Anoixis CORPORATION

Exposure – Response and Drug Development in the 21st Century

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Leader in pharmacometric service with design and analysis like no other.

Outline

- 21st century drug development
- The Pharmacometric imperative
- Exposure – response: issues of importance
- Examples
- Summary

21st Century Drug Development

- Understanding exposure – response relationship and factors that affect it is crucial to mapping a drug candidate's response surface.
- Cost of drug development is not likely to decrease in the near future.
- Knowledge based drug development under-girded with Pharmacometric principles /approaches will be key to successful drug development in this century.

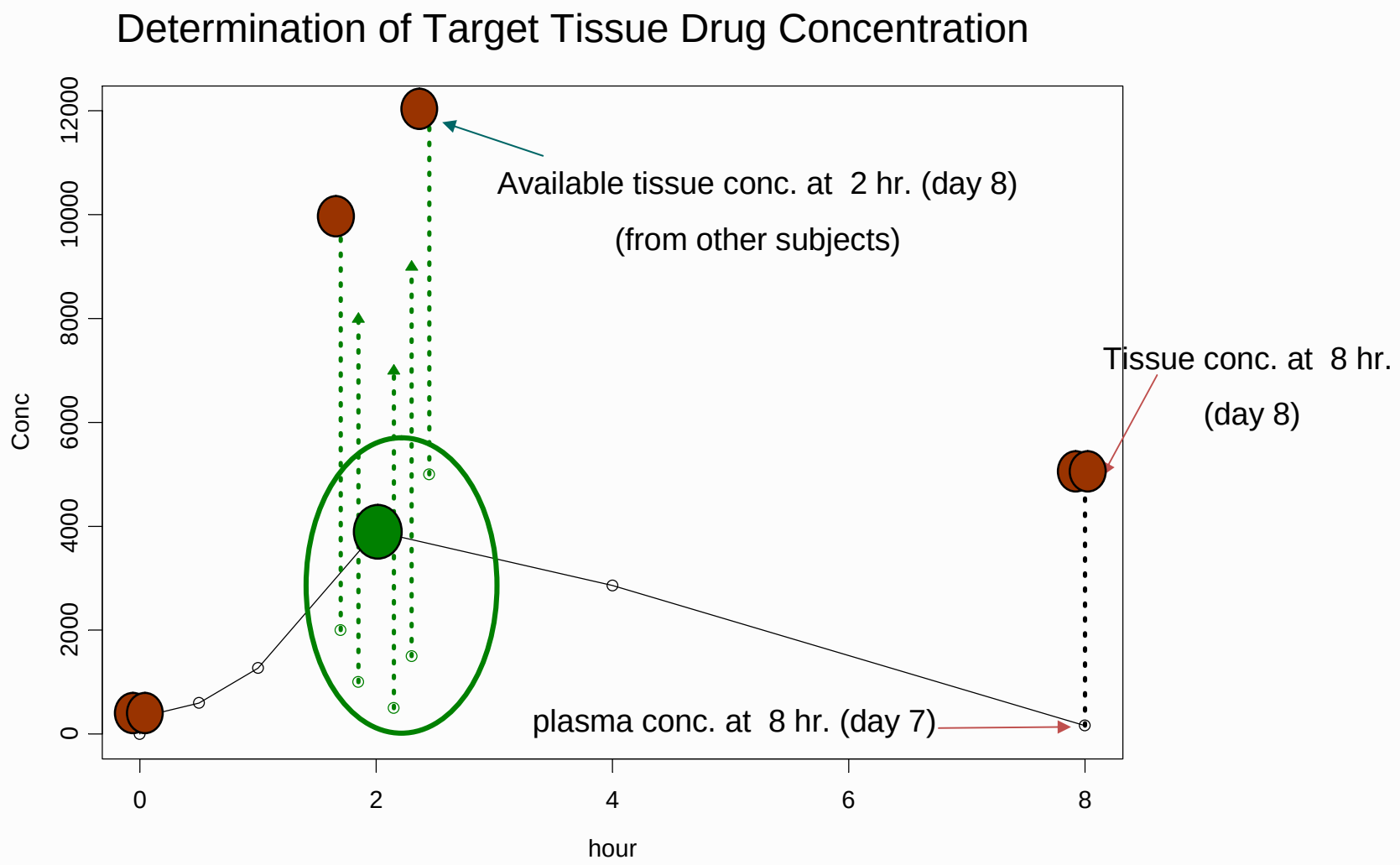
The Pharmacometric Imperative

- Cost drug development continues to escalate (≈$1.4B present estimate),
- Price of computation continues to decrease rapidly
- Elementary economics would dictate
  - Spending a larger and larger fraction of our drug development (preclinical to clinical) resources on pharmacometric methodologies:
    - To enhance knowledge extraction / generation from drug development studies about a drug candidate′s response surface.

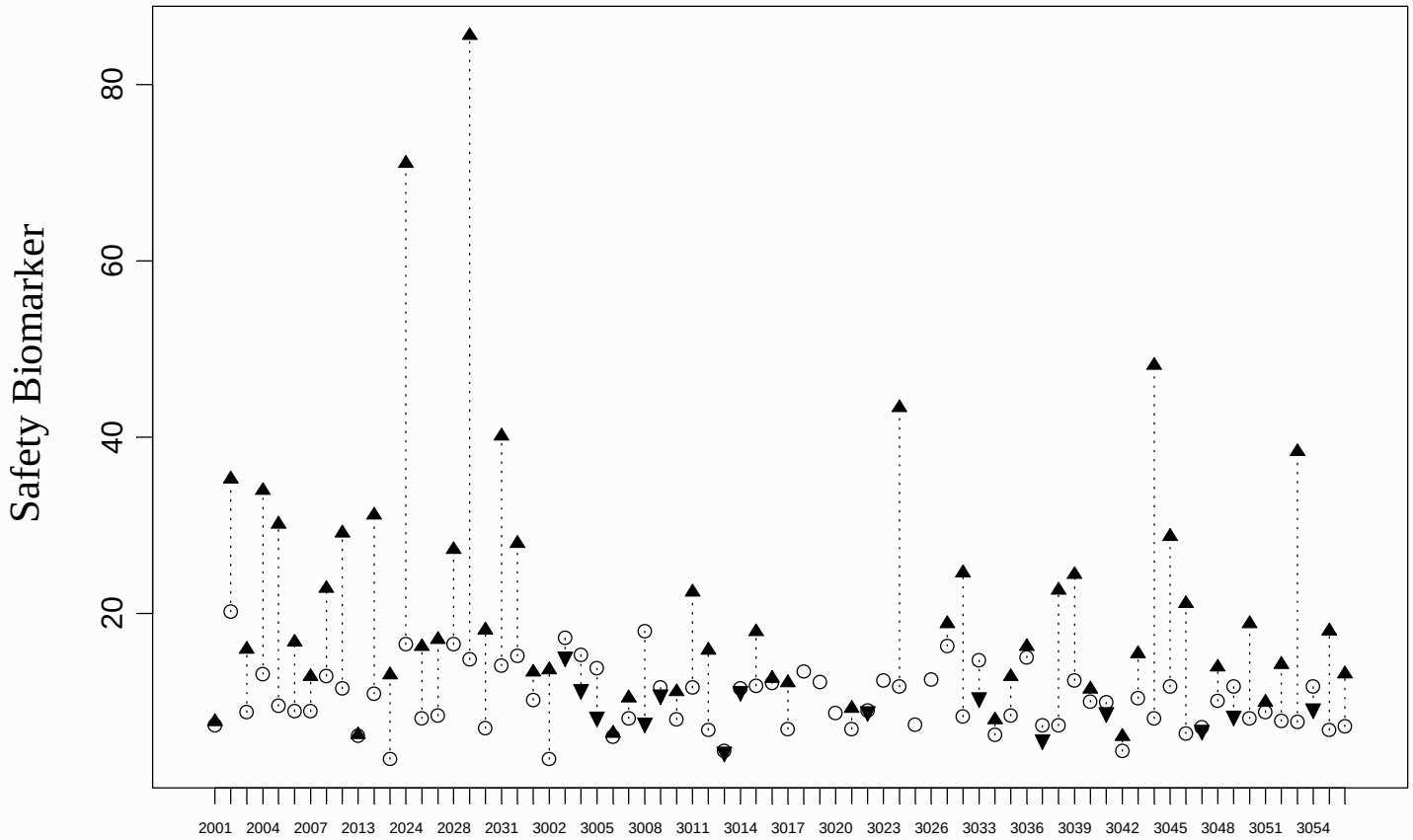
Exposure – Response: Issues of Importance

