The Role of Requirements in Model-Based Decision Making

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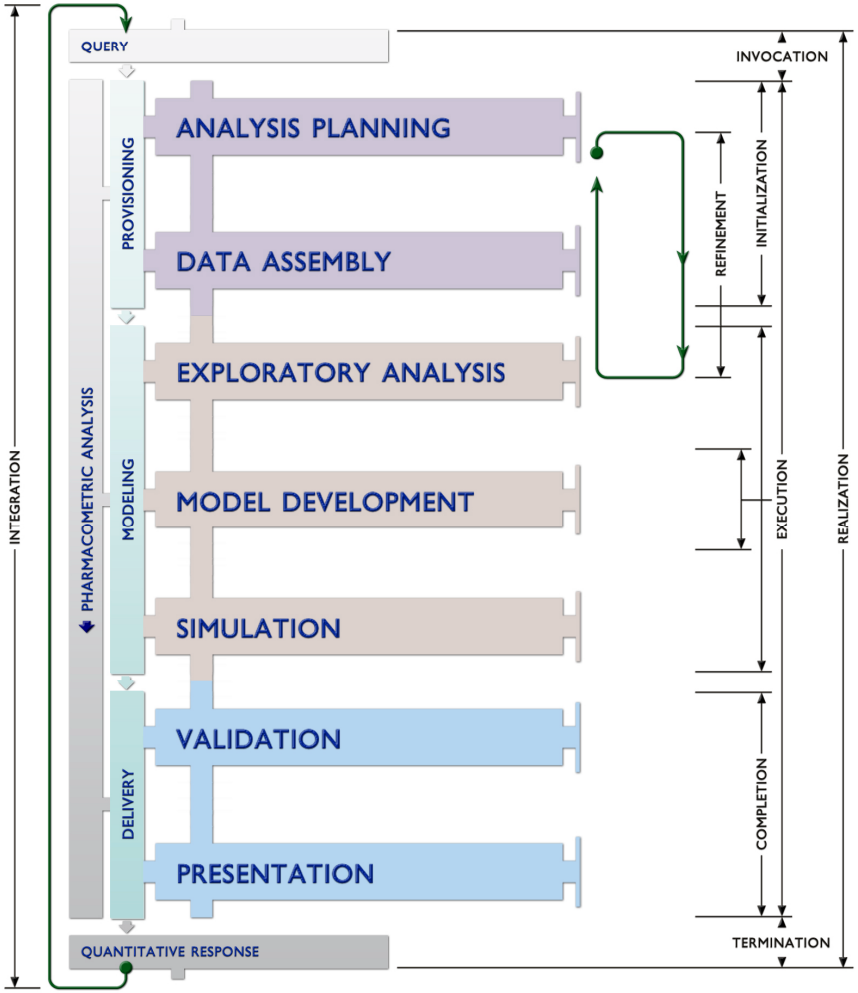
Requirements
Process



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Requirements
Definition

- The necessary attributes of a product or process that are defined before and during design

Sage and Rouse 1999

Requirements
Function

- Requirements provide a disciplined framework within which cross-functional teams can work together on separate, but related, smaller-scale problems
- A requirement must state what the system is to do, but should not specify how the system is to do it

Sage and Rouse 1999

Requirements
Types

- Mandatory
  - Specify the necessary and sufficient conditions that a minimal product or process must have in order to be acceptable. Are usually expressed with ***shall*** and ***must***.
- Preference
  - State the condition that would make the recipient happier. Are often expressed with ***should*** and ***want***.

Sage and Rouse 1999

Requirements
Lingo

What does it mean to you…

- Goals?
- Purpose?
- Objectives?
- Requirements?

Requirement: A single documented need for what a particular product or service should be or do.

