# Federal agency for medicines and health products

## Regulatory perspective on qualification of Modelling and Simulation based methods

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# Disclaimer

The views and opinions expressed in the following are those of the speaker and do not necessarily reflect the official position of the European Medicines Agency or the Belgian Medicines Agency.

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  - *Regulatory guidance documents referring to Qualification procedures for M&S tools*
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# Introduction

# *Regulatory guidance documents referring to Qualification procedures for M&S tools*


**ICH E14/S7B Implementation Working Group**

**Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential**

**Questions and Answers**

**E14/S7B Q&As**

Adopted on 21 February 2022

# *Regulatory guidance documents referring to Qualification procedures for M&S tools*

ICH
harmonisation for better health

**ICH E14/S7B Implementation**

**Clinical and Nonclinical Evaluation of QT/QTc Int Potential**

**Questions and An**

**E14/S7B Q&A**

Adopted on 21 February

**4. Principles for Proarrhythmia Models**

| # | Date of Approval | Questions | Answers |
|---|---|---|---|
| **4.1** | | The ICH S7B guideline (Sec on 3.1.4) states that directly assessing proarrhythmic risk of pharmaceuticals that prolong the QT interval would be a logical undertaking and interested parties are encouraged to develop these models and test their usefulness in predicting risk in humans. What are general principles to evaluate whether a proarrhythmic risk prediction model could be used as part of an integrated risk assessment strategy? | Different models, including *in silico, in vitro, ex vivo* and *in vivo* models, strategy to evaluate the proarrhythmic risk of QT-prolonging pharmaceuticals in humans. Use of *in vitro* and *in silico* models can also reduce animal use in accordance with the 3R (reduce/refine/replace) principles. Because these models have a common feature of using nonclinical experimental data as input and generating human proarrhythmia risk prediction as output, they can generally be referred to as proarrhythmia risk prediction models. The model input can vary among different models, for example, ion channel pharmacology data as input to *in silico* models, drug-induced changes in cellular repolarization and/or arrhythmia events as input to hiPSC-CM models, and drug-induced electrocardiographic changes as input to *ex vivo*/*in vivo* models. However, the model output (either discrete risk categories or continuous risk scores) is similar among different models. Such a feature makes it possible to develop generic principles for evaluating the predictivity of proarrhythmia risk prediction models without specifying the type of underlying experimental data used as model input. The following general principles should be applied to all proarrhythmia risk prediction models intended to be used as part of an integrated risk assessment for regulatory purposes. While the main focus of these principles is to evaluate a model's predictivity of TdP risk, they are general enough to guide the development of models predicting different types of proarrhythmia. |

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ICH
harmonisation for better health

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**Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential**

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Adopted on 21 February 2022

risk assessment for regulatory purposes. Some health authorities have procedures for the formal qualification of models that allow for a model to be used within the qualified context of use without the regulatory authority needing to reconsider and reconfirm its suitability. Model developers are encouraged to contact a regulatory agency about its specific model qualification procedures. After a model has been qualified, the use of such a model is not limited to the specific facility that submitted the qualification package. However, if another facility intends to use the qualified model, that facility should perform laboratory-specific calibration and validation of the model using a subset of the reference compounds that were originally used to develop the model. An illustrative process of performing laboratory-specific

# *EMA guideline on reporting of PBPK*

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

## Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

| | |
|---|---|
| **Draft agreed by Modelling and Simulation Working Group** | April 2016 |
| **Draft agreed by Pharmacokinetics Working Party** | May 2016 |
| **Adopted by CHMP for release for consultation** | 21 July 2016 |
| **Start of public consultation** | 29 July 2016 |
| **End of consultation (deadline for comments)** | 31 January 2017 |
| **Agreed by Modelling and Simulation Working Group** | October 2018 |
| **Agreed by Pharmacokinetics Working Party** | October 2018 |
| **Adopted by CHMP** | 13 December 2018 |
| **Date of coming into effect** | 1 July 2019 |

# *EMA guideline on reporting of PBPK M&S*

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

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# EMA guideline on reporting of PBPK M&S

## Appendix 1: Qualification of the PBPK platform

To certify that a PBPK platform can be used for an intended regulatory purpose, the ability of the platform to perform that specific type of simulation should be evaluated and in some cases, this requires that the PBPK platform should be qualified for the intended purpose. The extent of qualification required depends on the regulatory impact of the modelling (see below).

