

Using AI to Address Practical Challenges for Generic Drugs: Using Digital Twins to Serve as RLD

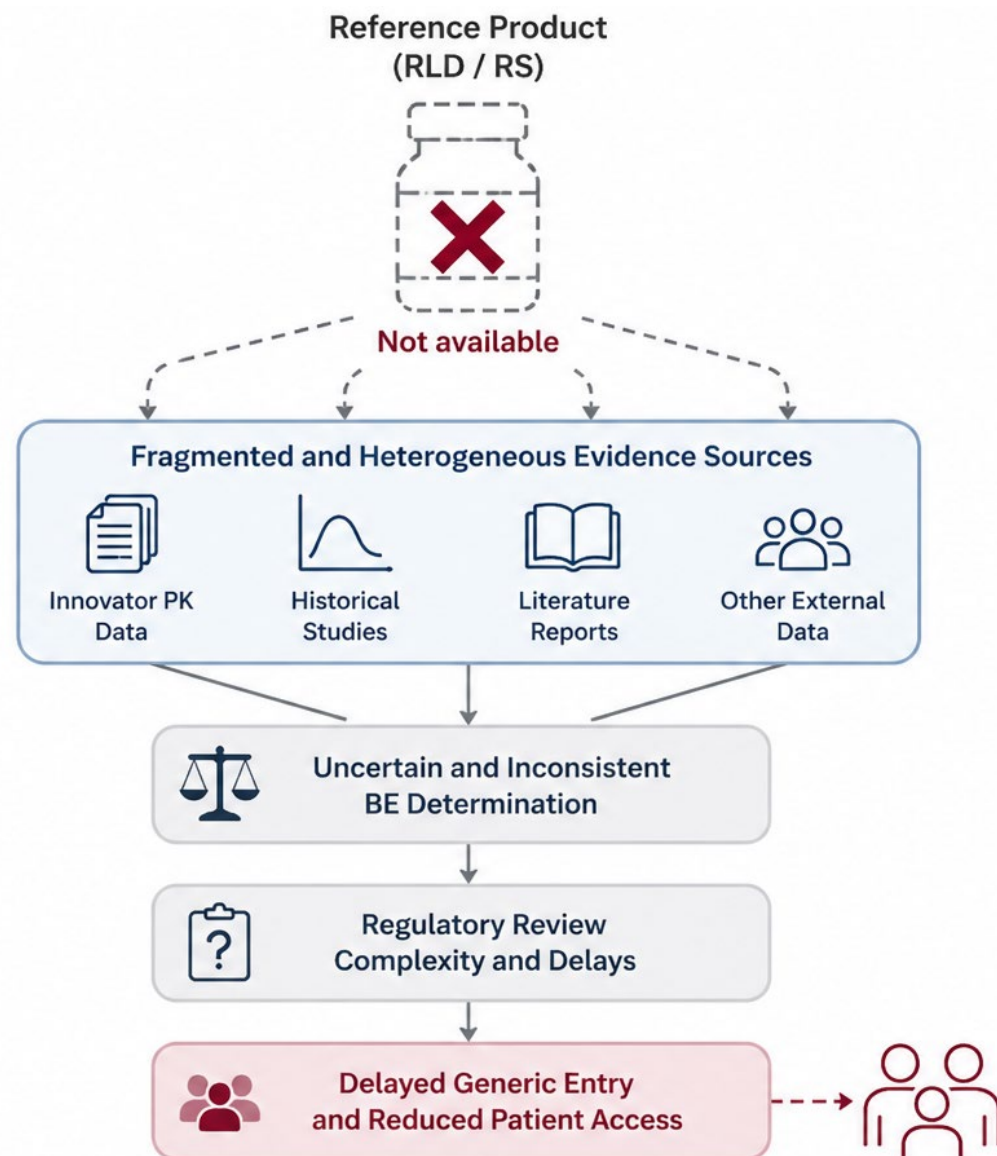
A Framework Perspective

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When the RLD / RS is unavailable

