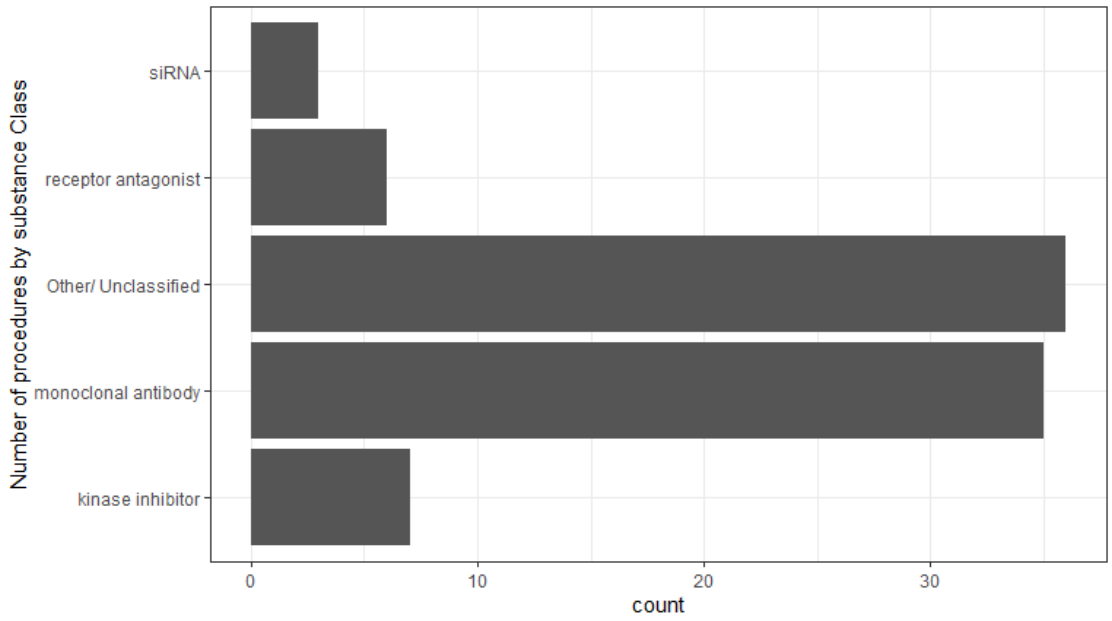

Figure 3: Number of procedures by substance class (n=87); siRNA: small interfering RNA, Other/ Unclassified: uncategorized substance classes, substance classes appearing in two or fewer procedures

Modelling context, model type, and model specification

Among the models included because of an associated UQ discussion, popPK models were the most common category. Together with combined popPK/PD or popPK/ER models, models based on popPK made up the overwhelming majority of all extracted models (see Figure 4). Ten specific PBPK models (n=10) were extracted, and fewer than five isolated QSP (n=3), ER (n=3). The extraction also included model types identified two or fewer times categorised as ‘other’ (such as in-silico models (n=2), and a dose-time response model (n=1)).

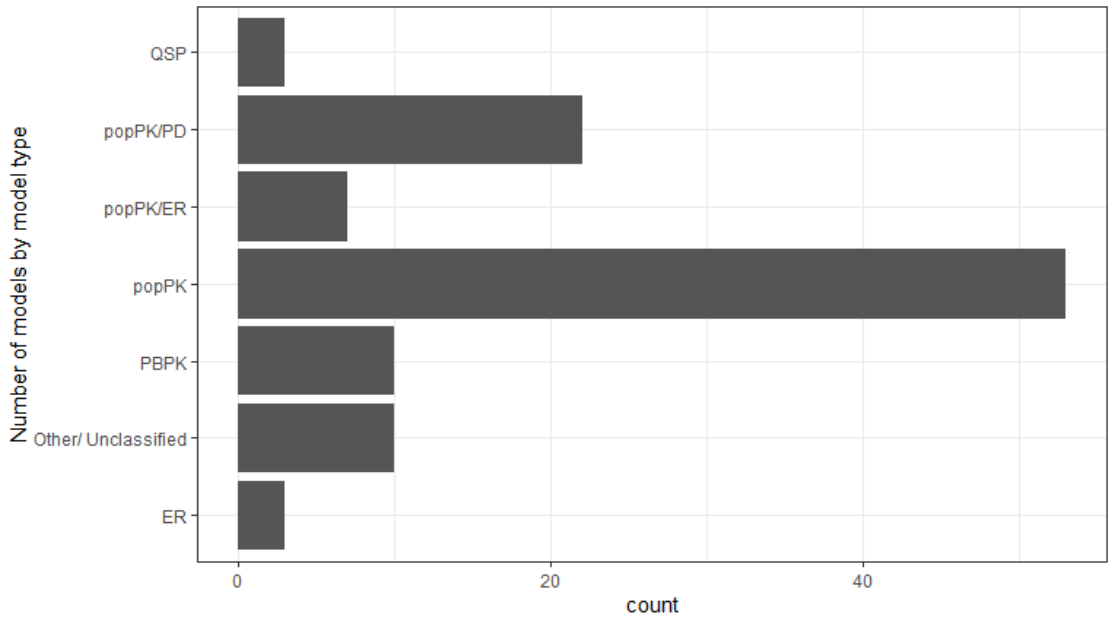

Figure 4: Number of models by type (n=108); QSP: Quantitative Systems Pharmacology, popPK/PD: population pharmacokinetics/pharmacodynamics, ER: exposure response, PBPK: Physiologically Based Pharmacokinetic, Other/Unclassified: model types identified two or fewer times

The modelling approaches (see Figure 5) were typically employed to inform drug posology during development (for e.g. to find the optimal dose and dosing regimen), and occasionally for determination or extrapolation of the posology to adolescent patients, pediatric patients, or alternative administration routes (five or fewer cases each). More rarely, the main modelling focus was on special populations and drug-drug interactions, or on the general development of a broader population PK model or pharmacokinetic/clinical pharmacological drug characterisation profile (all fewer than 7 cases). This may include for example population PK model-based simulations to validate the selection of PK sampling time-points.