The qualification could also be assessed within the context of a regulatory submission. However, a qualification issued within the context of a particular regulatory submission should be considered only valid for that particular submission and would need to be resubmitted and re-evaluated in future applications.

Qualification of a PBPK platform for an intended purpose may occur via a CHMP qualification procedure (EMA/CHMP/SAWP/72894/2008/Rev.3). If there is a CHMP qualification opinion supporting the intended use of the platform, then the qualification is presented on the European Medicines Agency's (EMA) web site and a reference to this location in a regulatory submission is sufficient. In this case, the qualification can be referred to in future applications with the same intended use.

Qualification can include published papers if the included validation dataset is sufficiently current and described in sufficient detail to allow a thorough understanding of the data by regulators. When the PBPK platform is used in a regulatory submission related to a certain medicinal product, the predictive performance of the drug-specific model needs to be evaluated (see Appendix 2).

'in case of doubt on the relevance or the robustness of available system data included in the platform, particularly if used for high regulatory impact simulations, the applicant is strongly encouraged to seek CHMP Scientific Advice for further guidance.

# *Scientific advice letters recommend Qualification procedures for M&S tools*

Example:

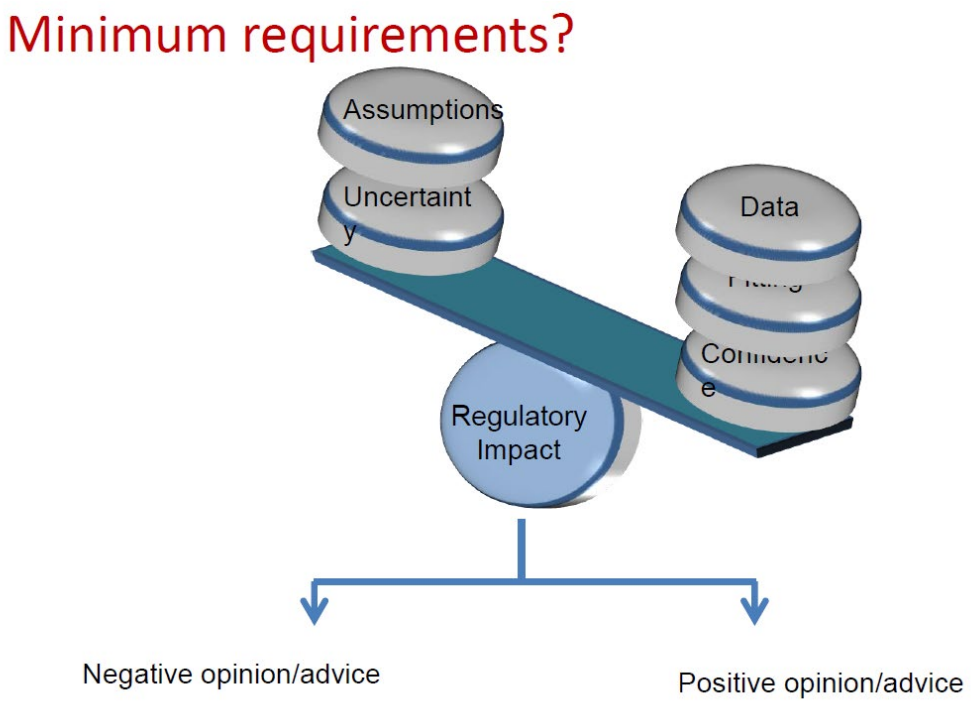
**Question 4**
**(…) the Sponsor will conduct a physiologically based pharmacokinetic (PBPK) modeling analysis to assess the DDI potential of [redacted] with highly protein-bound therapeutics, especially therapeutics with a narrow therapeutic index. Does the Agency agree that the PBPK modeling approach would be sufficient to adequately assess the potential DDI of [redacted] with highly protein-bound therapeutics and could support the filing of the MAA?**