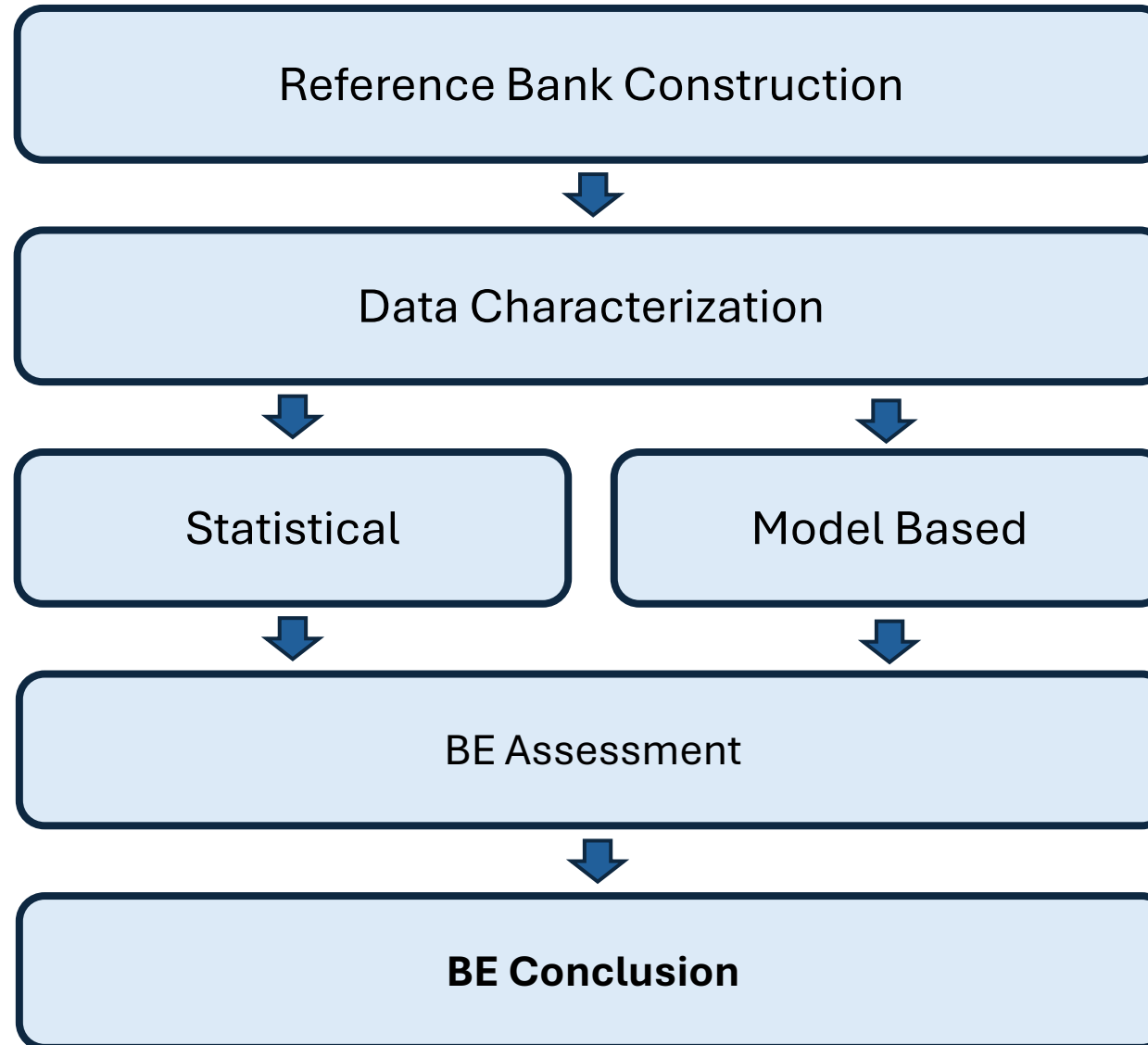


Potential Solutions

- Alternate reference standards (dose strength/formulation)
- Use of available data
 - Bridging using innovator or legacy studies
 - Statistical reconstruction or resampling approaches
 - Simulation-based reference construction
 - Model-informed approaches
 - Hybrid approaches combining data and modeling