Universal PK Objectives

- To develop a pharmacokinetic structural model using the data collected from X studies
- To estimate population pharmacokinetic parameters of Drug X in patients
- To examine the influence of patient covariates, such as age, gender, body weight, race, and renal function, on the pharmacokinetic parameters

Objectives ≠ Requirements

Requirements
Stakeholders

Stakeholder	Requirements
Pharmacometric Scientist	The model must describe the variability in the data.
Regulatory Reviewer	The model must be unbiased. The model must provide a basis for decision making and labeling.
Development Team	The model results must be easy to understand; results must be available at critical decision times
Health Care Provider	The dosing instructions must be clear; the drug must be efficacious/safe; the label must be informative
Patients	The drug must be easy to use; the drug must be effective; the drug should have no side effects

Case Studies

1. The impact of changing requirements on model development during a drug development program
2. The use of previously developed models in response or support of new requirements

Case Study 1
Development of Drug X

- Objective: To develop a model that describes the pharmacokinetic disposition for use in subsequent exposure-response analyses

Case Study 1
Development of Drug X

Requirements

Requirement 1 (R_1): The model must describe the PK disposition of Drug X
R_{1a}: The model must describe fasted administration
R_{1b}: The model must be able to support the Phase 2 dose

Model Development

Model 1 (M_1): Interim Model

Results

- Mixture model for absorption: 61% fast, 39% slow
- Empirical shift in clearance for dose
  - Due to potential non-linearity

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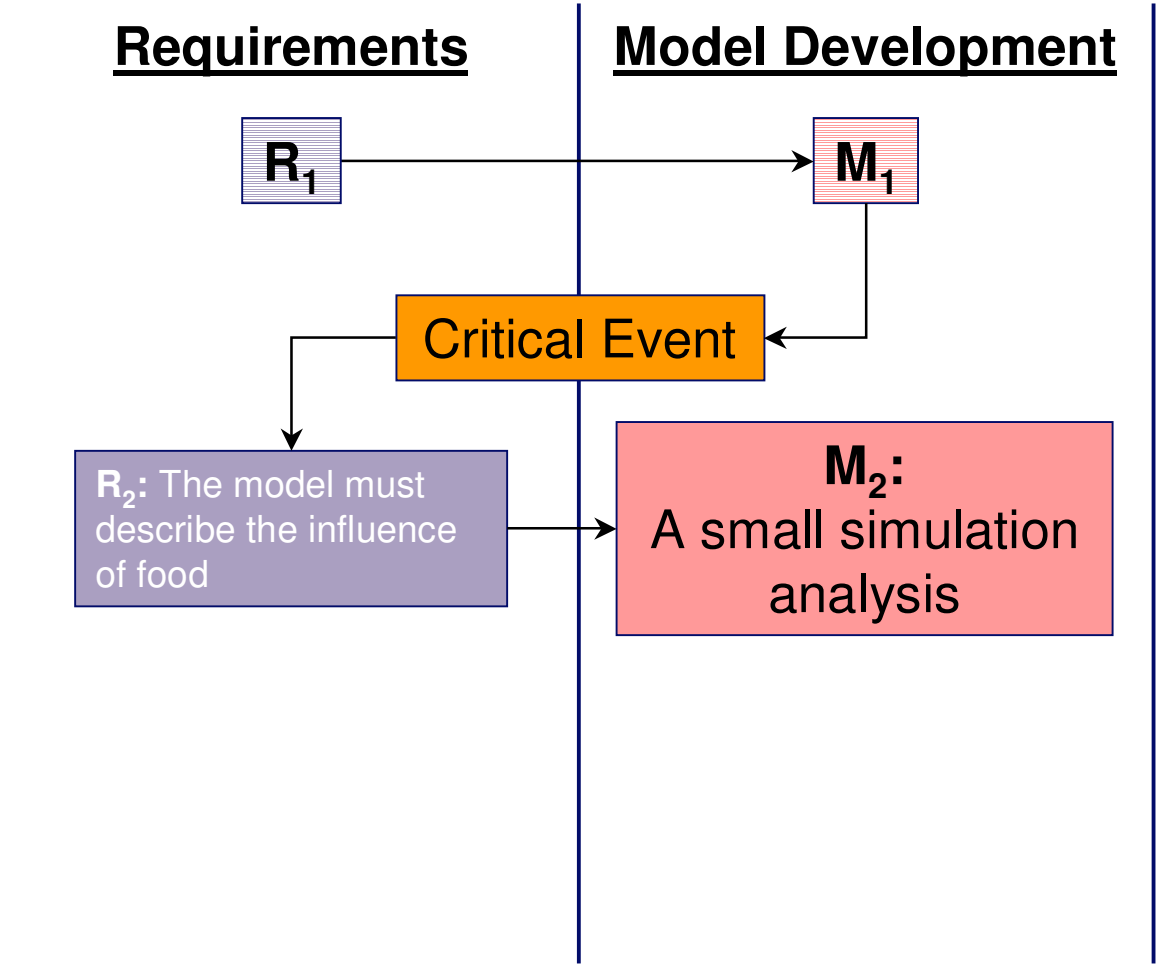
Case Study 1
Development of Drug X