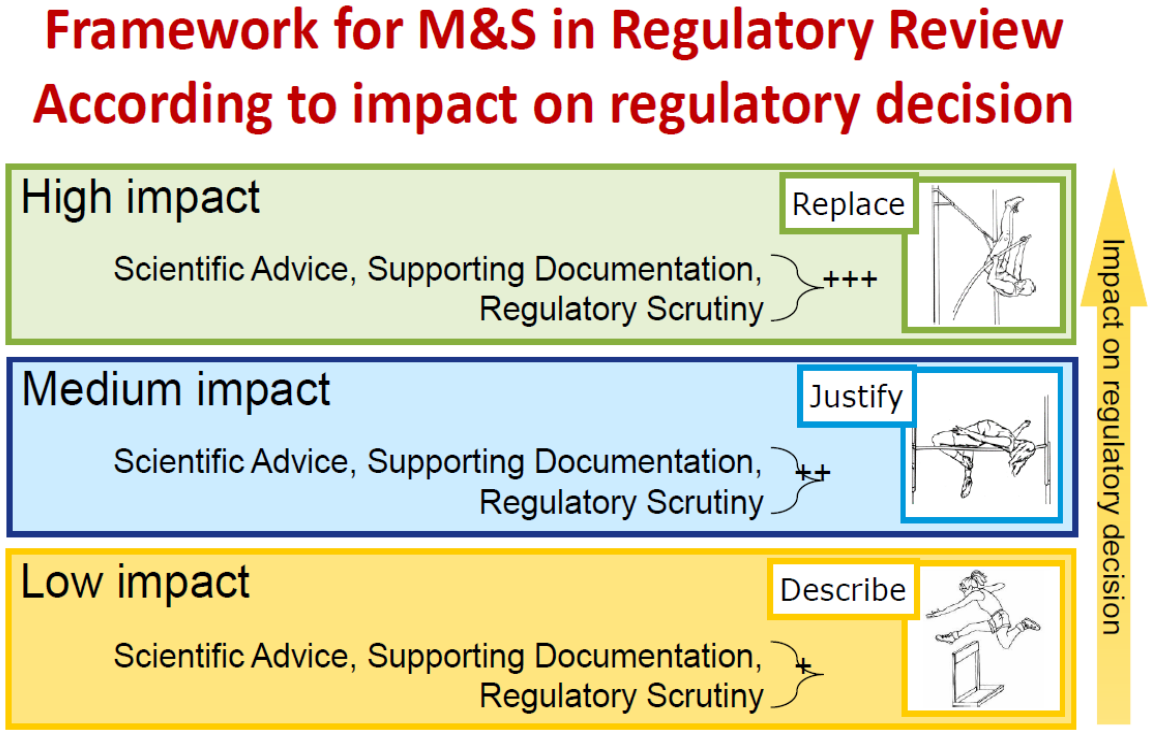
## Answer

The development of a PBPK model is endorsed since it may help to better understand and predict the impact of [redacted] with highly protein-bound therapeutics. The PBPK model will be used in a high regulatory impact scenario since it concerns a waiver for a confirmatory DDI clinical study. **As such, robust qualification of the PBPK platform** for the intended purpose is necessary in accordance with the EMA Guideline on the reporting of PBPK modelling and simulation (https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation).

# Qualification procedures are highly encouraged for M&S tools

- **In particular for:**
  - Platforms and models intended to be used in many drug development programs
  - Complex models and simulation tools built on retrospective (historical, literature) data
  - Modelling and simulation tools proposed for high regulatory impact applications