Alternative approaches rely on assumptions about the reference that are not directly observable and can influence bias, Type I error, and power, requiring explicit evaluation of when BE inference remains reliable in the absence of an RLD

A Quantitative Framework



A Quantitative Framework

Reference Bank Construction



Data Characterization



Statistical



Model Based



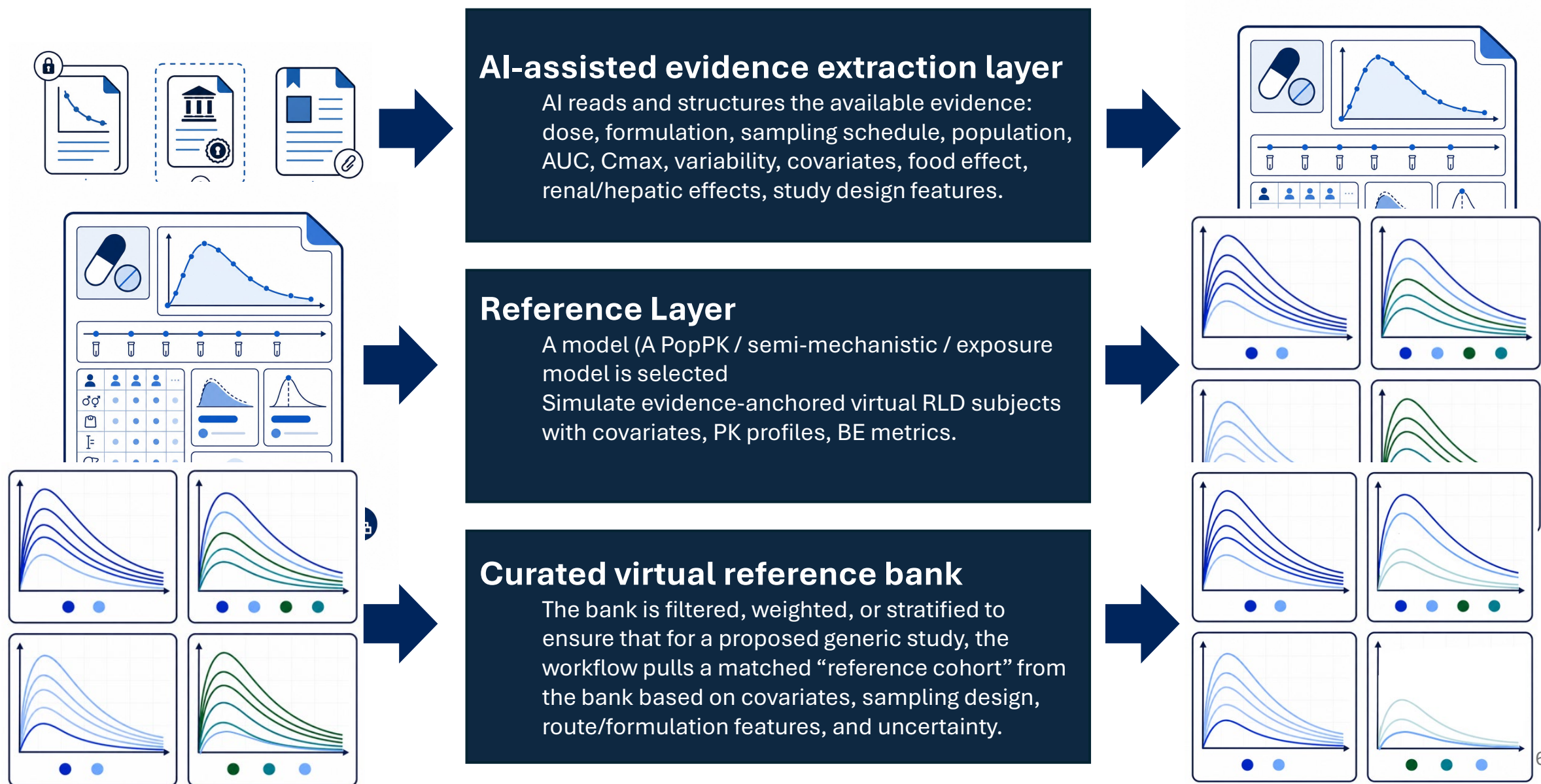
BE Assessment



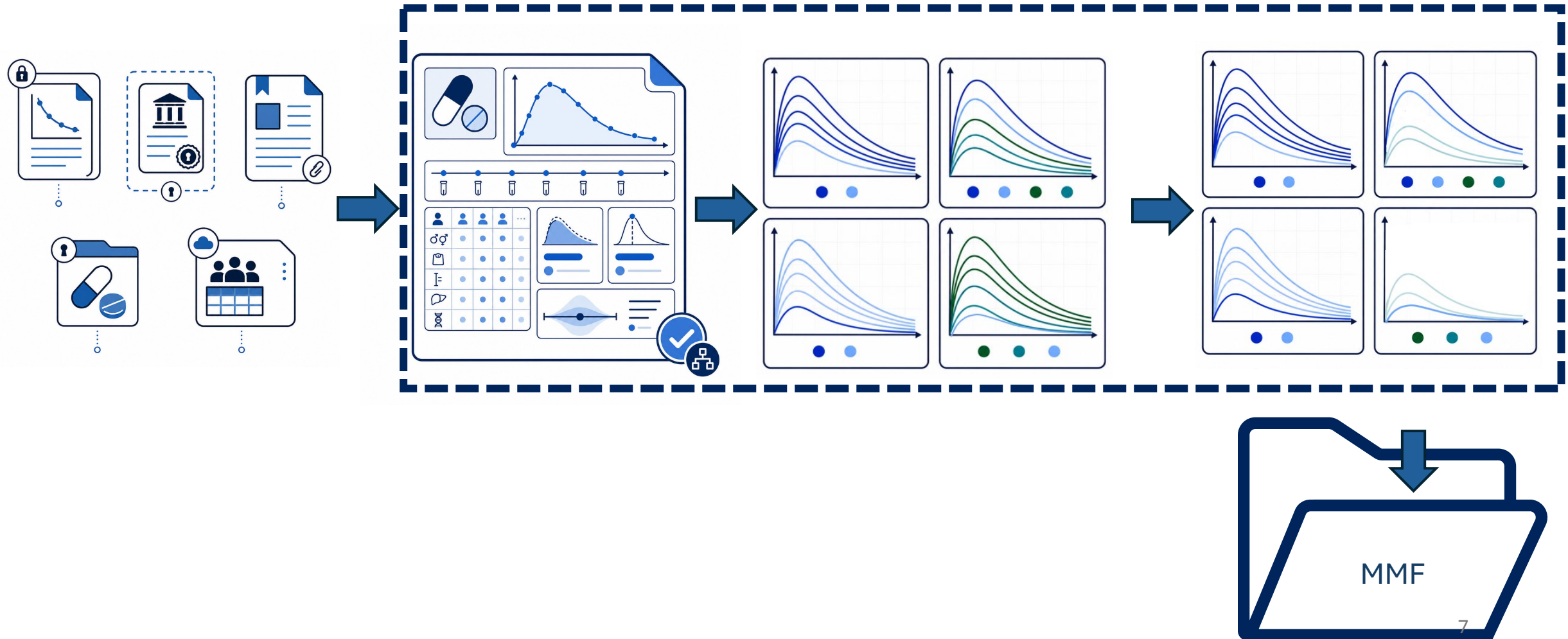
BE Conclusion

- Literature / PK model-derived
- Concentration–time data
- Innovator studies
- Variability + covariates