Critical Event 1

- Sponsor notes that administration with food increases exposure and decreases variability
  - Protocol Amendment to state that all subsequent doses be administered with food—creating a mix of fed and fasted data in Phase 2 protocols

Case Study 1
Development of Drug X



Results

- Incorporated 1 single dose food study to the data used for Model 1

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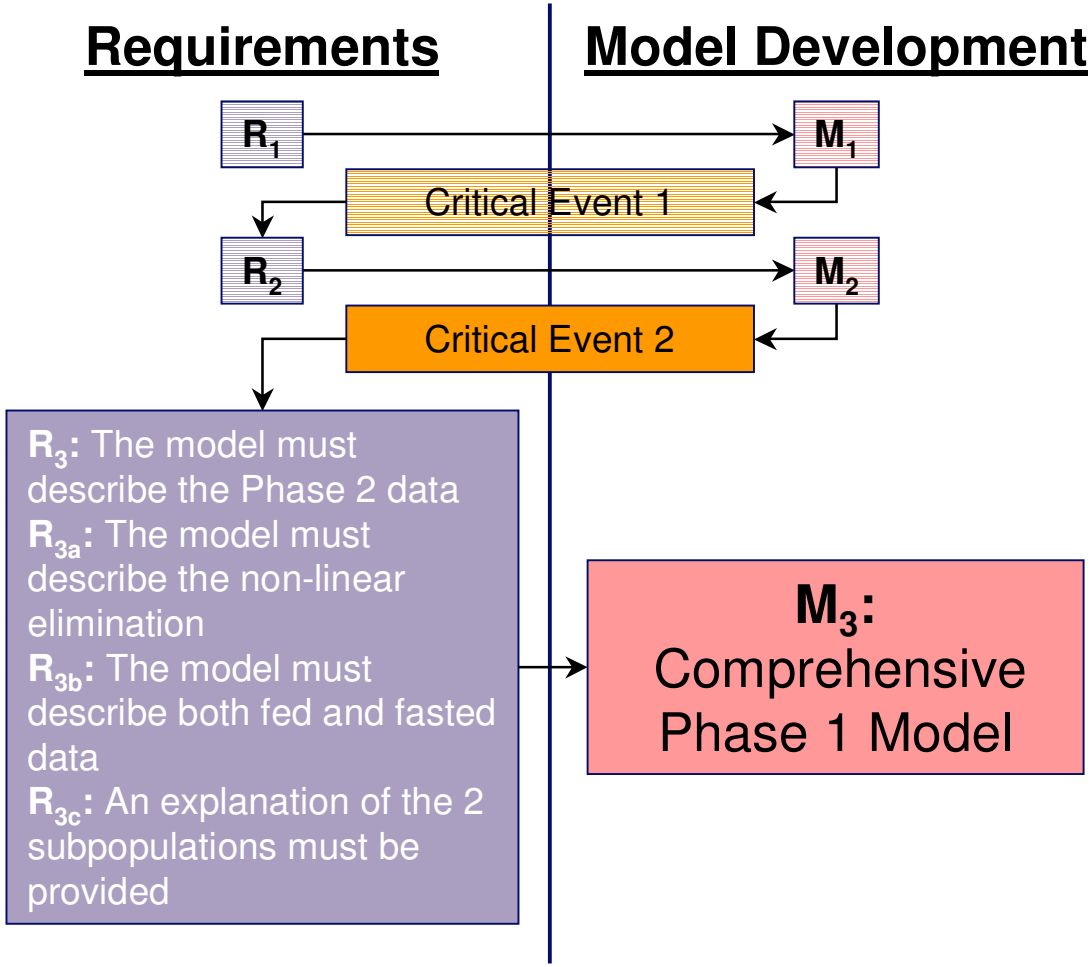
Case Study 1
Development of Drug X