- Design of studies
- **Informativeness of a data analysis**
  - **Use of appropriate methodology**
  - Model appropriateness
- Knowledge integration
- **Dose choice**
  - **Dose**
  - Dosing regimen / schedule

Informative Data Analysis: Making the Most of Study Data



Explanation for the Elevation of Safety Biomarker Needed

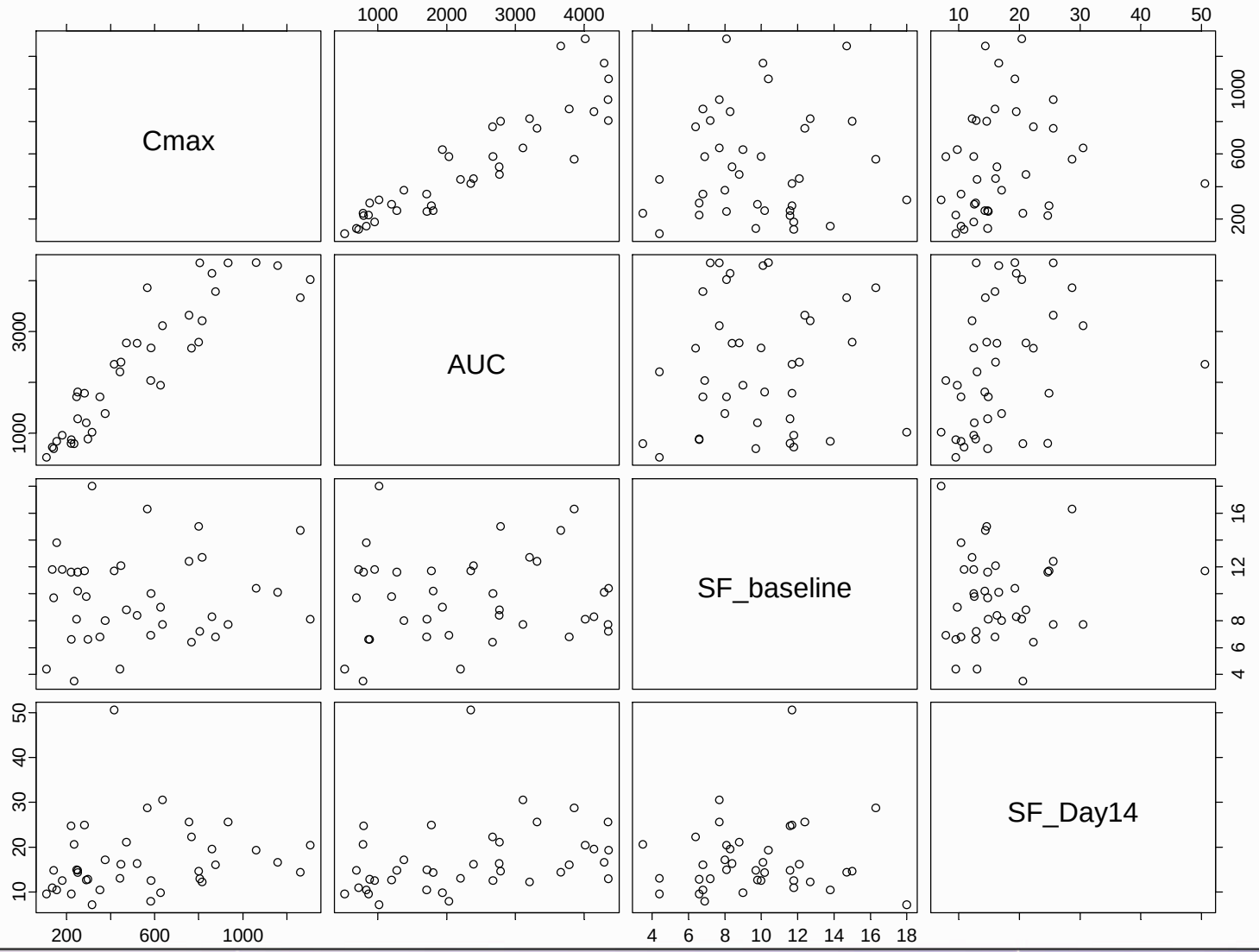


(Chu & Ette, 2007)

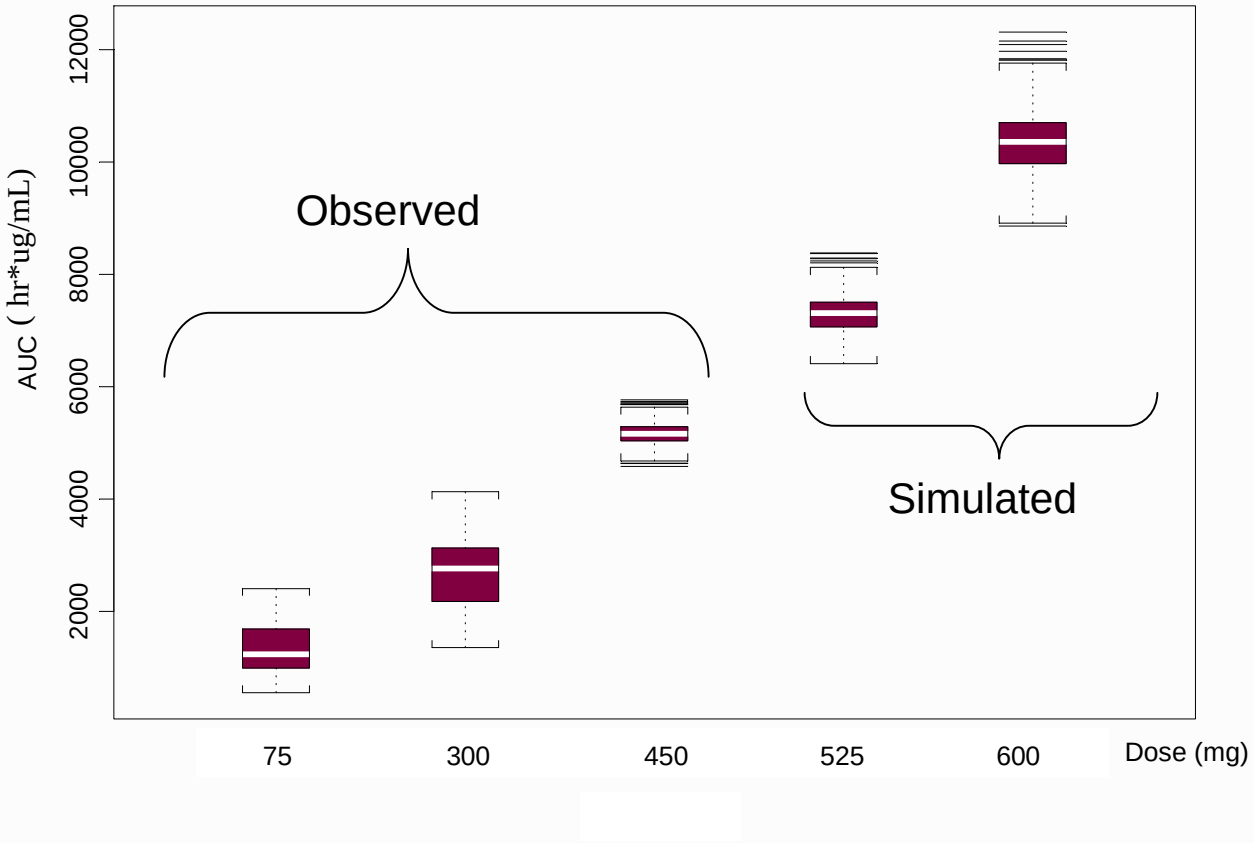
The Need to Understand the Safety of a Drug Candidate

