

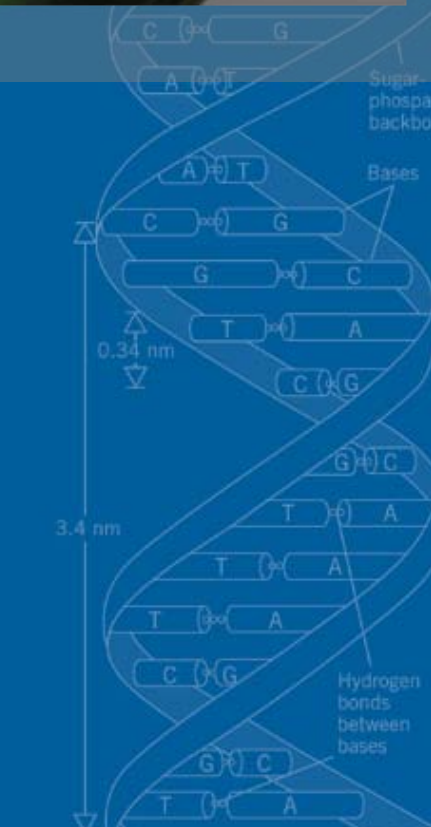
# BioAnalytical Method Development

From Basic Principles to Practical Solutions



## PK Assay Strategies Session October 7, 2008

**Genentech**  
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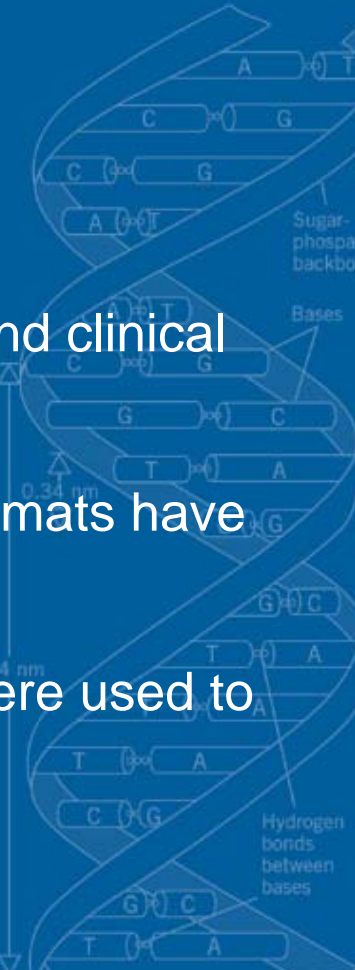
IIR Analytical Conference 2008

Speaker	Title	Affiliation	Schedule
Dr. Alyssa Morimoto	PK Assay Strategies for Biotherapeutics	BioAnalytical R &D, Genentech	1:30-2
Dr. Victor Wroblewski	Characterizing the in vivo Disposition and Clearance of Biotherapeutics: Influence of Bioanalytical Assay Format	Drug Disposition, Global PK/PD/TS, Eli Lilly	2-2:30
Networking Break			2:30-3
Dr. Jianfeng Lu	PK/PD perspective on the measurement of ligand level (free, and total etc. ) across different disease areas	Pharmacokinetics, AMGEN	3:30-4
Dr. Thi Migone	PK Assay Formats for Antibody Therapeutics	Clinical Immunology, Human Genome Sciences	4-4:30
Dr. Mark Ma	Assay Format Selection During Method Development-First Step	Pharmacokinetics and Drug Metabolism, AMGEN	4:30-5
Panel Discussion (all speakers)	Analytical Strategies for Measuring Protein Therapeutics-PK Assays		5-5:30
Session close			