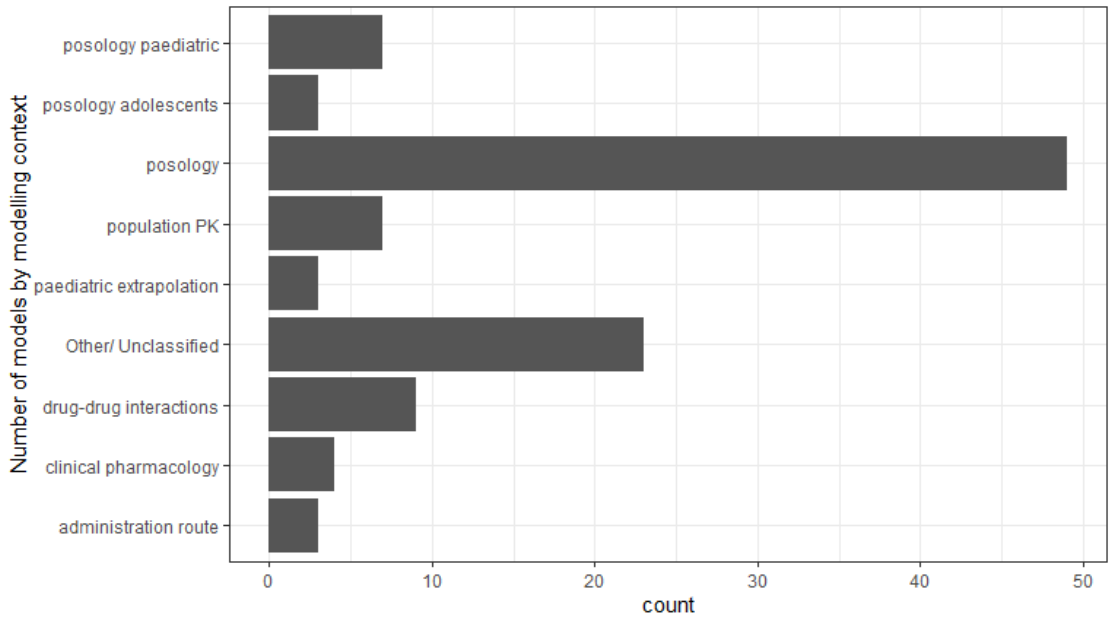

Figure 5: Number of models by modelling context (n=108); Population PK: population pharmacokinetics, other: modelling contexts identified two or fewer times.

Most often, precise model specifications were lacking in the documents available to reviewers (see Figure 6). More than 30 of the extracted models with detailed descriptions were 2-compartmental (combined) popPK models, and some of the other better described modelling approaches involved (combined) popPK models with 1,3, and 15 compartments, Bayesian non-linear mixed effects models for analysis of PK data, and Emax models for analysis of dose-response relationships (five or fewer cases each).

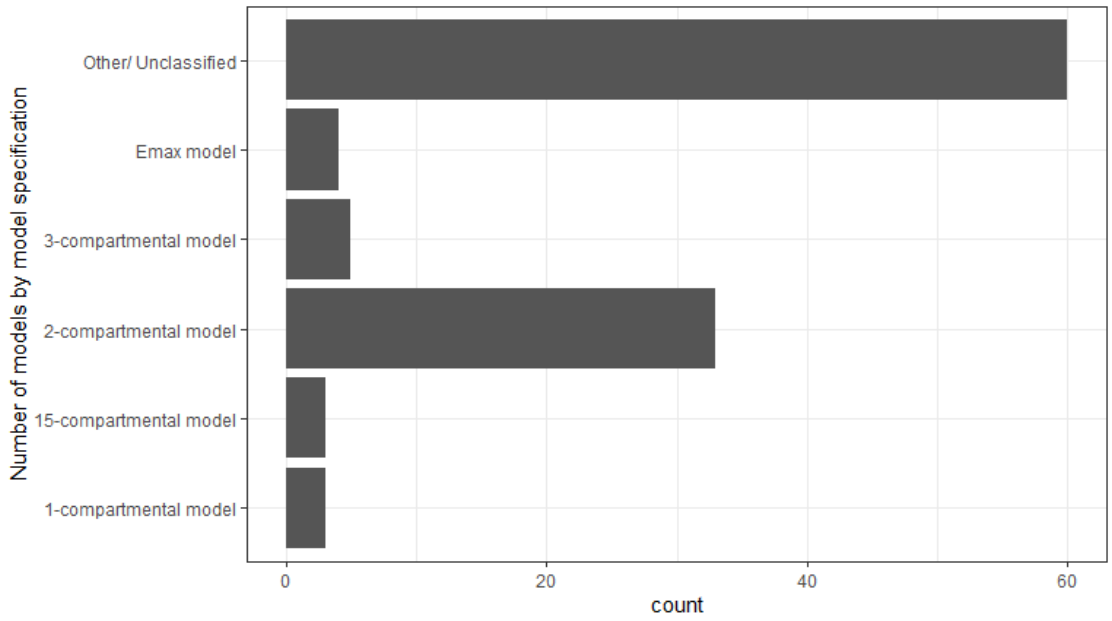

Figure 6: Number of models by model specification (n=108); Emax: maximum achievable effect, Other/Unclassified: models for which precise specifications were lacking, model specifications occurring two or fewer times.

Uncertainty quantification methods proposed

The most frequently applied/suggested method for uncertainty quantification was reporting of prediction intervals (see Figure 7). Following that, relative standard errors (RSE), visual predictive checks (VPC), and prediction corrected VPCs (pcVPC) were the most frequently occurring methods. Regularly, the absence of (pc)VPC plots in dossiers and briefing books was criticized and Applicants were recommended to provide them and evaluate corresponding measures according to the EMA guideline on the reporting of PBPK models (European Medicines Agency, 2018).

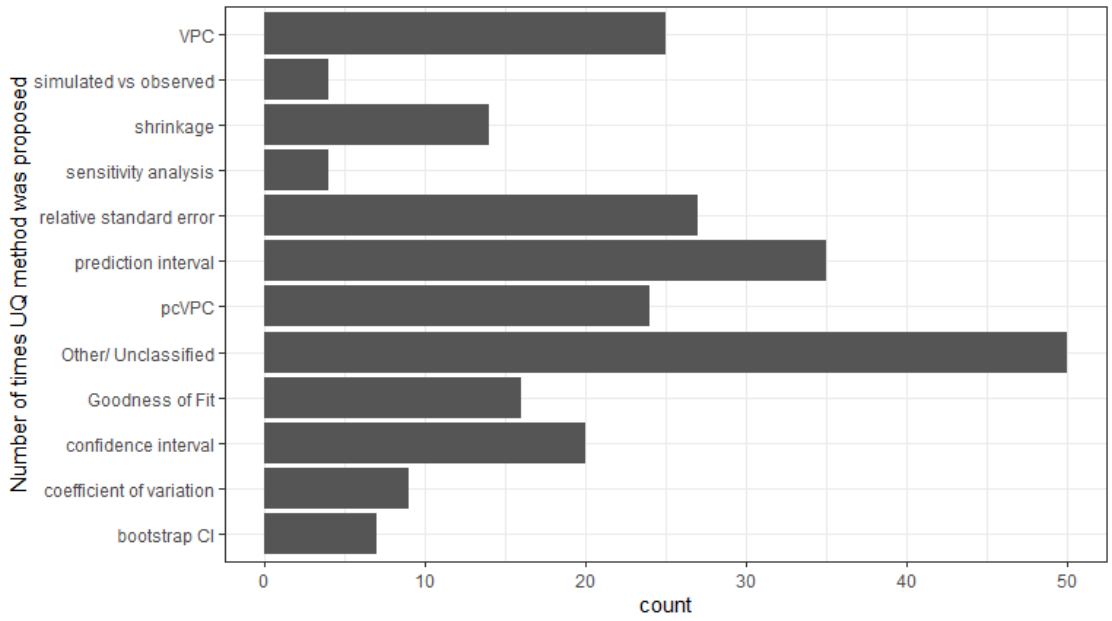

Figure 7: Number of models for which certain UQ methods were proposed either by applicant or regulators (n=108); VPC: visual predictive check, pcVPC: prediction-corrected visual predictive check, CI: confidence interval. Other/Unclassified: UQ methods suggested with two or fewer models. More than one UQ method may have been proposed for a single model.