Use of Digital Twins to Create a Virtual Reference



AI Creation of a Virtual Reference Bank

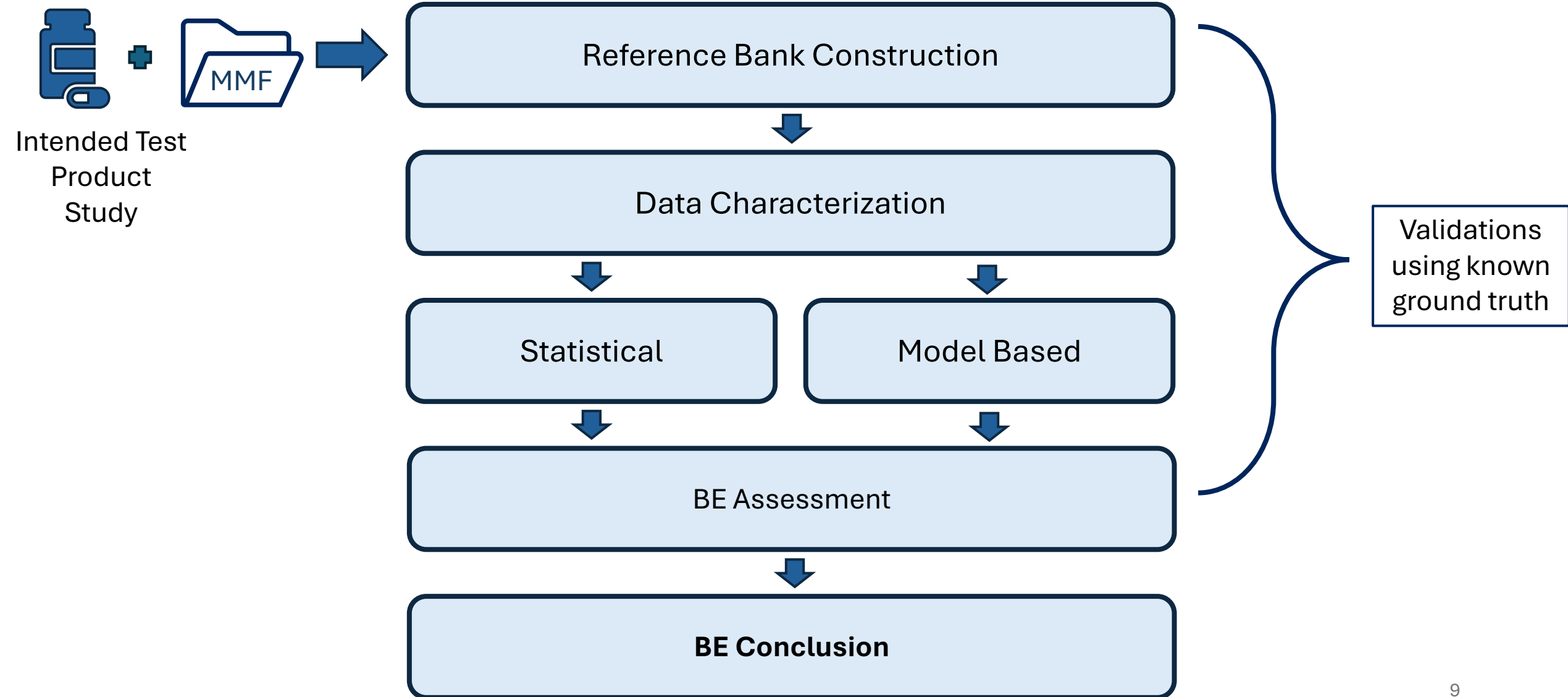


Qualifying Digital Twins for Use in a Virtual Reference Bank

- Not every simulated subject should automatically contribute equally to the virtual reference bank. Each digital twin can be evaluated for how well it represents the intended RLD comparison context.

Domain	What is evaluated?	Possible flag
Population similarity	Does the twin match the intended BE population in things like key covariates: Age, weight, sex, renal/hepatic function?	Low / Moderate / High match
Exposure plausibility	Are AUC, Cmax, Tmax, and profile shape within plausible RLD ranges?	In-range / Edge / Outlier
Evidence support	Is the twin anchored to observed RLD data or extrapolated beyond available evidence?	Direct / Inferred / Extrapolated
Model certainty	How much uncertainty surrounds the twin's exposure prediction?	Low / Moderate / High uncertainty
Study-design compatibility	Can the twin support the proposed BE endpoint and sampling design?	Eligible / Limited / Not eligible
Reference influence	Would this twin disproportionately affect the reference distribution or BE conclusion?	Stable / Influential