1. Which drug species are you trying to measure (unbound drug, drug bound to target, both) and why?

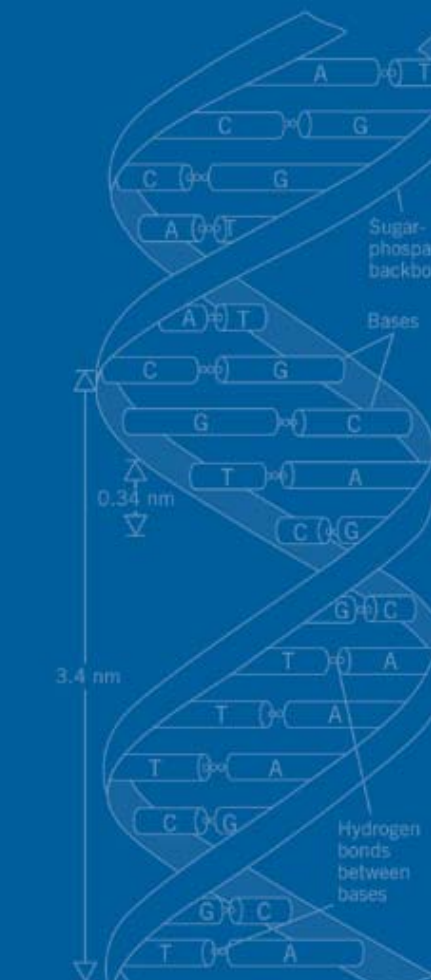


2. Are you using the same approach for non-clinical and clinical studies and why?
3. Do you have case studies where different assay formats have significantly affected the observed PK parameters?
4. If yes, which format/drug species measurements were used to support subsequent dosing plans? Why?



# PK Assay Strategies for Antibody Therapeutics

- Alyssa Morimoto, PhD, Scientist,  
BioAnalytical Research and  
Development, **GENENTECH**