Regulatory discussion of model uncertainty

In most cases (n=70, 65%) the regulatory discussion of uncertainty quantification was rather general and brief. Often only limited statements to the extent of ‘some residual variability is noted, however, the modelling approach is overall acceptable’, or ‘high residual variability is observed, the Applicant is advised to improve their model’ were provided. Even in cases such as the latter case, where there appear to be some concerns regarding the reported uncertainty, this did not necessarily appear to imply that the modelling exercise was rejected overall, especially if corresponding conclusions (dose-selection for subsequent clinical trials) could be confirmed or were expected to be confirmed in follow-up experiments (e.g. Phase III confirmatory trials).

The reporting of (pc)VPC was noted in many procedures, although the method is not necessarily considered an UQ method (since often some input parameters are fixed to values reported in the literature or in previous trial results). Examples of the consideration of VPC as a relevant diagnostic measure associated with uncertainty involved discussions on whether the corresponding prediction interval did/did not adequately describe the data. In some cases, pcVPC was preferred. If a PK parameter e.g., Cmax, was of special relevance due to safety or other relevant concerns, numerical predictive checks (e.g., a prediction interval) were often requested. In some procedures, regulators requested that the Applicant verify assumptions made during model building if model-based simulations were submitted as justification of key steps in the development programme (e.g., similarity of PK parameters between different patient populations). It was often advised to reassess model predictions once relevant clinical data became

available in later development stages and adjust dosing accordingly, which could also be considered a form of ‘sensitivity analysis’.

Only very few procedures contained a more detailed discussion of UQ methods. These included the following more commonly noted aspects of the UQ of the applied models: poor estimation precision (reflected in a high RSE%) that suggested that the model was over-parameterised, high shrinkage values, and deficiencies in model-based predictions (prediction intervals). Indeed, prediction intervals were the most frequent UQ measure identified. This may be related to the fact that modeling exercises were typically followed by simulations to evaluate the model (uncertainty) and to assess its predictive performance by comparing predictions to incoming data from ongoing studies to e.g. further inform/adjust the dosing regimen. Other methods that were specifically mentioned and sometimes discussed in detail included RSE%, shrinkage, sensitivity analysis, confidence intervals, and credible intervals. In some examples, additional methods (e.g. pcVPC) or even additional models (such as a PBPK model in addition to a popPK/PD model) were requested to better facilitate the evaluation of model uncertainty.

Regulatory assessment of model uncertainty

Reviewers were asked to assess whether the regulatory discussion indicated that UQ of the modelling approach—or the uncertainty reflected in the model results supported by various UQ methods—was considered adequate. Across the 108 models, 50 discussions suggested adequacy, 32 remained unclear, and 26 pointed to inadequacy.

Models where the regulatory assessment indicated inadequacy of model uncertainty included cases where comments questioned the reliability of the model, for example noting that it could not be relied upon or that its validity was in doubt. Models considered acceptable were those where regulatory recommendations appeared supportive of the approach or where the conclusions drawn from the modelling were regarded as sound. Models for which the regulatory assessment remained unclear included situations with unresolved controversies around structural design due to discrepancies between predicted and observed responses, as well as preliminary models developed from sparse data or few subjects that led to imprecise estimates and simulations. In such cases, regulators often recommended updating the model with more complete data before reassessing the associated uncertainty. Models where regulatory discussions on UQ were framed only prospectively, without a final conclusion, were also included in the unclear category.

Limitations

From the discussion reflected in some procedures, it is clear that only a limited amount of the regulatory assessment of individual modelling exercises is reflected in the final advice letters. For example, we frequently encountered advice that referred to separate assessment by the Modelling & Simulation Working Party, the PDCO, or to SAWP discussion meetings which are not reproduced in full in the letter. UQ methods like confidence intervals, (pc)VPC, and sensitivity analyses were not included as keywords in the search strategy, yet corresponding proposals were included as a form of

uncertainty quantification. Consequently, procedures where UQ is limited to corresponding approaches may have been missed. In addition, full descriptions of how uncertainty estimates were obtained (e.g. explicit derivations of prediction intervals) were generally not available in the documents reviewed.

Summary and conclusion

This scoping review identified EMA regulatory procedures in which uncertainty quantification (UQ) of mechanistic models was discussed. Of 357 procedures retrieved through database searches, 148 met initial eligibility criteria, and detailed data extraction was completed for 87. The most common therapeutic areas were oncology and neurology, with monoclonal antibodies and kinase inhibitors representing about half of the included products.

Across procedures, population PK models—often applied to questions of posology—were most frequently encountered. The second most frequently encountered category comprised models that extended population PK models to address additional aspects of drug response, such as exposure–response or pharmacodynamic relationships. However, also several other categories, including PBPK and QSP models with associated discussions on UQ could be identified and relevant information extracted. Corresponding procedures may serve as candidates to form case studies.

The methods for UQ mentioned in regulatory documents included prediction intervals, relative standard errors (RSE), and (prediction-corrected) visual predictive checks (VPC/pcVPC). However, descriptions of UQ approaches and the related regulatory discussions were generally brief and high-level.

Regulatory discussions of model uncertainty were mainly short and general, although regulators frequently accepted the level of uncertainty conveyed by the models, explicit assessments of the underlying UQ methods were less common, and in many cases conclusions were either ambiguous or critical. The main focus of the discussion was rarely the method of model uncertainty quantification itself but rather whether the employed model adequately informed the intended steps of the drug development process based on the reported results of UQ methods.

It should be noted that available texts in EPARs and EMA-SA Final Letters only represent summaries of broader assessments and discussions, and therefore cannot be assumed to reflect the full scope of regulatory evaluation. However, these findings provide a solid initial mapping of where and how UQ has featured in regulatory assessments and can serve as a basis for future studies.

Acknowledgements

This protocol is based on the JBI scoping review template (accessed on June 18th, 2025).

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Supplementary Information

Together with this report we submit

- *Supplement 1,* which is a print-out of the screening form,
- *Supplement 2,* which is a print-out of the extraction Form, and
- *Supplement 3,* which is a spreadsheet containing all text-based (excluding screenshots) extractions and derived variables from EPARs reviewed for the interim analysis, personal information of reviewers were removed.

References

Tricco AC, Lillie E, Zarin W, O’Brien KK, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018 Oct 2;169(7):467-473. doi: 10.7326/M18-0850. Epub 2018 Sep 4. PMID: 30178033.