Critical Event 2

- Sponsor conducts a new Phase 1 study to evaluate multiple dose administration with food
- Influential stakeholder requests explanation of 2 subpopulations identified previously by the mixture model

Case Study 1
Development of Drug X



Results

- Michaelis-Menten elimination
- Enterohepatic recycling
- Mixture model was no longer warranted after accounting for nonlinearity and influence of food

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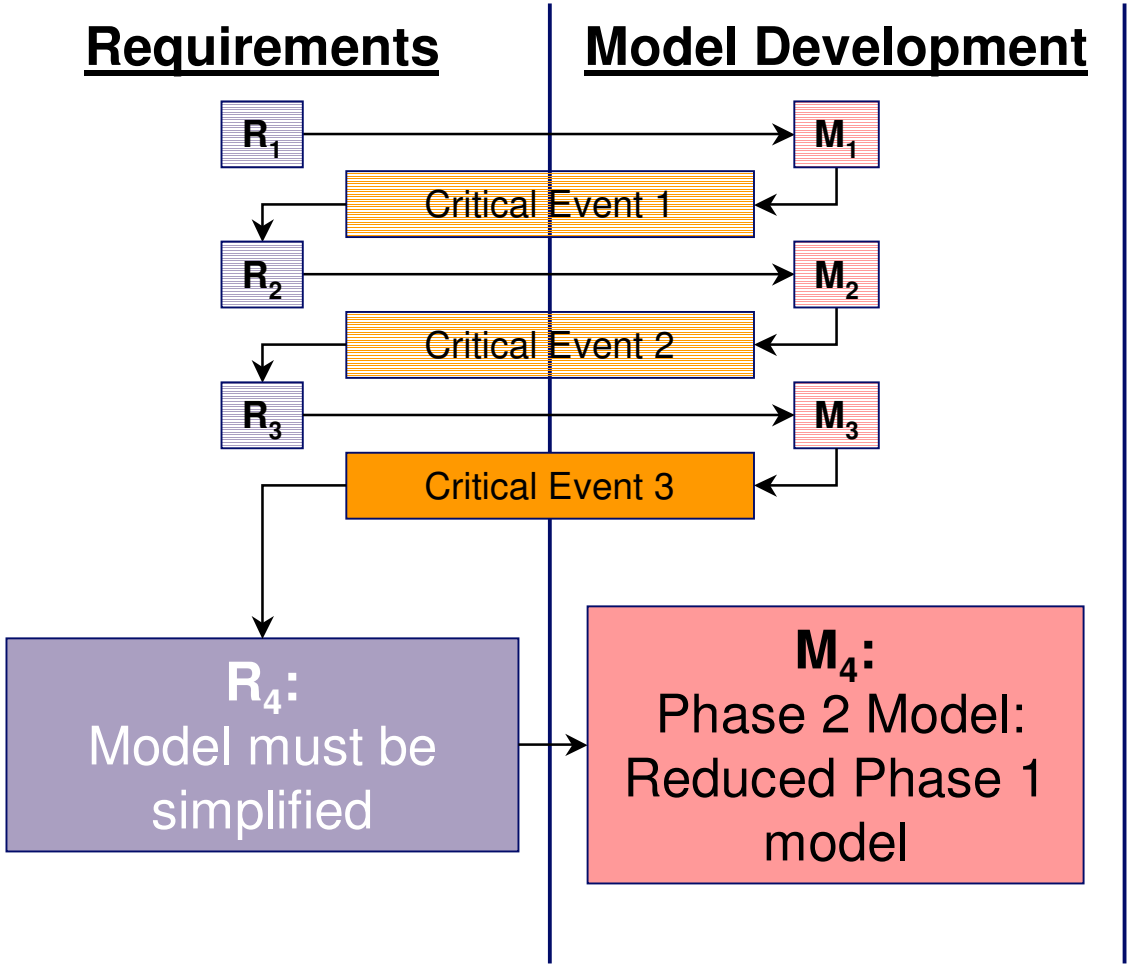
Case Study 1
Development of Drug X

