Navigating the Science: Exploring the Development and Validation of Dosing Guidance Tools

Harnessing Pharmacokinetics for Precision Dosing Guidance

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Disclosures for Martin Wolfsegger and Alexander Bauer

Employee	Martin Wolfsegger and Alexander Bauer are employees of Baxalta Innovations GmbH, a Takeda company
Shareholder	Martin Wolfsegger and Alexander Bauer are stock owners of Takeda

myPKFiT

- myPKFiT: The first pharmacokinetic (PK) dosing software cleared by the U.S. Food and Drug Administration (FDA) for use with hemophilia A patient
    - Patients with hemophilia A have excessive bleeding after injuries or spontaneous bleeding episodes because of the lack of a Factor VIII coagulation factor in their blood
- The software generates a patient's estimated individual PK profile, which aids healthcare professionals in personalizing a patient's prophylaxis dose and schedule
- Released in 56 countries and passed the 17,000 patient mark in 2024

Background

What is myPKFiT

- Approved dosing guidance tool to support licensed healthcare professionals in treatment of hemophilia A
- Uses individual patient's information and local FVIII laboratory activity measurements
- Dosing guidance produced by processing the individual patient data with a Bayesian algorithm

Based on few blood samples only

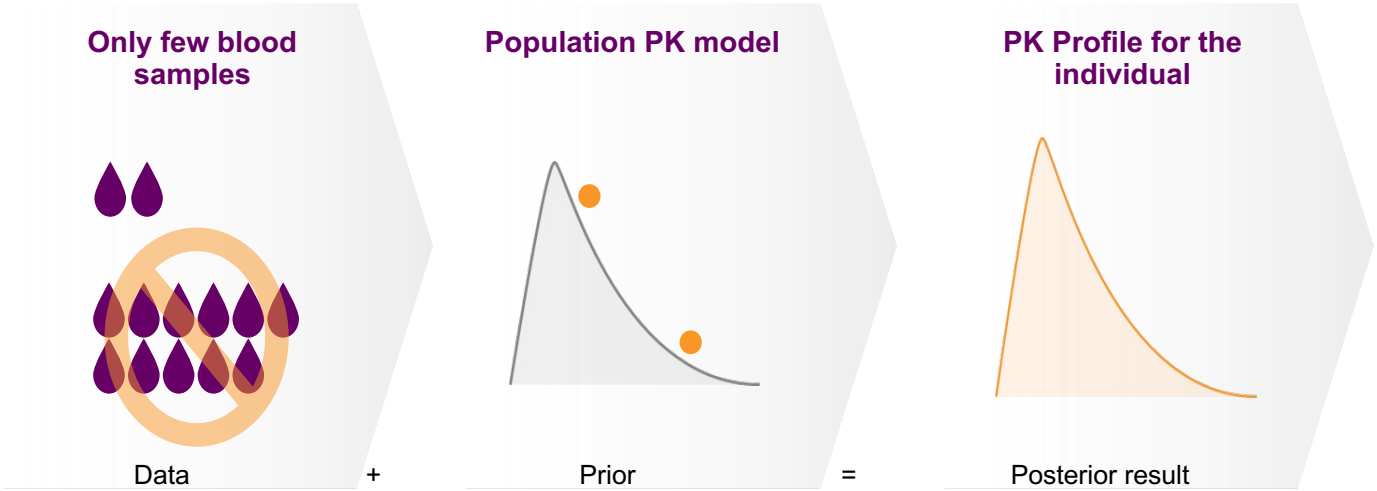
What can be done with myPKFiT

- Evaluation of various routine prophylaxis regimens
- Tailored to individual hemophilia A patient's needs
- Guide decisions on appropriate FVIII dose and dosing frequency to maintain FVIII activity

Enable patient management

Introduction

Complex Strategy



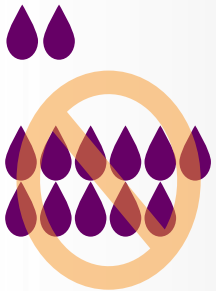
1) Technically it's a maximum a-posteriori probability (MAP) estimate

