**Title:** Qualifying Mechanistic Physiological Models for Use in Pharmaceutical Discovery and Development

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**Objectives:** Mechanistic physiological models are powerful tools for advancing research and supporting decision-making in drug discovery and development. The modeling process is not driven by data availability alone; rather, it is focused on the research context, making use of all relevant data and knowledge to address a research question. Physiological models are thus qualitatively different from statistical models. Statistical tests alone, while important, are neither sufficient nor appropriate for determining whether a physiological model is fit for purpose. We propose a standard method for qualifying mechanistic physiological models for use in drug discovery and development.

**Methods:** We employ concepts from statistics, dynamical systems modeling, decision analysis, and related fields to define a model qualification method that is both necessary and sufficient for ensuring that a mechanistic physiological model is fit for purpose.

**Results:** The model qualification method comprises eight criteria that address questions of relevance, dealing with uncertainty, dealing with variability, and matching test data. Statistical concepts are applied to delineate a rigorous statistical testing approach that is appropriate to this type of model. The model qualification method is complete, practical, research context-specific, and not dependent on the availability of specific data sets. Approaches and specific tests for satisfying each of the eight criteria are described and illustrated with examples from our collaborative research practice.

**Conclusions:** The model qualification method formalizes statistical requirements that mechanistic physiological models must meet and goes beyond these data-based tests to ensure that a mechanistic physiological model is qualified for use in drug discovery and development.