## ICH S6 Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals

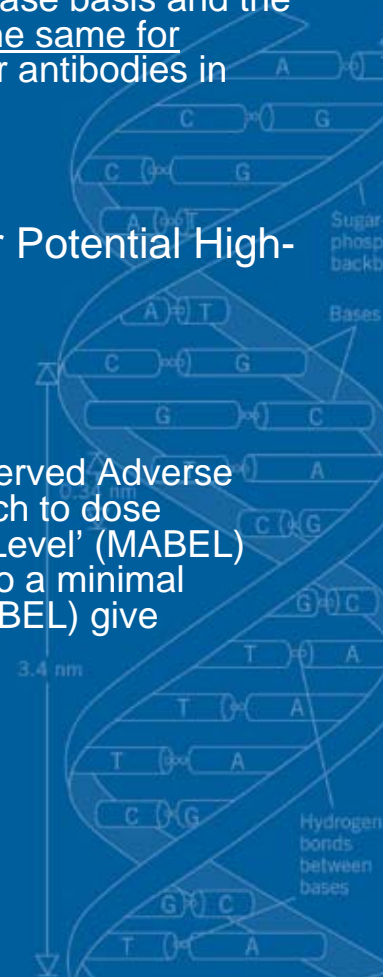
### 4.2.2 Assays

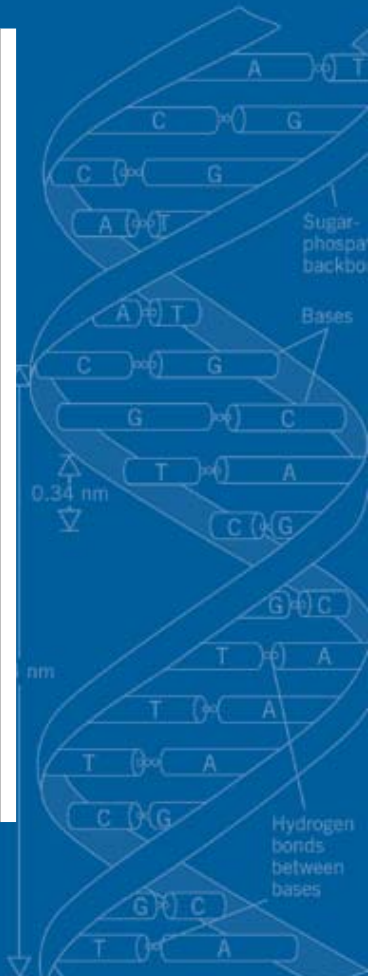
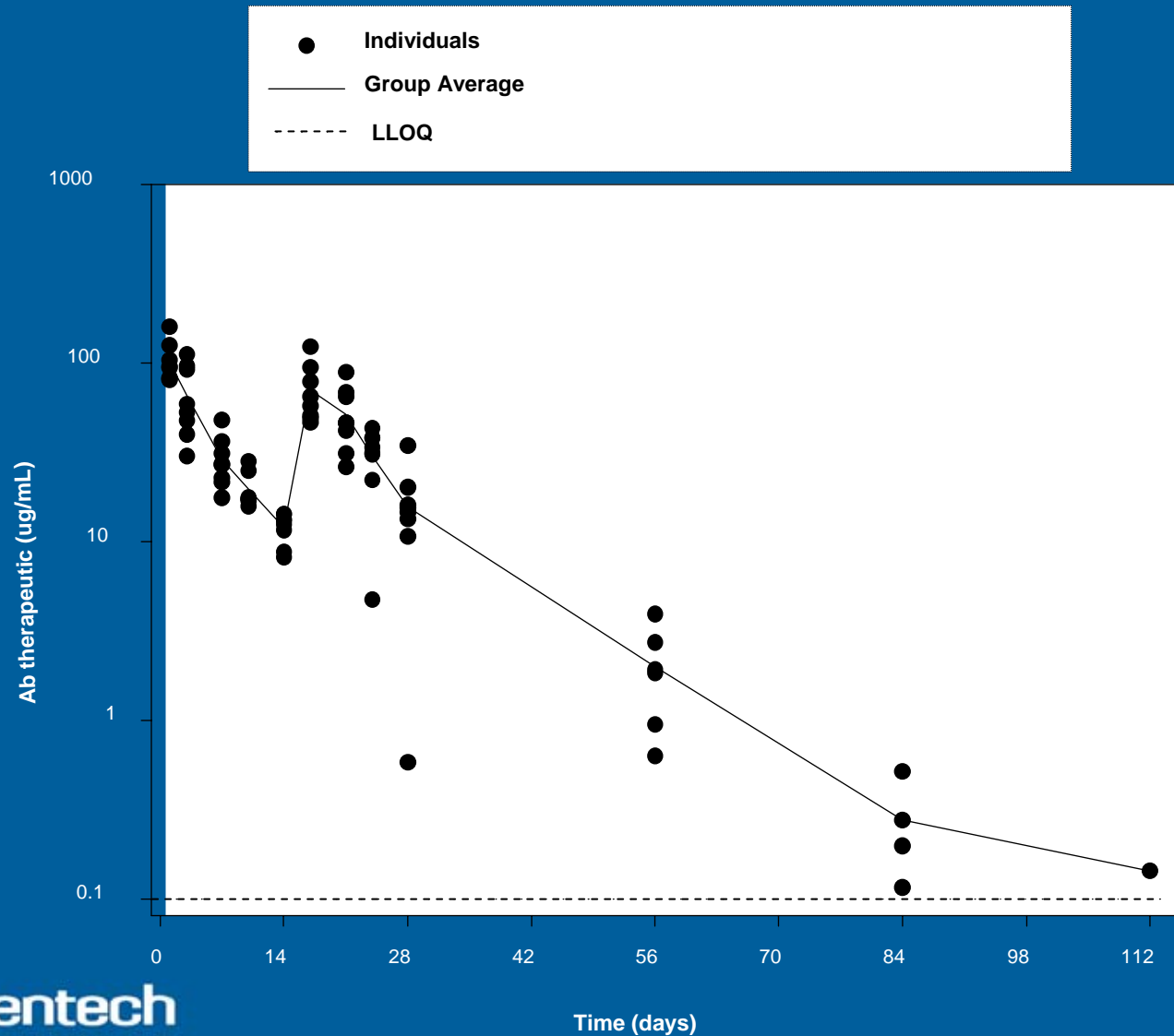
The use of one or more assay methods should be addressed on a case-by-case basis and the scientific rationale should be provided... Ideally the assay methods should be the same for animals and humans. The possible influence of plasma binding proteins and/or antibodies in plasma/serum on the assay performance should be determined.