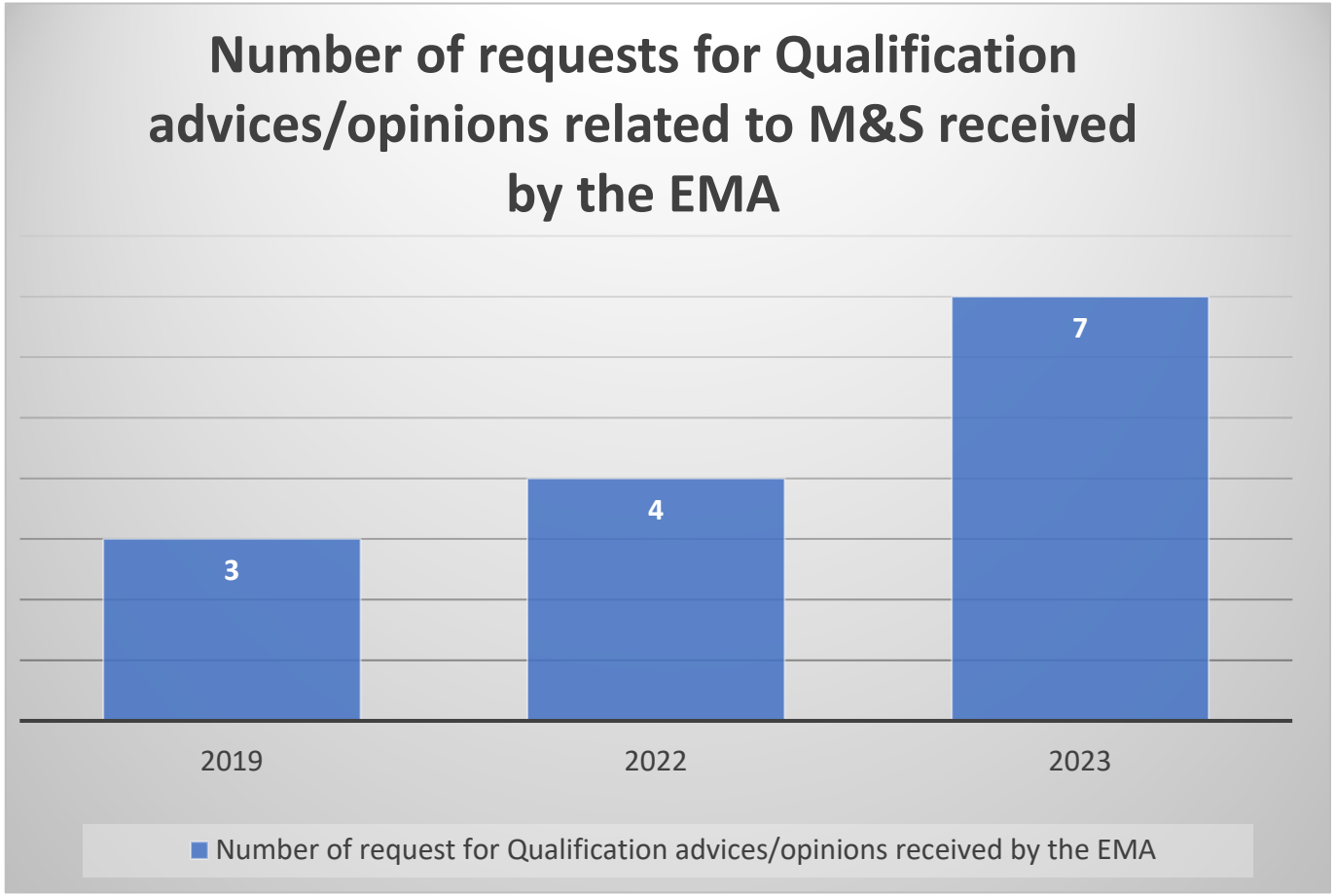


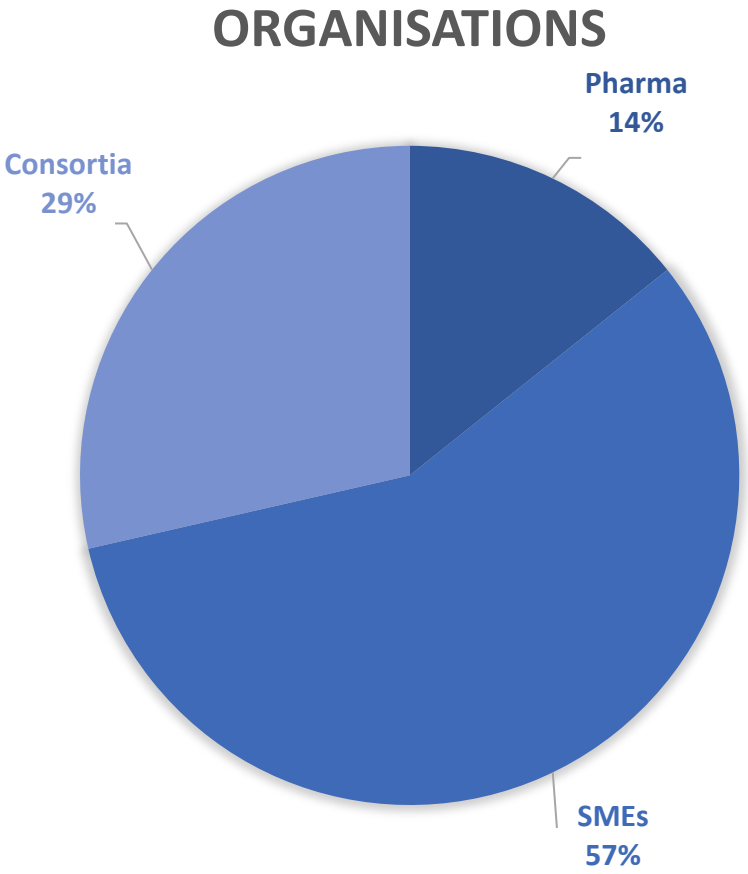




From EMA-EFPIA Modelling and Simulation Workshop, December 2011

# EMA 5 years experience

# *Requests received by the SAWP the last 5 years*



# *Requests received by the SAWP the last 5 years*