Introduction

Complex Strategy

PK → regimen[2)] → exposure → response

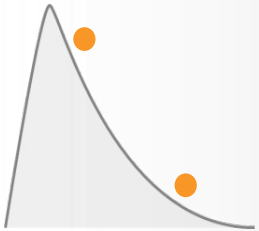
Only few blood samples



Data

+

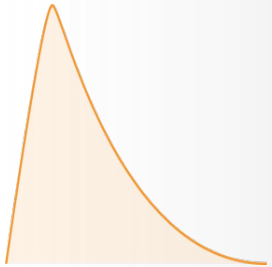
Population PK model



Prior

=

PK Profile for the individual



Posterior result

Personalized regimen

Empirical Bayes estimation[1]

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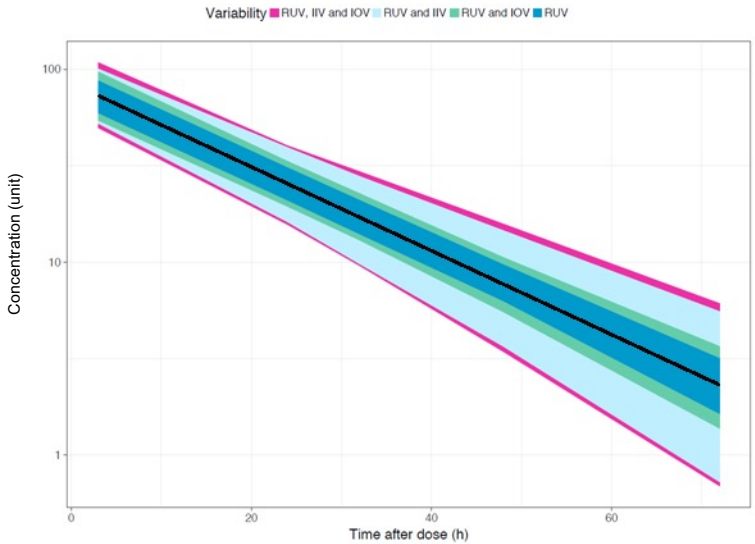
2) Limited by product label

Population PK and Bayes Estimates

Illustrative example:

IV bolus administration for a given subject
(black solid line = Population estimate for a specific combination of covariates)



RUV … residual unexplained variability; IIV … inter-individual variability, IOV … inter-occasion variability

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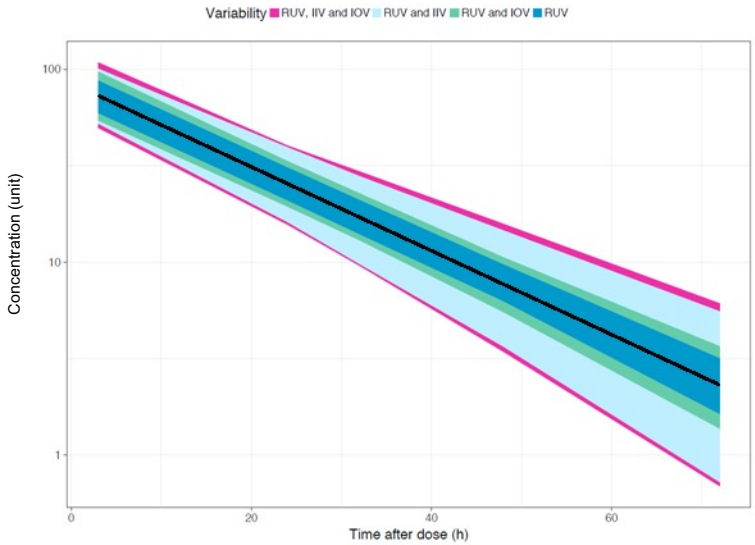

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Motivation for a Bayesian Approach

- Typically large IIV
- PopPK model → Prior information fixed
- Population estimate could be regarded as starting values for optimization within Bayesian framework