- **Questions**:
  - Can an adverse effect (i.e. elevation in a safety biomarker level) seen during drug development trials be explained?
    - Is there knowledge hidden in trial data sets that can be discovered to explain the adverse effect?
    - What would be the effect of a higher dose (600 mg), not previously studied?
- **Available Information**:
  - Data from 3 trials (2 in 50 healthy subjects and 1 in 60 patients)
    - Safety biomarker data
    - PK data
    - Doses studied: 75 to 450 mg bid

No Apparent Relationship between Exposure Metrics and Biomarker



Distribution of AUC Values



(Chu & Ette, 2007)

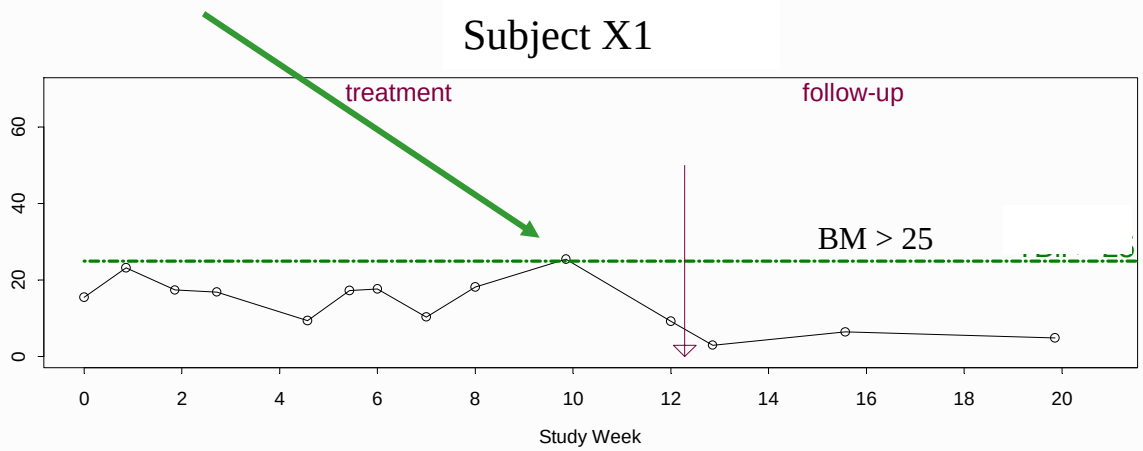
Understanding of Drug Safety: Duration Above an AE Grade