## Scope for Qualification Procedure related to M&S

**Preclinical development**

- Predict activity/safety
- Support waiver for (components of) nonclinical studies

**Clinical development**

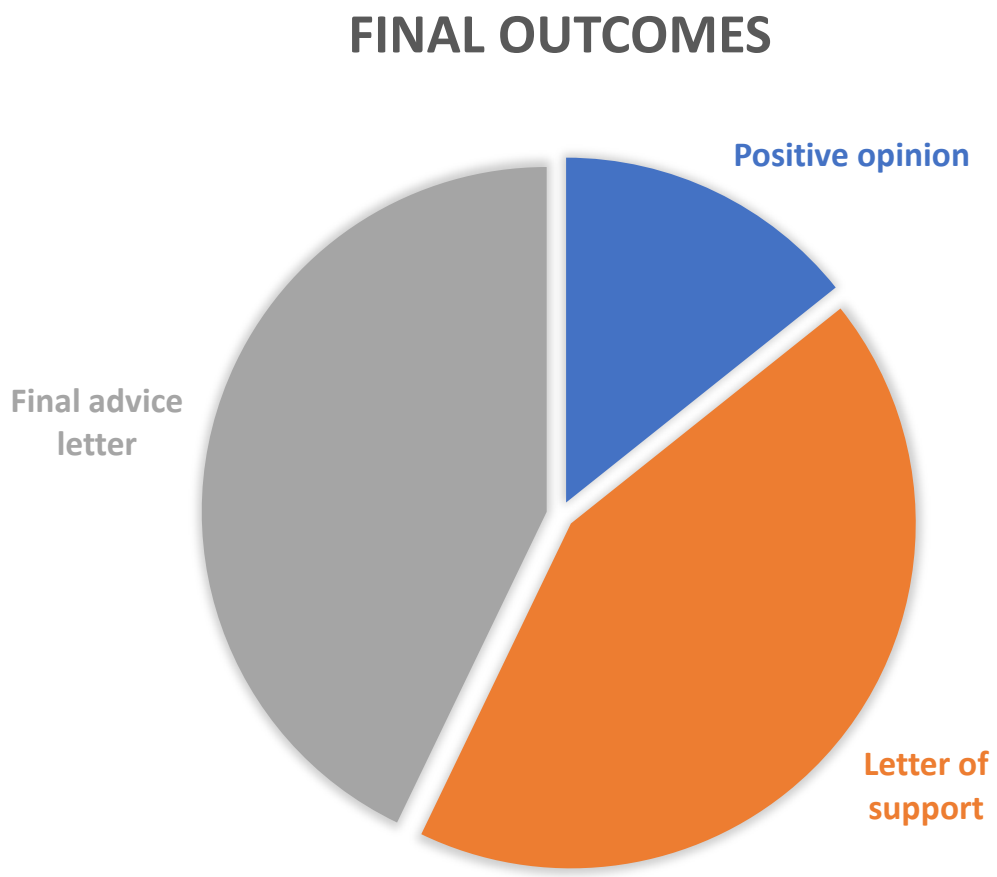
- dose-finding
- enrich population
- surrogate endpoint