Critical Event 3

- Review of Phase 2 data reveals missing critical information pertaining to the administration of food

Case Study 1
Development of Drug X



Results

- Due to missing data, model components pertaining to food could not be supported by data
- Phase 2 Model was a simplified, nonlinear elimination model for fed data only

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Case Study 1
Lessons Learned

- During the course of the development of the pharmacokinetic model 3 critical events occurred resulting in:
  - 4 changes to the requirements for the model
  - 4 different pharmacokinetic models, ranging in complexity: starting with empirical moving towards more mechanistic in nature
- Requirements work both ways—the growing complexities of a model may mandate increased quality and quantity of data to support the model
  - Lack of communication yielded loss of data and issues of model usability and acceptability

Case Study 1
Lessons Learned

- As the movement towards model-based development continues, models can not be developed in a silo
  - The roles and requirements of stakeholders must be considered/consulted at key decision points
- Dealing with changing requirements may require multiple models/refinements
  - Stakeholders' requirements may or may not be flexible in the face of refinements
  - Requirements must drive the level of model robustness
  - Without requirements, capriciousness could be a real problem
- In order to have the most robust model available to answer key questions, good communication with key stakeholders is essential

Case Study 2:
Modeling and Simulation for Gatifloxacin (TEQUIN®)

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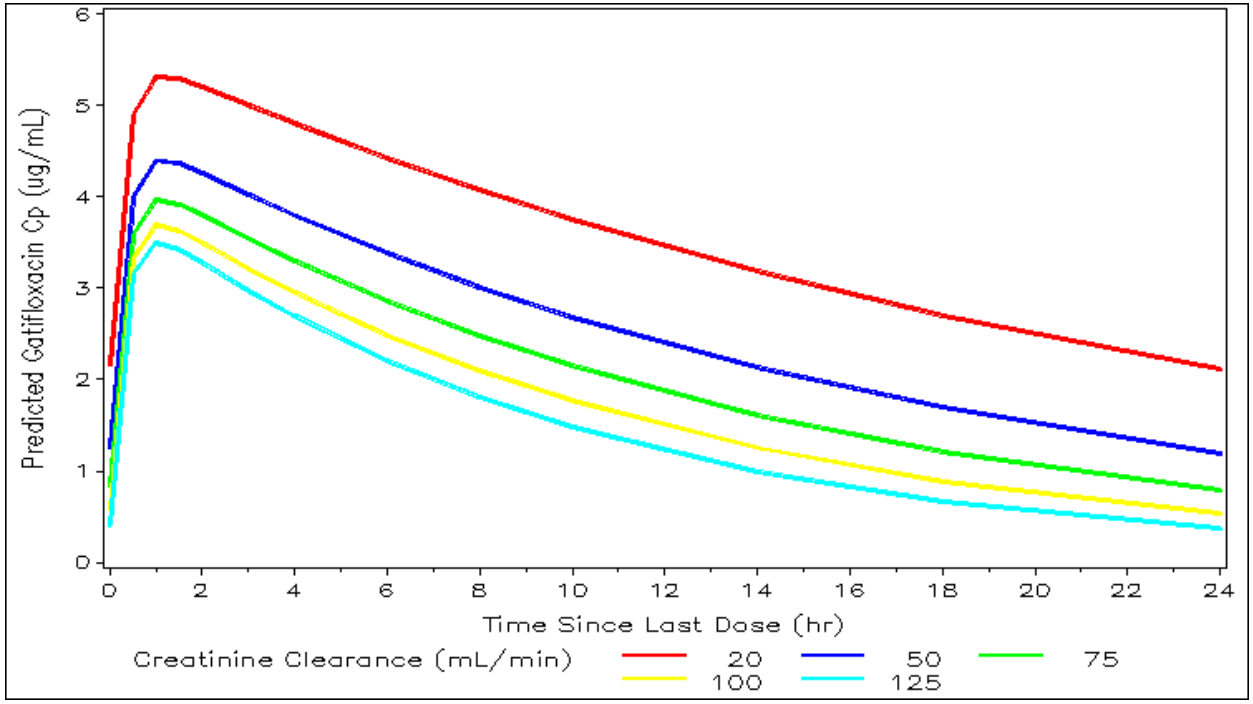
Requirements(R_1)
Pharmacometric Analyses