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National Cancer Institute. (n.d.). NCI Thesaurus. Retrieved on August 2nd, 2025 , from https://ncithesaurus.nci.nih.gov/

Wikipedia, Wikimedia Foundation, Wikipedia. https://www.wikipedia.org/ Accessed on August 17th, 2025

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Appendix A - Extraction Items

List of items extracted for included procedures

Item
ID
Document ID
Reviewer
Filename
Screening Status
Non-Proprietary Name
Invented Name
Substance Class
Indication
In case of exclusion eligibility criteria that are not met
Exclusion criteria met
Inclusion (Yes/No)
Number of Models discussed in the Procedure
Model ID in case of more that one Model
Section in EPAR / Question in EMASA-FL
First page number
Drug development question asked
Type of Model
Model Specification
Only brief and general discussion/mention of UQ by regulators
UQ considered adequate by regulators
Uncertainty Quantification Method Proposed / Applied
Recommendations Provided by EMA Regarding Uncertainty Quantification
Estimates of Model Parameters
Estimates of Uncertainty Measures
Did you save any screenshots in the corresponding procedure folder?
What screenshots did you include

Supplement 1:
print-out of the screening form

EMASA/EPAR Review Screening

Screening of EMASA/EPAR Search Results for Inclusion/Exclusion in the Review

* Erforderlich

1. Reviewer *

2. Search Result ID *

Ihre Antwort eingeben

3. Procedure Number

4. Inclusion Criteria Met

- [ ] 1. Regulatory procedures with a positive opinion (EPAR) or final advice letter (EMA-SA) (issued before June 1st 2025) where uncertainty quantification of mechanistic models was identified as an issue during regulatory assessment.
- [ ] 2. Initial authorization, variation e.g. extending the authorised use to another therapeutic area, or Scientific Advice Final Letter.
- [ ] 3. Procedures for which the EPAR or EMA-SA FAL discusses at least one mechanistic model to address some relevant aspect of the drug development programme.
- [ ] 4. Procedures for which the EPAR or EMA-SA FAL discusses at least one method for uncertainty quantification of a mechanistic model intended to inform regulatory conclusions on aspects of the drug development programme.
- [ ] 5. Procedures that contain a regulatory discussion of the UQ method.

5. Exclusion Criteria Met

- [ ] 1. Marketing authorization procedures currently under review.
- [ ] 2. EMA-SA procedures currently under assessment (i.e. EMASA FAL not yet issued by CHMP).
- [ ] 3. Marketing authorization procedures withdrawn by the Applicant or with a negative opinion.
- [ ] 4. Procedures that do not discuss at least one mechanistic model.
- [ ] 5. Procedures that do not discuss UQ.
- [ ] 6. Procedures where the discussion of UQ does not refer to a mechanistic model (e.g. confidence intervals for parameters estimated in a dose-finding clinical trial).
- [ ] 7. Procedures (mainly EMA-SA) where UQ is mentioned by the Applicant but not discussed in the regulatory assessment.

6. Included *

- ◯ Included
- ◯ Excluded

7. Notes

Supplement 2:
Print-out of the extraction Form

EMASA / EPAR Review Extraction UQ

Extraction of Information from EPARs and EMASA Final Letters selected in the previous screening

* Erforderlich

* Dieses Formular wird Ihren Namen aufzeichnen. Bitte tragen Sie Ihren Namen ein.

Document & Reviewer

this fields shold be pre-filled by the link, don't edit manually

1. Document ID *

2. Reviewer *

3. Filename - copy and paste link to file *

4. Screening Status *

Procedure

fill out once per document, if you submit the form multiple times to input information about multiple models, fill this section for the first model and leave it empty for all subsequent models

5. Non-Proprietary Name

6. Invented Name

7. Substance Class (look up in the Background information on the product - XXX is a ...; or About the Product)

8. Indication

Inclusion

fill out once per document, if you submit the form multiple times to input information about multiple models, fill this section for the first model and leave it empty for all subsequent models

9. In case of exclusion elegibility criteria that are **not met**

- [ ] 1. Regulatory procedures with a positive opinion (EPAR) or final advice letter (EMA-SA) (issued before June 1st 2025) where uncertainty quantification of mechanistic models was identified as an issue during regulatory assessment.
- [ ] 2. Initial authorization, variation e.g. extending the authorised use to another therapeutic area, or Scientific Advice Final Letter.
- [ ] **3. Procedures for which the EPAR or EMA-SA FAL discusses at least one mechanistic model to address some relevant aspect of the drug development programme.**
- [ ] 4. Procedures for which the EPAR or EMA-SA FAL discusses at least one method for uncertainty quantification of a mechanistic model intended to inform regulatory conclusions on aspects of the drug development programme.
- [ ] 5. Procedures that contain a regulatory discussion of the UQ method.

10. Exclusion criteria **met**

- [ ] 1. Marketing authorization procedures currently under review.
- [ ] 2. EMA-SA procedures currently under assessment (i.e. EMASA FAL not yet issued by CHMP).
- [ ] 3. Marketing authorization procedures withdrawn by the Applicant or with a negative opinion.
- [ ] 4. Procedures that do not discuss at least one mechanistic model.
- [ ] 5. Procedures that do not discuss UQ.
- [ ] **6. Procedures where the discussion of UQ does not refer to a mechanistic model (e.g. confidence intervals for parameters estimated in a dose-finding clinical trial).**
- [ ] 7. Procedures (mainly EMA-SA) where UQ is mentioned by the Applicant but not discussed in the regulatory assessment.

11. Inclusion *

- ◯ Yes
- ◯ No

Model

fill out once per model, if one document contains multiple models submit the whole form multiple times

12. Number of Models discussed in the Procedure *

Der Wert muss eine Zahl sein.

13. Model ID in case of more that one Model (i.e. fill a form for each model) *

Der Wert muss eine Zahl sein.

14. Section in EPAR / Question in EMASA-FL (for multiple questions separate by comma) *

15. First page number (as displayed by word/acrobat) *

Der Wert muss eine Zahl sein.

16. Drug development question asked (Question in EMA-SA, Section number/title in EPAR)

17. Type of Model *

- ◯ popPK
- ◯ PBPK
- ◯ QSP (quantitative systems pharmacology)
- ◯ QST (quantitative systems toxicology)
- ◯ popPK/PD
- ◯ Sonstiges

18. Model Specification (e.g. two compartmental model) - please provide a screenshot of the model specification below

19. Only brief and general discussion/mention of UQ by regulators *

- ◯ Yes
- ◯ No

20. UQ considered adequate by regulators (put no in case if there is a mention that UQ is not considered appropriate or not sufficient evidence/data to determine whether sufficiently precise estimates will be able to derive, put yes if modelling approach is considered adequate, put unclear otherwise or in case the model in itself may not be adequate) *

- ◯ No
- ◯ Yes
- ◯ Unclear

21. Uncertainty Quantification Method Proposed / Applied (in case of more than one separate by ";")

22. Recommendations Provided by EMA Regarding Uncertainty Quantification

23. Estimates of Model Parameters

24. Estimates of Uncertainty Measures

Screenshots

Include screenshots of model formulae, plots, parameter estimate tables, etc. if available. Limit to things presented in the main file (i.e. company position of final advice letter, EPAR).