### EMA: Guideline on Requirements for First-in-Man Clinical Trials for Potential High-Risk Medicinal Products (draft version March 2007)

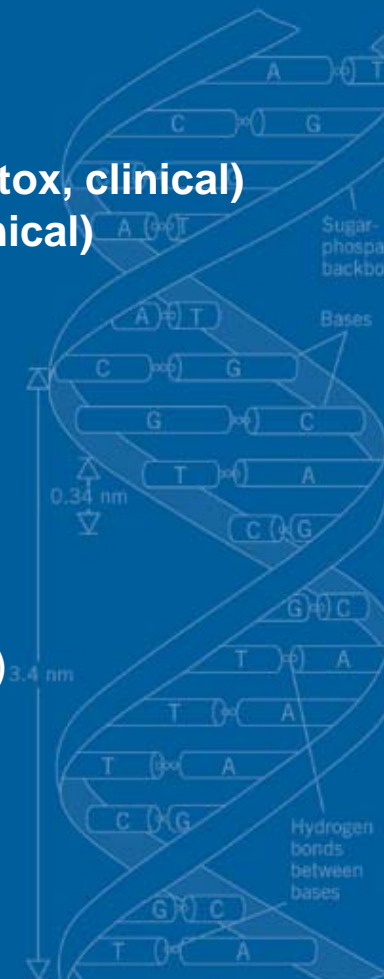
#### 4.3.6 Calculation of the first dose in man

“In general, calculation of the first dose in man is based on No Observed Adverse Effect Level (NOAEL)...for high risk-medicinal products, and additional approach to dose calculation should be taken. The use of ‘Minimal Anticipated Biological Effect Level’ (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect in humans...When the methods of calculation (eg NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used.”



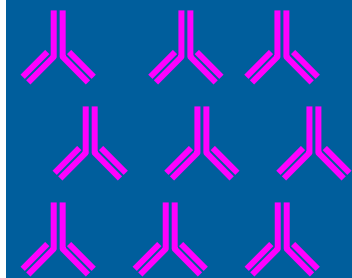


1. Establish common terminology and learn from institutional knowledge base and “lessons learned”
2. Define assay format to be utilized
  - **Which drug species need to be measured (developers, PK, tox, clinical)**
  - **Consider for the entire project lifetime (non-clinical and clinical)**
3. Define target sensitivity requirements
4. Reality check
  - **Reagent inventory and supply**
  - **Other project needs (eg timelines)**
5. Develop (including characterization of target interference)
6. Validate