1. The model must describe the pharmacokinetic disposition of gatifloxacin
2. The model should evaluate Phase 1, 2, and 3 data
3. The model must provide unbiased parameter estimates for patients with select infectious diseases
4. The analyses must assess the influence of patient characteristics on the PK parameters

Case Study 2
Pharmacometric Analysis Results

- Phase 2 (134 Cps from 73 subjects)
- CrCL significant predictor of clearance



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Grasela, et al. 1998

Case Study 2
Pharmacometric Analysis Results

- Phase 3 Model (111 Cps from 67 patients)
  - Age 50 (± 17) years
    - 24 greater than 60 years
  - CrCL 91.0 ± 30/3 mL/min
- CrCL and weight significant predictors of clearance
  - Predicted $CL_j = 84.3 + 0.36 \bullet (CrCL_j - 91.0) + 0.073 \bullet (wt_j - 82.5)$

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Ambrose, et al. 2003

Case Study 2
Critical Events 1

BMS Submits NDA Package to FDA

FDA Approves TEQUIN®

- 1999 Product Label
  - No dose adjustments for age alone
  - A dose reduction recommended for subjects with CrCL ≤ 40 mL/min

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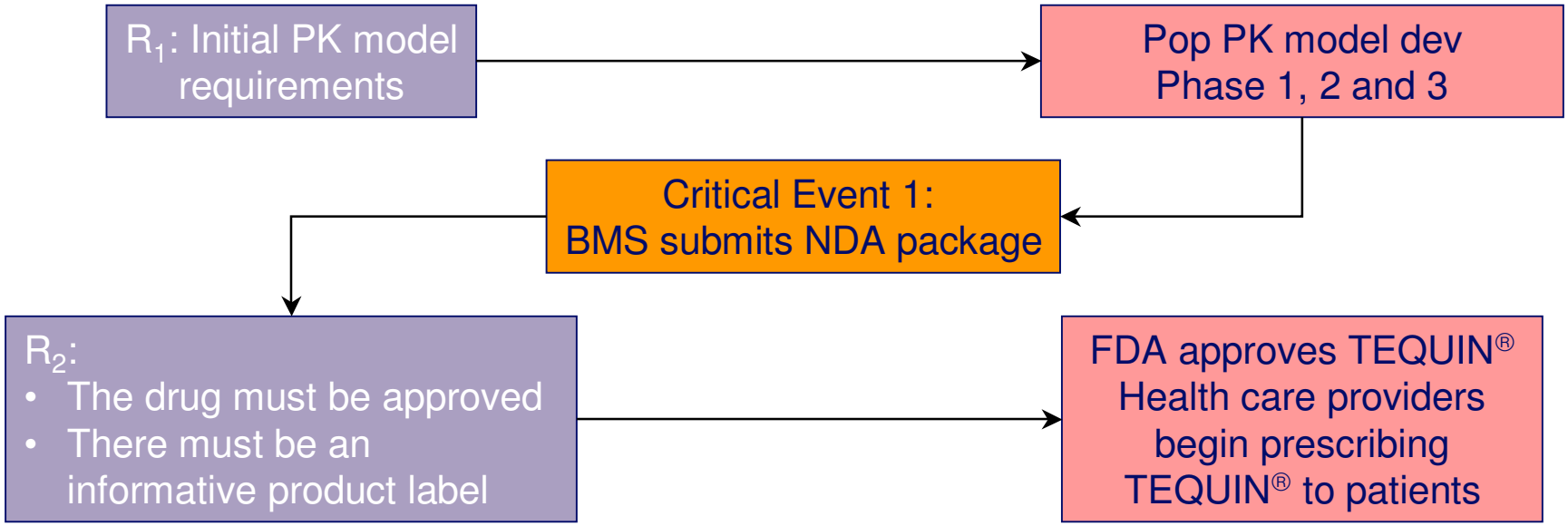
Bristol-Meyers Squibb 1999