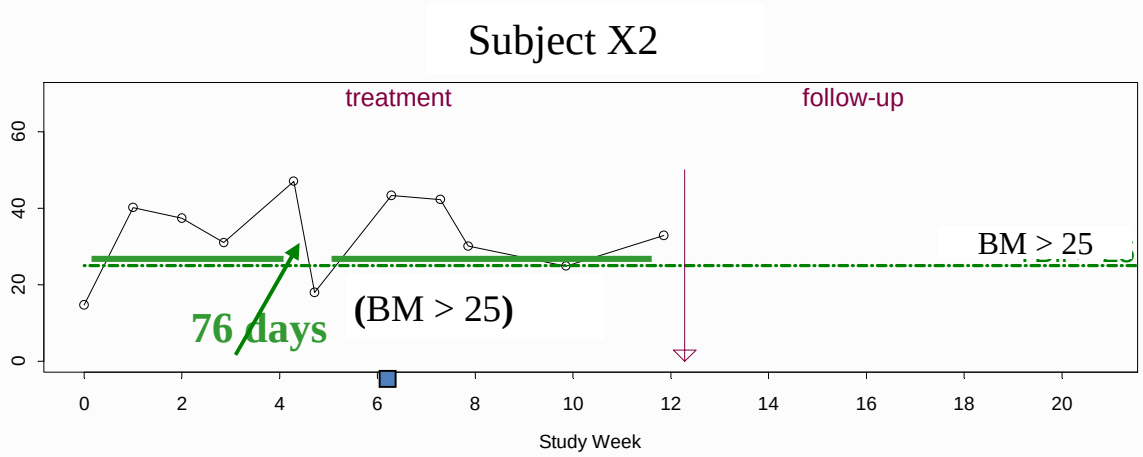
BM above Grade 1

300 mg		
days	quantile	prob
1.35	0.39	61%
1.71	0.43	57%
2.39	0.48	52%
2.60	0.52	48%
7.59	0.57	43%
11.86	0.61	39%
11.96	0.65	35%
18.01	0.70	30%
20.11	0.74	26%
37.43	0.78	22%
49.62	0.83	17%
49.66	0.87	13%
66.06	0.91	9%
75.96	0.96	4%

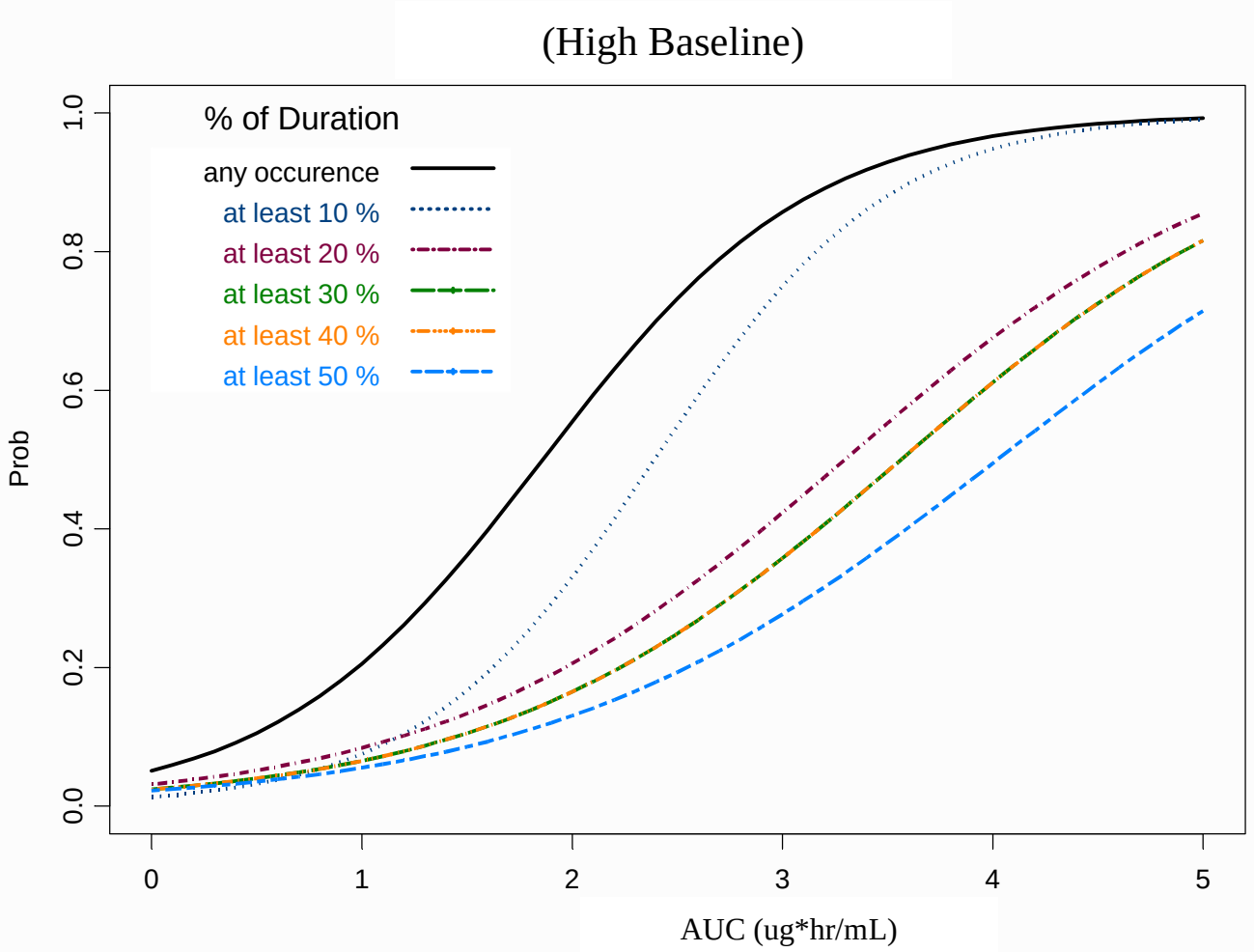
(Chu & Ette, 2007)