# Common Terminology: Drug Species

Slide 8



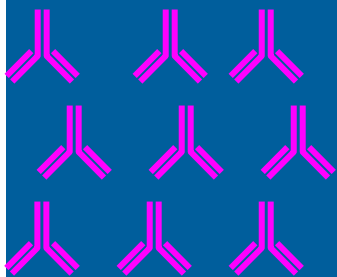
Monoclonal Drug

+



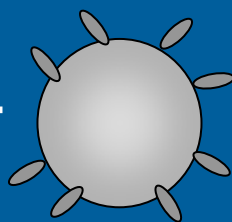
Soluble target

OR



Monoclonal Drug

+



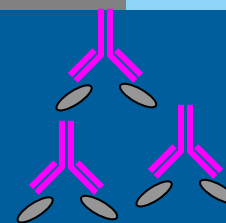
Cell bound target

Target cleaved, shed, released from lysed cells

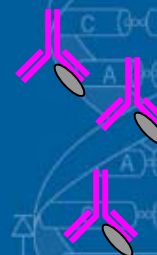


**“TOTAL” DRUG**

**“FREE” DRUG**



**FULLY COMPLEXED DRUG**



**PARTIALLY COMPLEXED DRUG**



**UNBOUND DRUG**

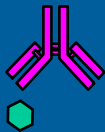
in circulation

Does concentration=

(I) Unbound drug = BIOLOGICALLY ACTIVE



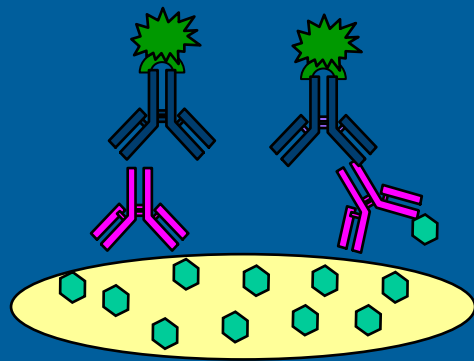
(II) Target partially bound drug = DEPENDS ON MOA, MAY BE BIOLOGICALLY ACTIVE



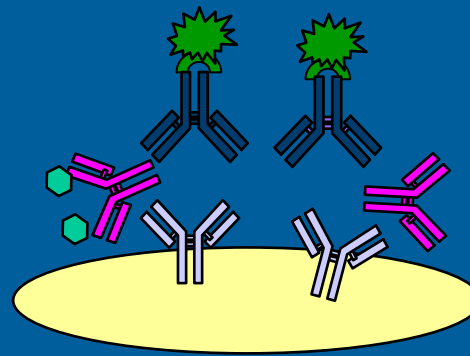
(III) Target fully bound drug = IS ANTIBODY BOUND TARGET NEUTRALIZED?  
IS THERE A SPECIFIC CONCERN ABOUT THE TARGET-DRUG COMPLEX?



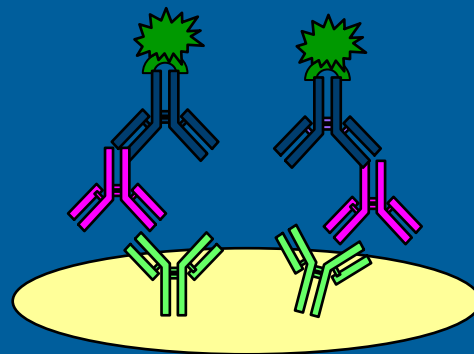
(IV) Total = all of the above



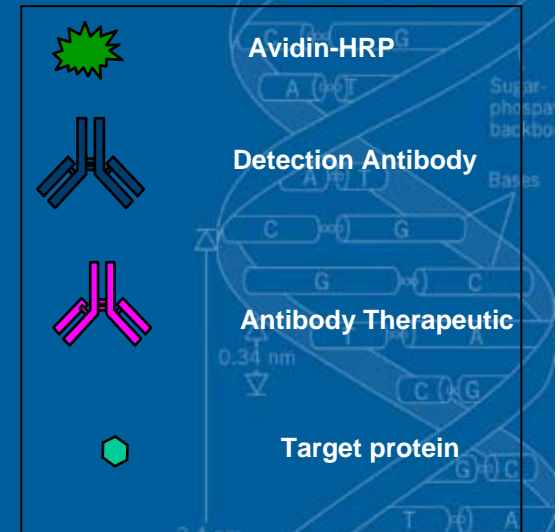
Target coat



Anti-IgG Fc coat



Anti-Id mAb or pAb coat



# Decision Tree

Slide 11

Drug is  
2<sup>nd</sup> generation/NME/franchise/for combo