25. Did you save any screenshots in the corresponding procedure folder? *

- ◯ Yes
- ◯ No

26. What screenshots did you include (brief description, comma separated) - for tables and figures copy/paste the figure/table caption if available

Supplement 3:

Spreadsheet containing all text-based (excluding screenshots) extractions and derived variables from EPARs reviewed for the interim analysis, personal information of reviewers was removed.

ID	Document ID	Non-	Invented	Indication	Number of	Model ID in	Section in	First page	Drug	Modelling	Type of	Type of	Model Specification	Model	Only brief	UQ	Uncertainty Quantification Methods Proposed	Methods proposed (derived)	Recommendations Provided by EMA Regarding Uncertainty Quantification	Estimates of	Estimates of	Did you save	What	Therapeutic
90	EPAR_14	satralizumab	Enspryng	monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of adult and adolescent patients from 12 years of age with neuromyelitis optica spectrum disorders (NMOSD)		1	2.4.2. Pharmacokinetics	38	Pharmacokinetics	pharmacokinetics	popPK	popPK	2-compartment model with a linear and a non-linear (Michaelis-Menten) clearance and first order absorption	2-compartmental model	Yes	Yes	bootstrap 95% confidence intervals, RSE%, CV%, shrinkage, prediction interval	bootstrap ci, rse, cv, shrinkage, pi	Goodness of fit graphs show that higher concentrations were better described when IOV was included in the model. Since goodness of fit is nevertheless acceptable with the old model, and the residual error is not very different, it could be accepted that the old model was used. A concern was raised regarding the adequacy of the covariate analysis in the target population. None of the covariates had a significant effect, therefore the model was not updated. It is therefore acceptable not to update the model.	see screenshot	see screenshot	Yes	Table 3 popPK Parameter estimates, Table 3 popPK Parameter estimates2	Neurology
88	EPAR_15	cannabidiol	Epidyolex	seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS)		2	2.4 Clinical Pharmacology	54	NA		popPK	popPK	Technically 3 popPK models with same set-up: Single- and multiple-dose arms of a healthy subject trial used for the construction of a popPK model which was then applied to the pivotal trials in adults and children with LGS, and to a lesser extent in children with DS: 2-compartments with linear disposition, apparent clearances and volumes of distribution independent of baseline WT, absorption followed zero-order absorption kinetics without lag time with a constant duration	2-compartmental model	No	Yes	primarily pcVPC (in addition to discussion of model goodness of fit)	pcvpc, gof	EMA had previously asked the Applicant to analyse repeated dose data for estimates of intra-individual variability of the principal PK parameters resulting in better model predictions	NA	NA	No	NA	Neurology
91	EPAR_15	cannabidiol	Epidyolex	seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS)		2	2.4. Clinical Pharmacology	29	DDI, exposure prediction in very young pediatric patients	drug-drug interactions	PBPK	PBPK	No good description - Applicant will provide updated full model and results post marketing		Yes	Unclear	primarily pcVPC (in addition to discussion of model goodness of fit)	pcvpc, gof	NA	NA	NA	No	NA	Neurology
3	EPAR_19	Dostarlimab	Jemperli	Dostarlimab is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.		1	Dose proportionality and time dependencies	48	Pharmacokinetics in the target population	pharmacokinetics	popPK	popPK	2-compartment model: The final model incorporated several covariates: albumin on central clearance, alkaline phosphatase on central volume, alkaline phosphatase on central clearance, SLDR on central clearance, sex on central volume, positive ADA on central clearance, and age on central clearance.	2-compartmental model	Yes	Yes	Prediction corrected VPC, prediction interval	pcvpc, pi	Model predictability was demonstrated for the VPC which showed the majority of the observed concentrations were contained within the 95% prediction interval for each presentation	See screenshot	See screenshot	Yes	Table 20: population PK parameters of covariate model 814;	Oncology
166	EPAR_19	dostarlimab	jemperli	endometrial cancer		1	2.4.2. Pharmacokinetics	48	dosing and schedule, exposure response	posology	popPK/PD	popPK/PD	popPK: 2-compartment model with IIV on clearance (CL) and central volume of distribution (V1) with a proportional residual error model and an off diagonal correlation between CL and V, includes sevesal covariates exposure-response: Emax exposure-efficacy: Cox NPH	2-compartmental model	Yes	Yes	RSE, VPC	rse, vpc	NA	NA	NA	No	NA	Oncology
138	EPAR_2	concizumab	Alhemo	Alhemo is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding in patients with: • haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors ≥ 12 years of age. • haemophilia B (congenital factor IX deficiency) with FIX inhibitors of any age.		1	Clinical efficacy - Dosing level investigations	125	PK in phase 3 - Proposed (new) concizumab dosing regimen upon restart of phase 3 trials	posology	popPK	popPK	2-compartment model with combined linear clearance	2-compartmental model	Yes	Yes	Prediction interval	pi	The first model was developed based on phase 1 data only, while the second model also used phase 2 data. The new, phase 2 PK model was better able to predict exposure and showed that exposure was underpredicted in the first model. To get the most accurate description of the concizumab PK, the TMDD PK model was initially developed based on richly sampled PK data from the phase 1 trials, which ensured stability of the model. The concizumab PK model was used to evaluate covariate effects on concizumab exposure, the impact of maintenance dose setting on concizumab exposure and the effect of changing timing intervals between doses based on predicted steady-state average concizumab plasma concentration. A good fit was seen between the observed phase 3 exposure results (blue squares), and the TMDD model predictions (solid blue line and shaded area, Figure 57-). The MM model underpredicted the mean exposure and the variability in data.	NA	see screenshot	Yes	Figure 37-popPK prediction vs obs , Figure 38-popPK prediction vs obs1	Hematology (non-malignant)
13	EPAR_20	ivacaftor	Kalydeco	co-pilot: treatment of cystic fibrosis (CF) in patients aged 1 month and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation		1	Special populations	28	Special populations	special populations	popPK/PD	popPK/PD	Nothing included/discussed in the EPAR. Only sentences such as "Population PK/PD modelling has been developed".		Yes	Unclear	prediction interval	pi	Due to design problems the PK/PD model cannot be validated and cannot be refuted. Full paragraph from the EPAR, p38: There are two possible explanations for the controversy between the observed responses and the responses predicted by the structural model regarding relationship of FEV1 and sweat chloride outcomes. First, FEV1 measurements are associated with a high degree of variability. This variability is also true for the sweat chloride measurements, although to a lesser extent. Second, in the population PK/PD model, many of the data points lie well into the flat part of the exposure/response range, occurring at or near maximal response. Given these maximal responses and the observed variability for FEV1 and sweat chloride, it is not surprising that individual changes in FEV1 do not correlate with individual changes in sweat chloride. These results highlight that due to design problems the PK/PD model cannot be validated and cannot be refuted. Therefore PK/PD model-based predictions, particularly extrapolations, should be considered as hypothesis-generating rather than hypothesis confirming predictions	No plots was included in the EPAR.	No plots was included in the EPAR.	No	no screenshots	Pulmonology / Respiratory
95	EPAR_23	ritlecitinib	Litfulo	treatment of severe alopecia areata in adults and adolescents 12 years of age and older		1	2.6.2. Clinical Pharmacology	67	Clinical Pharmacology	exposure-response	E-R Model		NA		Yes	Yes	GOF Plots, VPC	gof, vpc	Goodness-of-fit and VPC plots indicate that the developed model adequately described the observed data.	NA	NA	No	NA	Dermatology
53	EPAR_24	maribavir	Livtencity	treatment of post-transplant cytomegalovirus (CMV) infection/disease		1	2.6 Clinical Pharmacology	47	Clinical Pharmacology	clinical pharmacology	popPK	popPK	a two-compartment disposition model with first-order absorption and elimination, and an absorption lag-time	2-compartmental model	No	Yes	Residual Standard Error, Confidence Interval, pcVPC	rse, ci, pcvpc	pcVPCs revealed that these differences were only partly described through the model leading to an underestimation of plasma concentrations in CMV patients. The pcVPCs indicate slight model misspecification mainly for the first 2 hours but overall look reasonable. The preliminary PPK model showed high unexplained variability and had no covariates included, except of body weight in the allometric functions on clearance and volume terms. In the final model, body weight was not found to be a significant predictor of maribavir PK, but it was retained in the model. The preliminary PPK model, which was used to calculate AUC0-12 Cmax and Cmin, is considered not robust enough as a base for exposure response modelling. However, similar results were observed in the final exposure response with a different data base from phase 3. The popPK model is considered adequate for descriptive purposes.	See screenshot	See screenshot	Yes	Table 9 Parameter Estimates of Final PopPK Model; Figure 3 Prediction-Corrected Visual Predictive Check for the final PK Model (Run 171);	Infectious Diseases