1.35 days (BM > 25)





Exposure-Response Curves Characterized by % of Duration Above Grade 1 Adverse Event



(Chu & Ette, 2007)

Predicted Probability of Biomarker Elevation for Higher Doses Compared with the 300 mg bid Regimen

Prob. of having Grade 1

High Baseline

	mean (SD)			
	450 mg	525 mg	600 mg	300 mg
any occurrence	74 (5.03)	76 (4.94)	79 (4.80)	62 (5.76)
10% of Duration	72 (5.74)	75 (5.59)	79 (5.37)	55 (5.37)
20% of Duration	58 (7.35)	62 (7.41)	66 (7.36)	42 (5.3)
30% of Duration	56 (6.25)	60 (6.47)	63 (6.61)	39 (5.11)
40% of Duration	56 (6.98)	60 (7.20)	65 (7.30)	39 (5.22)
50% of Duration	48 (7.83)	52 (8.30)	56 (8.65)	31 (4.57)

Prob. of having Grade 2

High Baseline

	mean (SD)			
	450 mg	525 mg	600 mg	300 mg
any occurrence	58 (7.58)	63 (7.71)	67 (7.71)	40 (4.65)
10% of Duration	50 (6.37)	55 (6.77)	59 (7.07)	35 (4.81)
20% of Duration	35 (6.42)	39 (7.04)	42 (7.65)	24 (3.8)
30% of Duration	35 (5.67)	38 (6.28)	41 (6.90)	23 (4.12)
40% of Duration	36 (5.96)	40 (6.56)	44 (7.11)	
50% of Duration	35 (6.47)	38 (7.24)	42 (8.01)	

Prob. of having Grade 3

High Baseline

	mean (SD)			
	450 mg	525 mg	600 mg	300 mg
any occurrence	26 (6.87)	29 (7.98)	33 (9.06)	17 (3.53)
10% of Duration	14 (4.08)	15 (4.6)	17 (5.17)	9 (2.69)
20% of Duration	11 (4.43)	12 (5.03)	13 (5.73)	7 (2.62)
30% of Duration				

Summary

- Efficient and informative study designs are indispensable to informative data analysis.
- It is important to deploy methodologies that permit the utmost extraction of hidden knowledge from study data.
- Pharmacometric knowledge integration is important in exposure-response analysis for the characterization of a drug candidate's response surface.
- Defining and using appropriate doses and regimens are crucial to the success of a drug development program.
- 21st century drug development must be knowledge based and under-girded with Pharmacometric principles /approaches.

Reference

- Chu H-M, Ette EI. The Confluence of Pharmacometric Knowledge Discovery and Creation in the Characterization of Drug Safety. In: *Pharmacometrics: the Science of Quantitative Pharmacology*. Ette EI, Williams PJ (eds). Hoboken: John Wiley & Sons, 2007, pp 1175-1196.

Acknowledgement

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Thank You