Key premise for Bayesian approach
IOV ≪ IIV

Bayesian Algorithm and Leverage to PopPK Model

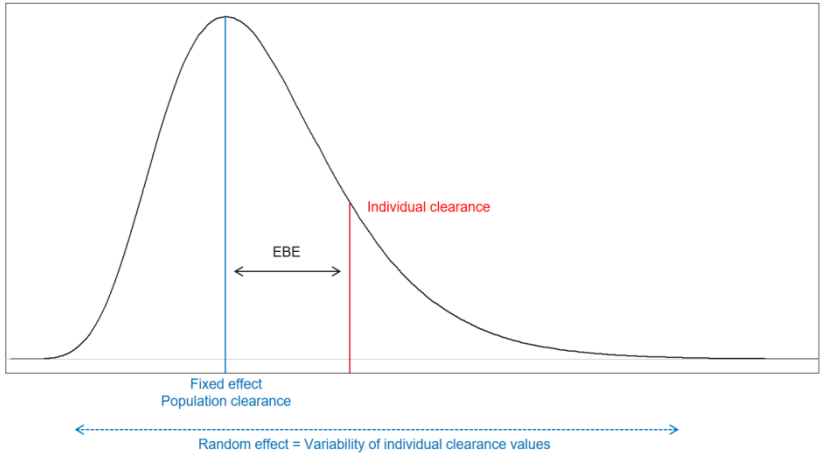
Simplified example: IV bolus

One-compartmental with IIV on CL and V with combined additive and proportional residual error

The Bayes algorithm estimates the individual random effects (IIV) for clearance η_{CL} and volume of distribution η_V by minimization of the following weighted least-squares objective cost function

$$O_{WLS}(\eta_{CL},\eta_V) = \sum_{i=1}^{n} \frac{(y_i - \hat{y}_i)^2}{\sigma_{add}^2 + \left(\hat{y}_i \cdot \sigma_{prop}\right)^2} + \frac{\omega_V \cdot \eta_{CL}^2 - 2 \cdot \omega_{CL,V} \cdot \eta_{CL} \cdot \eta_V + \omega_{CL} \cdot \eta_V^2}{\omega_{CL} \cdot \omega_V - \omega_{CL,V}^2}$$

- y_i represents the post-dose concentration at time point i ($1 \le i \le n$)
- $\hat{y}_i$ represents the estimated concentration at time point i from the covariate sub-models of the PopPK model
- Inter-individual variances on the log-domain for CL and V are ω_{CL} and ω_V
- The corresponding covariance is represented by $\omega_{CL,V}$



Bayesian and Pharmacokinetic Considerations

A fundamental question in Bayesian framework is the amount of information contained in the prior

Classical Bayesian: effective sample size[1)]

- Large effective sample size → the prior, rather than the data, dominate the posterior result
- Small effective sample size → the data, rather than the prior, dominate the posterior results

Pharmacokinetic application

- Additional layer of complexities
  - Number of samples per subject
  - Best[2)] location of sampling time points including allowable deviations
  - RUV model of PopPK model
  - Subpopulations requiring different set of sampling time points
  - …

Not aware of a theoretical publication which links the effective sample size concept to empirical Bayes estimation in pharmacometrical applications which is essential to understand the corresponding operational characteristics

1) Morita S, Thall PF, Müller P. Determining the effective sample size of a parametric prior. *Biometrics*. 2008;64(2):595–602.
2) Best does not necessarily imply optimal → clinical feasibility

Bayesian and Pharmacokinetic Considerations

Individual PK curve *"close"* to the population mean

- The closer the individual PK curve is to the population mean, the better the fit in case of few samples per subject
- Individual PK curves "far away" from the population mean are not fitted well based on few samples per subject
  - ➢ The prior, rather than the data, dominate posterior result

Individual PK curve *"not close"* to the population mean

- More samples per subject are required in case of PK curves "not close" to the population mean
- For large number samples per subject, the Bayesian prediction should lead to an individual fit
  - ➢ The data, rather than the prior, dominate posterior result

Our current understanding of the operational characteristics
True PK curves "far away" from the population mean cannot be estimated well using Bayesian prediction based on few samples per subject