Case Study 2
Course of Events



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Case Study 2
Critical Event 2

Med-Watch Reports

- FDA Med-Watch reporting system documented rare (but serious) hyperglycemia in elderly patients
- BMS adds information about risks of low blood sugar and high blood sugar to the WARNINGS section of the label
- H_o: A factor contributing to these events may be gatifloxacin over-exposure due to age-related decreases in renal function in elderly patients predisposed to glycemic alterations

Ambrose, et al. 2003

Case Study 2
Dose Reduction Rationale

- Requirements(R_3)
  - Analysis must examine gatifloxacin exposure in patients with severe hyperglycemia reported with Med-Watch
  - Analysis should provide a PK/PD rationale for a potential age-related dose reduction to avoid high exposures
  - Simulations should evaluate the likely impact of a dose reduction on clinical efficacy in this specific patient population

Ambrose, et al. 2003

Case Study 2
A Potential Age Related Dose Reduction

- Characterize the range of exposures [$AUC_{(0\text{-}24)}$] for 400 mg QD in patients with severe hyperglycemia
- Utilize a previously developed Pop PK model to predict $AUC_{(0\text{-}24)}$ following 400 mg and 200 mg QD for elderly patients from 2 NDA databases
- Examine the range of $AUC_{(0\text{-}24)}$ among elderly patients and the probability of obtaining $AUC_{(0\text{-}24)}$ values similar to those patients with severe hyperglycemia using 400 mg and 200 mg QD
- Utilize Monte Carlo Simulations to assess the probability of elderly patients achieving optimal PK/PD target exposures ($AUC_{(0\text{-}24)}$:MIC ratio $\geq$ 30)

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Ambrose, et al. 2003

Case Study 2
Exposure in Med-Watch Reports

- 10 patients
- 4 with a history of diabetes mellitus
- Mean age=80 years (range, 53-98 years)
- Predicted $AUC_{(0\text{-}24)}$=74 mg•hr/L (range, 57-96)
  - Based on the Phase 3 Population PK model

Ambrose, et al. 2003

Case Study 2
Monte Carlo Simulations

- Percentage of patients with predicted gatifloxacin $AUC_{(0\text{-}24)}$ greater than 70 mg•hr/L increased with age

Exposure Measurement	Age Group ≥ 65 Years QD Dose (mg)	
	200	400
$AUC_{(0\text{-}24)} > 70$	0.92%	35.08%
$AUC_{(0\text{-}24)}$:MIC ≥ 30	98.9%	99.5%