107	EPAR_3	garadacimab	andembry	recurrent inherited angioedema (phrophylaxis)	1	1	Sections 2.6.2. Clinical pharmacology, 2.6.3. Discussion on clinical pharmacology	46	dosing and exposure - response (efficacy and safety)	posology	popPK/PD	popPK/PD	2-compartment PK model with a direct effect sigmoidal Emax model	2-compartment model	Yes	Yes	pcVPC, prediction interval,	pcvpc, pi	The final model provided a reasonable description of the FXIIa-mediated kallikrein activity POB, indicated by the goodness of fit plots. The visual predictive check for the final population PKPD model showed simulated FXIIa-mediated kallikrein activity percent change was similar to observed FXIIa-mediated kallikrein activity percent change at the 5th, 50th, and 95th percentiles across the full time after dose and garadacimab concentration profile for each study. New predictions conditional upon new observed dosing and the patient empirical bayes estimates from the PKPD model were generated and compared to the newly observed kallikrein percent change observations. While some evidence of overprediction was present, the majority of the data is well spread within the prediction intervals (PIs).	NA	NA	Yes	Table 4: Population Simulations: HAE Relative Risk by AUCtau,ss in the Adult and Adolescent Population (CSL065F-Report-ER)	Immunology
122	EPAR_33	enfortumab vedotin	padcev	locally advanced or metastasised urothelial cancer	2	1	2.6.2. Clinical Pharmacology	73	dose schedule vs covariates	posology	popPK and exposure (efficacy, safety)	popPK/ER	3-compartment model with first-order elimination and a 2-compartment model with first-order elimination and time-varying conversion rate from enfortumab vedotin was used to characterise the concentration-time data of enfortumab vedotin and free MMAE	3-compartment model	Yes	Yes	1. popPK: 95% CI and bootstrap simulations -> pcVPC on final population, and general diagnostics 2. linear mixed model to relate exposure: 95% CI	bootstrap ci, ci, pcvpc	NA	NA	NA	Yes	NA	Oncology
123	EPAR_33	enfortumab vedotin	padcev	locally advanced or metastasised urothelial cancer	2	2	2.6.2 Clinical Pharmacology	77	DDI	drug-drug interactions	PBPK	PBPK	NA		Yes	Yes	NA		NA The clinically population PK modelling report states only 5% of healthy adults and the suspension formulation data was provided.	NA	NA	Yes	NA	
27	EPAR_34	Ritonavir	Paxlovid/Norvir	Treatment of HIV-1 infection, in combination with other antiretroviral agents, It may also be used in combination with other medications to treat hepatitis C and COVID-19.	1	1	Population PK modelling	59	Population PK modelling	population PK	popPK	popPK	a linear 2-compartment model with first-order absorption, a dose-dependent absorption (see screenshot)	2-compartment model	No	No	RSE%, prediction interval	rse, pi	The residual error model appears to be mis-specified. In one hand, the additive term, estimated to 339 ng/L, is considered too high (30-fold) compared to lower limit of quantification (10 ng/mL). In the other hand, the proportional error (even low =3.36%) was estimated with very poor precision (RSE% = 111%). This questions the validity of the model. To minimise the large additive error (higher than the target IC90% value of 292 ng/mL), the residual errors was excluded in the simulations. This approach is not endorsed as it would imply estimation of PK parameters and associated variabilities necessary different from that in the final model. Therefore, model-based PK predictions should be considered with caution (as issued from a model whose adequacy to the observed data has not been demonstrated). Large discrepancy (more than 2-fold) for the estimation of the terminal half-live T1/2 between the population approach (15h) and the NCA calculations (7h) was observed. This should be justified and its impact on model-based predictions should be further discussed. Only very limited data in healthy volunteers (n=20) are part of the analysed dataset. The lack of PopPK model with all completed data from healthy volunteers and especially more full data from patients in pivotal phase 2/3 studies (very sparse data essentially steady state Ctrough are actually available) was consider critical caveat by the CHMP; it is deemed to better inform the model. The update Population PK model should be submitted by 31 March 2022 (LEG).	see screenshot	see screenshot	Yes	PopPK model specification, Parameter estimates for the final population PK model based on preliminary data from Study C4671001, Predicted C12h and Percentage of Simulated Subjects Achieving C12h above IC90 of 292 ng/mL (IIV in CL Inflated to 60%)	Infectious Diseases
164	EPAR_38	ASPARAGINASE	spectrila	lymphatic leukemia	1	1	2.4.2 Pharmacokinetics	36	dosing	posology	popPK	popPK	The final base structural PK model was a 2-compartment model with IIV estimated on CL and V1 and interoccasion variability (IOV) on CL. Body weight was included as a scaling factor for all structural parameters (CL, V1, Q and V2). Combined additive and proportional error model.	2-compartment model	Yes	Unclear	RSE, etc	rse	NA	NA	NA	No	NA	Oncology
34	EPAR_42	faricimab	Vabysmo	neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), Macular Edema following Retinal Vein Occlusion (RVO)	1	1	Population PK analysis of faricimab	39	Population PK analysis of faricimab	population PK	popPK	popPK	This was a 3-compartment linear model, composed of the VH compartment, where the drug is injected, the AH compartment, and the plasma compartment with clearance (CL) and volume (Vc) (Figure 12). Bioavailability (F) was assumed to be 1. The volume of VH compartment (VVH) was fixed to the literature value of 0.0045 L (Hutton-Smith et al, 2016).	3-compartment model	No	Yes	RSE% ; CI ; CV% ; shrinkage ; pcVPC ; prediction interval	rse, ci, cv, shrinkage, pcvpc, pi	The methods used for model development and evaluation are acceptable. All final model parameters were estimated with adequate precision. There was high shrinkage (~50-60%) of plasma CL and Vc as well as the AH elimination rate constant (KAH). However, the reliability of AH and systemic faricimab PK parameters, as reported in the SmPC, were adequately justified by the applicant. Importantly, shrinkage of KVH was low (5%). As such, predicted VH exposure and VH elimination half-life, which were used as predictors in the PK-PD analyses, can be considered reliable. The goodness-of-fit diagnostic plots indicated that the final model described the observed data adequately. The visual predictive checks showed that the final model captured both the central tendency and the interindividual variability of faricimab PK in AH and plasma reasonably well. However, the model does show deviations at the later time points, starting from around day 50. The Applicant acknowledged these shortcomings and argued that this is mainly due to the increasing number of BLQ-values in the dataset. This can be followed. Nevertheless, respective simulations for later timepoints have to be interpreted with care.	NA	NA	Yes	popPK steady state exposure estimates, popPK GOF plot (AH), popPK GOF plot (plasma), popPK parameter estimates (inclusing LQ measures), popPK model specification, popPK pcVPC	Ophthalmology