Identification of patients "far away" from the population mean

External “Outlier” Detection

Biological

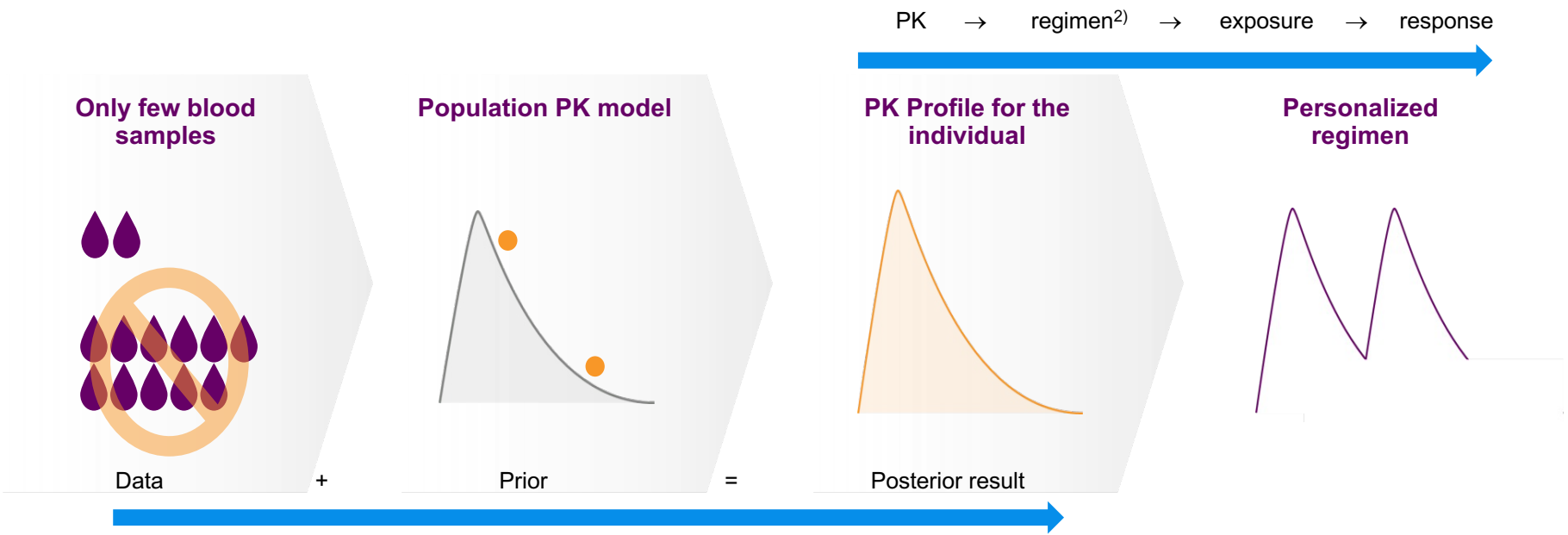
- Rare polymorphism or even a whole subpopulation not accounted for in model
- This can be viewed as a deficiency of the structural, covariate and/or inter-individual variability components of the model

Error in data

- Incorrect concentration
- Incorrect sampling time point
- …

“Outlier” diagnostics requires a simple approach such as traffic lights (red, orange, green)