**Drug utilisation**

- optimise target population
- guide treatment regimen

# *Requests received by the SAWP the last 5 years*

## Final outcomes of completed qualification procedures




**Positive opinion**

- The applicant submitted the request for opinion after an qualification advice procedure
- Raw data and code submitted
- Some of the analyses performed by QTeam
- In total 2 DMs and several interactions in writing, or teleconferences

**Letters of support**

- Requested by the applicant
- To facilitate the obtention of additional data

# *Requests received by the SAWP the last 5 years*

## Scope of questions received from the applicant

- **Context of use**
- **Relevance of the Data**
- **Methodology**
  - Method/data used for model buiding
  - Methods/data used for model validation/evaluation
- **Adequacy of the package** to support a Qualification opinion

# *Requests received by the SAWP the last 5 years*

## Scope of questions in the list of issues from the QTeam

- **Context of use:** Formulation (too broad, need to refine, restrict), (in)adequacy with the available data
- **Relevance of the Data**: Issues with quality of data used for model building or evaluation, limitations of the data given the context of use
- **Methodology**
  - Method/data used for model buiding : Key information missing, limitation in implementation
  - Methods/data used for model validation/evaluation: model misspecifications, incomplete evaluation, unacceptable results, etc.
- **Adequacy of the package** to support a Qualification opinion: Need for additional data or analyses

# Examples

# Example 1

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

**CONFIDENTIAL**
Doc Ref: EMADOC-1700519818-911245
Case No.: EMA/SA/0000076855
Human Medicines Division

Amsterdam, 15 September 2022

Initial Qualification Procedure

# Qualification advice request for a model-based tool for dose-selection in osteoporosis

# Example 1

## Questions on Clinical development

### Question 1

**Does EMA agree that the definition of Biomarker as "A biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals" can broadened so as to include an in silico-based prediction and therefore that term Biomarker applies also to [redacted]?**

### CHMP answer

**This question is not judged very important nor relevant** for the primary objective of this procedure which is the qualification of [redacted].

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Of note in the present case, it can be considered that measured variables (which are the actual biomarkers) are patients' mass (weight), height and (…). These biomarkers are proposed to be analysed using a model-based approach. What would be qualified in case of positive qualification opinion would be an innovative method, not only the biomarkers.

There is therefore not a need to change the definition of a Biomarker per se.

In summary, the **EMA is not going to change the definition of a biomarker**. (…)

# Example 1

**Questions on Clinical development**

**Question 2**

**Does EMA agree that the Context of Use clearly describes how [redacted] will be used to provide a new surrogate of the fracture endpoint in Phase II clinical Trials?**

**CHMP answer**

In response to the feedback received by the qualification team the Applicant modified the context of use 3 times throughout the qualification procedure. The last context of use reads as follows:

(…)

CHMP is in principle supportive of the development of novel endpoints for [redacted] trials. However, there are uncertainties on the technical aspects of [redacted] and the Applicant does not intend to pursue a clinical validation satisfying the regulatory requirements, **which makes the proposal unacceptable.**

# Example 1

**Questions on Clinical development**

**Question 3**

**Does the EMA agree that the proposed technical validation strategy is acceptable to assess the precision and accuracy of the for [redacted] methodology in predicting the absolute risk of [redacted] ?**

**CHMP answer**

Several issues were identified by CHMP on the technical validation plan. (…)

The Applicant expressed in their answer to the list of issues and during the discussion meeting that **they are not planning to request a qualification opinion for this model** in its current form. According to their own statement, this submission aims to highlight potential issues in the regulatory qualification of drug development tools based on physics-based and physiology-based patient-specific models. They also indicated that, in their opinion **it is highly unlikely anyone will conduct the clinical validation studies of the requested size, duration and cost to validate a tool to merely improve dose-response studies.**

The Applicant is therefore first reminded that the technical comments made as part of a qualification advice procedure are in principle intended to prepare a qualification opinion. Moreover, the CHMP qualification advice and opinion procedures are dedicated to biomarkers and innovative methods planned to effectively be used in drug development, which, as the Applicant argued during the discussion meeting, is not the case anymore for [redacted] methodology.