101	EPAR_46	Danicopan	Voydeya	Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of signs or symptoms of extravascular haemolysis (EVH) in adult patients with paroxysmal nocturnal haemoglobinuria (PNH)	1	1	2.6.2 Clinical Pharmacology	40	Dosing	posology	popPK	popPK	two-compartmental model with linear elimination	2-compartmental model	Yes	Yes	RSE, Shrinkage, pcVPC, predicted percentiles	rse, shrinkage, pcvpc, predicted percentiles	Model evaluation through GOF plots suggest a slight over-prediction in the low range of PK concentrations. The visual inspection of prediction-corrected VPC stratified by study is challenging, since no clear evaluation could be performed around the Cmax region and initial sampling times. In addition, the y-scale is too limited in several pcVPC for representing the prediction interval of the lowest percentile. Analysing the pcVPC of the Phase 3 study, a slight under-prediction of Cmax is observed for the 50th percentile, which could bias the exposure-safety and exposure-QTc analyses. The Applicant provided additional pcVPC using semi-log scale and normal scale. pcVPC plots by study during the absorption phase for the final PK model with 95% prediction intervals of the 5th, 50th, and 95th percentiles were constructed. pcVPC of study ALXN2040-PNH-301 (PNH patients) showed under estimation of the inter-individual random effects on the median and 95th percentile. The numerical predictive check over the exposure metrics (Cmax, AUC and Ctrough) has been provided stratified by study design conditions (multiple dose and single dose). Overall, the population PK model tends to under-predict the exposure of danicopan. Although the under-prediction is of minor relevance for AUC and Ctrough, the under-prediction on Cmax ranges from 5-35% compared to the observed median. This is of special relevance in case the population PK model is used for predicting	see screenshot	see screenshot	Yes	Table 13 - Final popPK parameters, Figure 3 - pcVPC	Hematology (non-malignant)
42	EPAR_49	belzutifan	Welireg	Renal cell carcinoma (RCC) Welireg is indicated for the treatment of adult patients with advanced renal cell carcinoma that progressed following immune checkpoint and anti-angiogenic therapies. Assessment report EMA/18425/2025 Page 18/186 von Hippel-Lindau (VHL) disease-associated tumours Welireg is indicated for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) haemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable.	2	1	2.6 Clinical pharmacology	51	Effect of covariates on exposure, special populations	special populations	popPK	popPK	2-compartment model with first-order absorption and linear elimination	2-compartment asms model	No	Yes	RSE, CI, Shrinkage, pcVPC, Goodness of fit plots, non-parametric bootstrap analysis	rse, ci, shrinkage, pcvpc, gof, bootstrap ci	Model parameters were estimated with reasonable precision (all relative standard errors [RSE] below 37.4%). In addition, pcVPCs provided per individual study indicated adequate predictive erformance of the model. The impact of intrinsic/extrinsic factors on PK can therefore be evaluated and exposure estimates for PK-PD modelling can be obtained using the final popPK model described. Although the established popPK model appeared to be reasonably accurate, the high shrinkage on the established volume of distribution suggests overprediction. Therefore, further clarification of the reasoning and possible clinical impact was requested during the procedure. The model qualification performed by the applicant is considered acceptable as a prediction-corrected visual prediction check (pcVPC) and a non-parametric bootstrap analysis were presented demonstrating the robustness of the final population pharmacokinetic (PK) model. The final population PK model successfully predicted the observed median, 5th, and 95th percentiles of observed drug concentrations	see screenshot	see screenshot	Yes	Table 12 Final popPK Model Parameters, Figure 9: GOF Plots Final popPK Model, Figure 10: pcVPC per Study for Final popPK Model	Oncology
127	EPAR_49	belzutifan	Welireg	Renal cell carcinoma (RCC) Welireg is indicated for the treatment of adult patients with advanced renal cell carcinoma that progressed following immune checkpoint and anti-angiogenic therapies. Assessment report EMA/18425/2025 Page 18/186 von Hippel-Lindau (VHL) disease-associated tumours Welireg is indicated for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) haemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable.	2	2	6/2/02	55	DDI	drug-drug interactions	PBPK	PBPK	unclear		Yes	Yes	unclear		NA	NA	NA	Yes	NA	
6	EPAR_6	erdafitinib	balversa	treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma (UC), harboring susceptible fibroblast growth factor receptor 3 (FGFR3) genetic alterations with disease progression during or following at least one line of therapy containing a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor in the locally advanced unresectable or metastatic treatment setting.	1	1	Population PK-PD Modelling	77	Population PK-PD Modelling	population PK	popPK/PD	popPK,PD	An Emax model described the erdafitinib effect on PO4 driven by free concentrations in the effect compartment (see also screenshot).	Emax model	Yes	Yes	RSE% of parameter estimates, 95%CI, goodness-of-fit plots and pcVPCs	rse, ci, gof, pcvpc	Diagnostic plots showed an underprediction for the first 6 months of the study as well as an underprediction of the variability but overall described the effect of erdafitinib on [PO4] reasonably well.	see screenshot	see screenshot	Yes	model description, model parameters estimates, GOF and pcVPC	Oncology
165	EPAR_7	nirsevimab	beyfortus	RSV-associated LRTI	1	1	2.6.2.2 Pharmacokinetcs	40	NA		popPK	popPK	a linear 2-compartment model with variance terms estimated for CL and V2 . IM absorption was modelled using a first-order rate constant. Residual error was described by a proportional error model.	2-compartmental model	Yes	Unclear	NA		NA	NA	NA	No	NA	Infectious Diseases
8	EPAR_b10	lutetium (177lu) vipivotide tetraxetan	Pluvicto	Pluvicto is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy	1	1	2.6.3. Discussion on clinical pharmacology	43	2.6.3. Discussion on clinical pharmacology	clinical pharmacology	popPK	popPK	The final popPK model was a three-compartment model with a delayed 0-order absorption and linear elimination.	3-compartmental model	No	Yes	Coefficient of Variation; Relative Standard Error; Shrinkage; Confidence Intervals;	cv, rse, shrinkage, ci	The small sample size of N=30 patients sampled only in cycle 1 is regarded as limited data for population PK analysis. It is strongly recommended to update the popPK model with more PK data when possible, especially to provide more insight on the high variability. In addition, exposure-toxicity analyses could gain from data later treatment cycles, because more adverse events might occur in later treatment cycles	See screenshots	See screenshots	Yes	Table 4: Parameter estimates from the final PopPK model	Oncology
157	EPAR_b13	amivantamab	rybrevant	non-small cell lung cancer (NSCLC)	1	1	2.6.2 Clinical Pharmacology	47	dosing schedule	posology	popPK and exposure/response		popPK: 2-compartment model with a parallel linear and saturable (ie, Michaelis-Menten) clearance mechanism ER: Emax	2-compartmental model	Yes	Yes	NA		NA	NA	NA	Yes	NA	Oncology
11	EPAR_b14	deucravacitinib	Sotyktu	Sotyktu is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy	2	1	Clinical pharmacology	53	Pharmacokinetics in target population	population PK	popPK	popPK	2-compartment model,	2-compartmental model	No	Unclear	Residual Standard Error, Confidence Interval	rse, ci	In general, the population typical values were precisely estimated (low RSE% <20%, except for Tlag where RSE was 22.4%). However, several covariate effects were poorly estimated At the CHMP request, the applicant refined and updated the PK models. With the updated model, the number of model parameters increased by five (plus the fixed Tmax parameter), compared to the previous model, but the model performance was comparable with the previous model and exposures remained similar. Therefore, the initial model is considered final, although the population PK models show some deficiencies, the overall results and predictive performance is considered sufficient to provide supporting information on the expected PK behaviour, exposures, as well as exposure-response for efficacy and safety.	See screenshots	See screenshots	Yes	Table 5 Parameter estimates of the final population PK model for deucravacitinib	Rheumatology / Immunology
79	EPAR_b15	Trametinib	Spexotras	Low-grade glioma (LGG) Spexotras in combination with dabrafenib dispersible tablets is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy. High-grade glioma (HGG) Spexotras in combination with dabrafenib dispersible tablets is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment	1	1	2.6. Clinical Pharmacology	33	Clinical Pharmacology	clinical pharmacology	popPK	popPK	two-compartment disposition model	2-compartmental model	Yes	Yes	goodness-of-fit plots, pcVPC,	gof, pcvpc	Based on various goodness-of-fit plots and changes in the OFV, it is deemed acceptable to rely on estimated coefficients according to the final model. The applicant presented parameter estimates and various goodness-of-fit plots for the final model which is considered overall relevant. The parameter estimates were overall reasonable and with reasonable precision. An important diagnostic plot within the current procedure is pcVPCs (using actual time after dose as the independent variable) which were provided stratified by different weight-/age groups, formulation and occasion/steady state.	See screenshots	See screenshots	Yes	Table 6. Final model parameters, Figure 2 & 3 Prediction-corrected VPC	Oncology