A Quantitative Framework



Strengths and Limitations

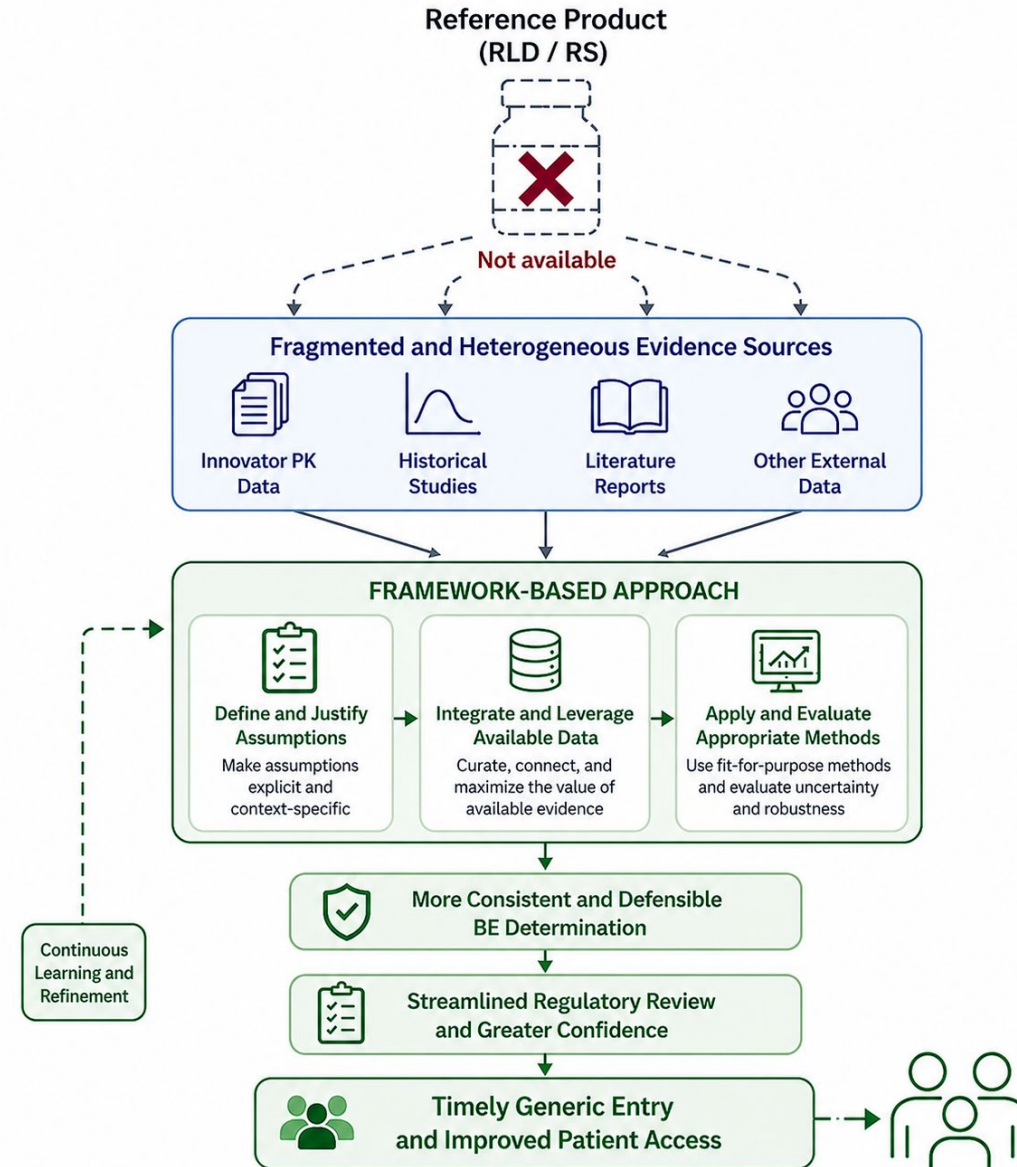
Strengths

- AI operationalized framework
- Uses available data in RLD-unavailable settings
- Evaluates methods under controlled conditions
- Structured and Reproduceable Framework

Limitations

- Dependent on quality of available data
- Scope limited to pre-evaluated scenarios

Practical Impact





Looking Forward & Next Steps



Thank You