Predictive Performance: Validation



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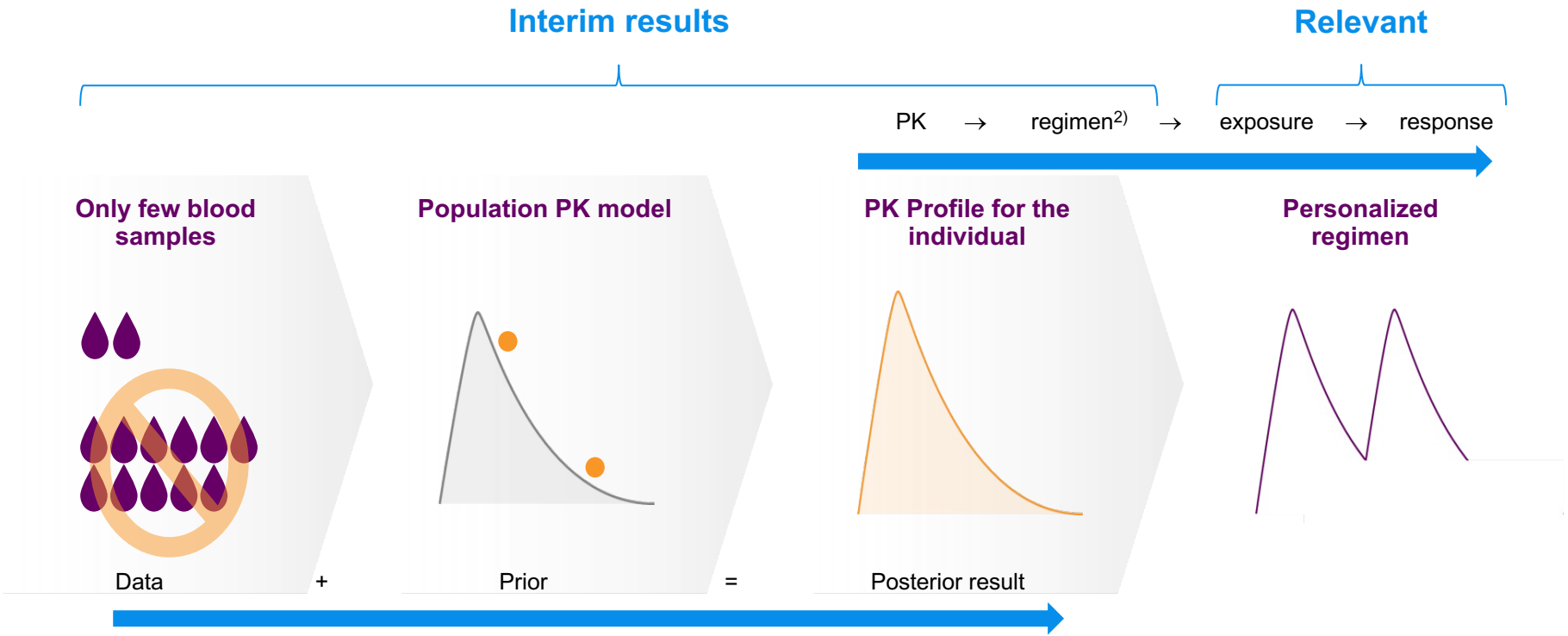

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Predictive Performance: Validation Roadmap

Validation Data Set

- Independent from the trainings data set
- Spread of covariates (heterogeneity)
- Prospective versus retrospective
- Sample size: Performance goal $\rightarrow$ formal sample size calculation delicate
  - Performance goals are **numerical target values pertaining to effectiveness or safety endpoints** in single-arm medical device clinical studies

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Parameters

- Each of the necessary PK parameters
- Sparse sampling versus extensive sampling (=reference)
- PK for reference: independence from PopPK model
- Method comparison study[1)]

Additional

- Impact of covariates (additional resources, adequate prediction for the whole range, …)
- Impact of between laboratory variability and/or differences
- Impact of Inter-occasion variability
- Handling of pre-dose samples
- Sub-populations
- …

1) Carstensen B, 2010, Comparing Clinical Measurement Methods. Wiley, Chichester

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Exposure

- Not a PK calculator
- Variety of parameter combinations may yield essentially the same curve
- Metric depend on the PK/PD relation of the compound
- Evidence for underlying premises (mechanistic models can help)
- Product label
- *Adequate exposure based on a regimen derived from PK estimated from sparse sampling?*

1) Carstensen B, 2010, Comparing Clinical Measurement Methods. Wiley, Chichester

Discussion and Conclusion

Adequate external validation of such a tool is much more complex and time consuming than building or validation of a PopPK model

Further thoughts (not included in myPKFiT): PK/PD model

“Simple” approach

- Investigation of the relationship between FVIII activity level and instantaneous risk of a bleed based on clinical study data
- Linking the FVIII activity time-course, including variation across dosing intervals, to the time-course of the PD response (i.e. recurring bleeding events)
- Estimated FVIII activity level used as a time dependent covariate within an recurrent events model

➢ Can lead to biased results due to attenuation bias

More sophisticated approach

- Uncertainty in predicted FVIII activity levels at time of onset of bleed
- Requires a method to correct for the attenuation in covariate effects that would otherwise arise due to the discrepancy between estimated and true FVIII activity level

Titman A, Wolfsegger MJ, Jaki TF (2021).
Recurrent Events Modelling of Haemophilia Bleeding Events.
Journal of the Royal Statistical Society Series C: Applied Statistics,
Volume 70, Issue 2, March 2021, Pages 351–371.