41	EPAR_b17	tezepelumab	Tezspire	add on therapy for the treatment of adults and adolescents 12 years and older with severe asthma	1	1	2.6.2. Clinical pharmacology	36	2.6.2. Clinical pharmacology	clinical pharmacology	popPK	popPK	2-compartment model with first-order absorption and elimination	2-compartmental model	Yes	Yes	RSE; Bootstrap CI; Shrinkage; pcVPCs; numerical predictive checks	rse, bootstrap ci, shrinkage, pcvpc	In the dosage range tested, a two-compartment linear model best described tezepelumab PK. Model parameters were estimated with adequate precision. The shrinkage of CL and Vc in both the base and final model were low, indicating that EBEs for these parameters can be considered reliable. As shown in the diagnostic plots, individual fits, pcVPCs and numerical predictive checks, the final model described the PK data well and is considered adequate for performing simulations.	See screenshot	See screenshot	Yes	Table 3. Summary of final population PK parameters	Pulmonology / Respiratory
15	EPAR_b2	Sugemalimab	Cejemly	Cejemly in combination with platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small-cell lung cancer (NSCLC) with no known sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations. 1.2. Legal basis, dossier conten	1	1	Discussion on clinical pharmacology	36	Pharmacokinetic data analysis	population PK	popPK	popPK	two-compartment model with time-dependent elimination	2-compartmental model	Yes	Yes	sampling importance resampling, VPC	sampling importance resampling, vpc	An overall standard battery of graphical and numerical diagnostics was used during the popPK model development, which is acceptable. Parameter uncertainty estimation was performed using sampling importance resampling (SIR), which is considered acceptable. Prediction- and variability-corrected VPCs were generated, which is considered a key diagnostic.	See screenshots	See screenshots	Yes	Figure 2: Schematic of the final population PK model, Table 4: Parameter estimates of the final population PK model	Oncology
120	EPAR_b6	trastuzumab deruxtecan	enhertu	unresectable or HER2+ breast cancer	1	1	2.6.2. Clinical Pharmacology	64	NA		popPK	popPK	NA		Yes	Yes	NA		NA	NA	NA	Yes	NA						
33	EPAR_b7	dabrafenib	Finlee	Low-grade glioma (LGG) Finlee in combination with trametinib powder for oral solution is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy. High-grade glioma (HGG) Finlee in combination with trametinib powder for oral solution is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment	1	1	2.6.2. Clinical pharmacology	32	posology and dosing, DDI	posology	popPK	popPK	two-compartment model with a delayed first-order absorption model with two separate depot compartments and an inducible dose- and time-dependent clearance (CLind/F).	2-compartmental model	Yes	Yes	Confidence Intervals, prediction corrected visual predictive check	ci, pcvpc	The Applicant presented parameter estimates and various goodness-of-fit plots for the final model which is considered overall relevant. The parameter estimates were overall reasonable and with reasonable precision. An important diagnostic plot within the current procedure is pcVPCs (using actual time after dose as the independent variable). The pcVPCs show that the final model gives acceptable description of the data (Figure 2)	see screenshot	see screenshot	Yes	Table 7. Final model parameters, Figure 2. Prediction-corrected VPC for dabrafenib final PopPK model stratified by formulation.	Oncology