Thus, an in-depth **technical discussion is considered obsolete** at this stage.

# Example 2

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 March 2022
EMA/CHMP/SAWP/186420/2022
Committee for Medicinal Products for Human Use (CHMP)

## Qualification Opinion of Islet Autoantibodies (AAs) as Enrichment Biomarkers for Type 1 Diabetes (T1D) Prevention Clinical Trials

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-islet-autoantibodies-aas-enrichment-biomarkers-type-1-diabetes-t1d-prevention_en.pdf

# Example 2

**2. Answers to applicant's questions**

**Based on the coordinators' reports the CHMP gave the following answers to the questions by the applicant:**

**Question 1:**

**Does EMA agree with the COU?**

**CHMP answer**

The qualification exercise included a modeling exercise that also identified the relevance of additional clinical parameters (sex, baseline age, blood glucose measurements from the 120-minute timepoints of oral glucose tolerance test (OGTT), and haemoglobin A1c (HbA1c) levels).

Individuals defined as 'At risk' were defined in this context as being a first degree relative (FDR) of a T1D patient or those having a specific human leukocyte antigen (HLA) subtype of risk (HLA-DR3/3, DR4/4, DR3/4, DR3/X [X≠3], DR4/X [X≠4]), excluding individuals with baseline fasting glucose ≥ 126mg/dL (7.0 mmol/L) or stimulated 2-hour glucose ≥ 200 mg/dL (11.1 mmol/L).

Positivity for two or more of the islet AAs, determined in this population, in addition to the relevant characteristics as described in the model, can be used for enrichment of clinical trials focusing on the delay or prevention of the clinical diagnosis of T1D.

The proposed COU is overall agreed. The clinical interest of identifying good biomarkers for Type 1

# Example 2

**Question 2:**

**Does EMA agree that the data sources are adequate to support the proposed COU?**

**CHMP answer**

The data sources are judged largely relevant, consistent with the recommendation during the QA procedure. From a modeling perspective, this approach is endorsed, and the 3 data sources seem adequate. Potential covariate distribution and correlation were presented and discussed as requested during the qualification procedure.

The baseline data intended for modeling are relatively well defined, as well as the binary endpoint (T1D diagnosis).

# Example 2

**Question 3:**

**Does EMA agree the AFT survival model and its covariates represent adequate evidence for the qualification of islet AAs as enrichment biomarkers for T1D prevention trials?**

**CHMP answer**

***Conclusion***

After the interactions with the SAWP, the applicant has provided a library of models, resulting in acceptable predictive performances for T1DM onset over a 6 years period.

It should be noted that additional covariates were also included in each of the proposed models beside positivity to at least 2 Islet AAs. These additional predictors include HbA1c, blood glucose measurements from the 120-minute timepoints of an OGTT, baseline age and sex of patients. The magnitude of the covariate effects for each of these predictors as well as their combination (OGTT, HbA1c, age and sex) was found to be higher than that of the Islet AAs alone. As a consequence, the impact of the added-value of the positivity will for example be much less important for the patients with already impaired OGTT (120-minute value between 7.8 and 11.1 mmol/L) and pre-diabetes (fasting b-glucose 5.6 to 6.9 mmol/L).

The use of the Islet AAs as a biomarker to optimize the design of clinical trials for the prevention of T1DM should therefore always be done also considering these additional patient characteristics.

# Take home message

# *Take Home message*

## Qualification procedures are highly encouraged for M&S tools

- **In particular for:**
  - Platforms and M&S tools intended to be used **in several drug development** programs
  - **Complex** modelling and simulation tools
  - M&S built or validated **on retrospective (historical, literature) data**
  - Modelling and simulation tools proposed for **high regulatory impact** applications