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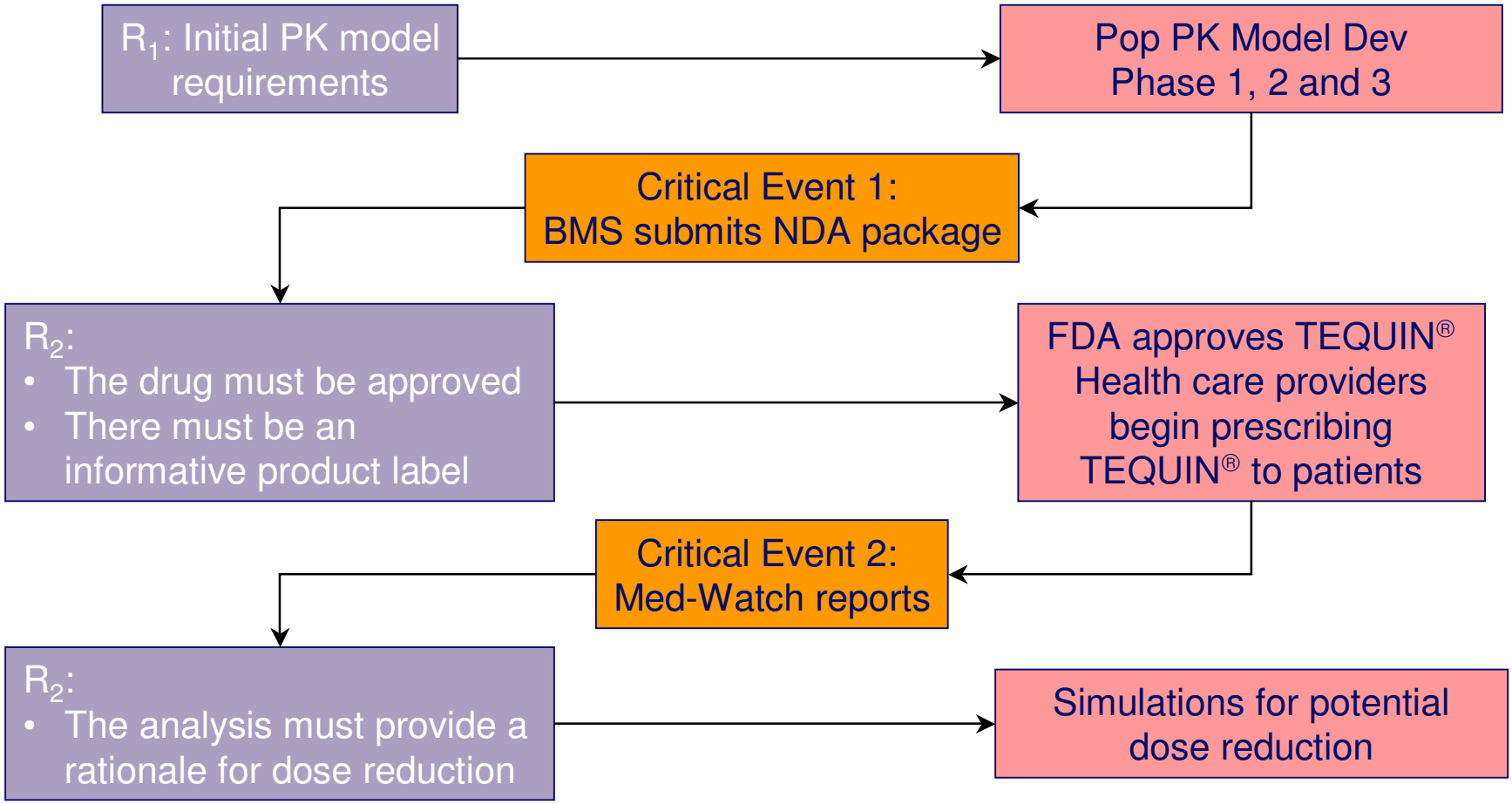
Ambrose, et al. 2003

Case Study 2
Course of Events



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Case Study 2
Dose Reduction Rationale: Conclusions

- Demonstrated a significantly decreased probability of higher exposure associated with 200 mg QD
- Suggested a potential dose reduction in the elderly would result in a decreased risk of severe hyperglycemia
- The drug is primarily used as an outpatient basis
  - It is not standard practice for clinicians to order serum chemistry panels to estimated renal functions
  - Recommendations for dose adjustment based upon age may be viewed advantageous from the clinician and patient perspectives

Ambrose, et al. 2003

Case Study 2
Lessons Learned

- One cannot predict the future; as products are launched into the general population, new requirements may emerge
- When a covariate is identified that strongly influences exposure, a new requirement should be that you understand and document the behavior in this region
  - If something does arise, there is a high probability that you will need that part of the model urgently
    - Appropriate response and documentation to the PK model allowed for rapid response to the Med-Watch reports

Overall Conclusions

- We should utilize requirements at all stages of a drug's life-cycle to inform and guide model-based development
- Taking advantage of emerging knowledge (or not) to update requirements and inform key stakeholders is critical

Overall Conclusions

- At first, it can be difficult to elicit requirements prospectively
  - With experience, becomes easier
- Don’t wait until the end for the true requirements to emerge. Using requirements will avoid the statement, “Oh, I thought I was going to get something different from you.”

Thank You

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Additional Resources

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