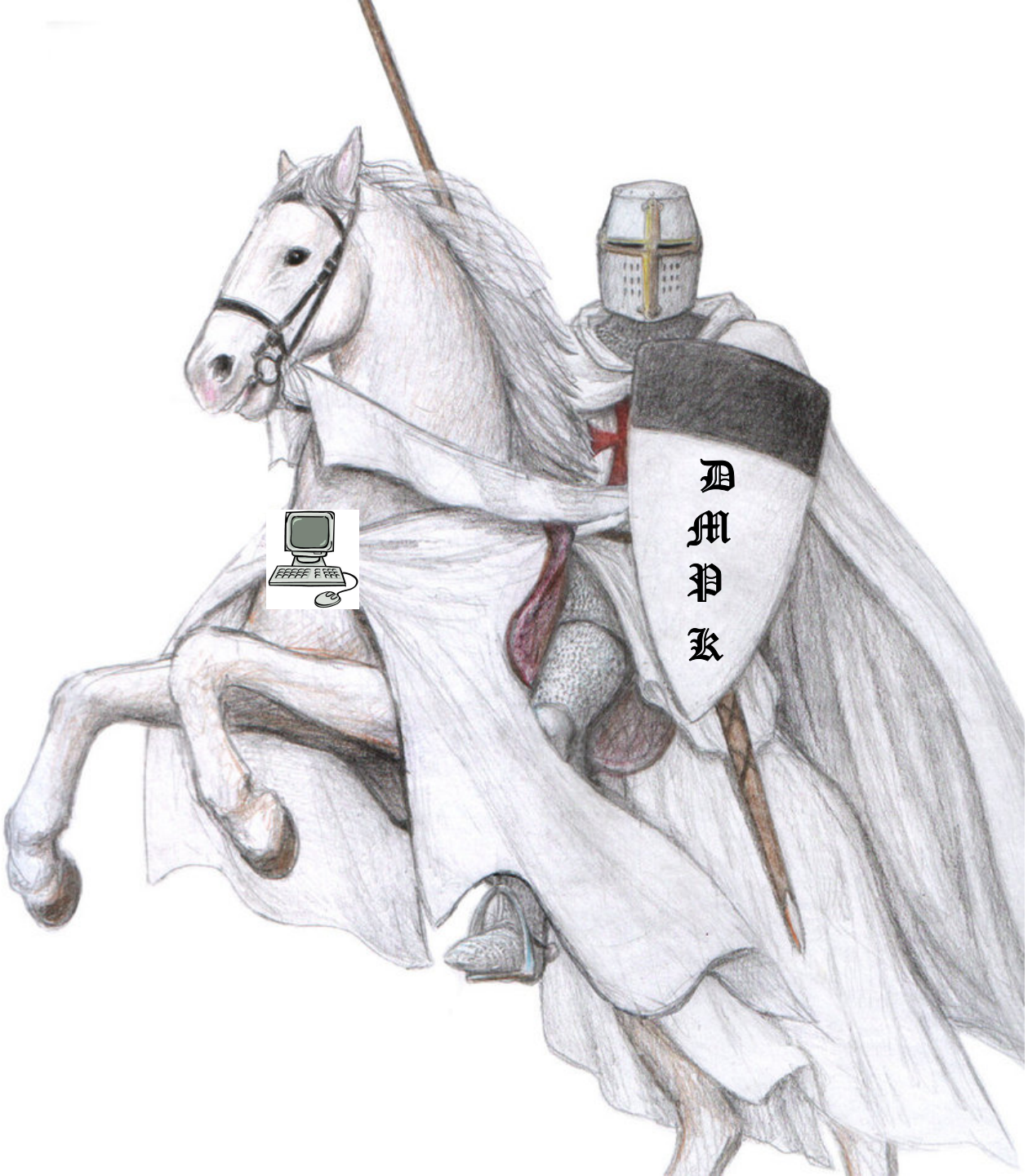
Protein Therapeutic Research and Development: A Growing Role for the DMPK Scientist

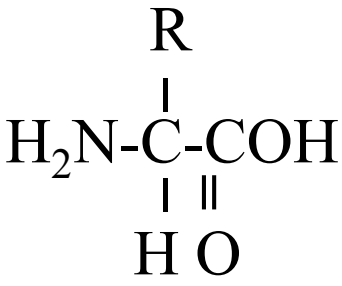
Jerry Galluppi
Director, DMPK
Biogen Idec


DMPK

Presentation Outline:

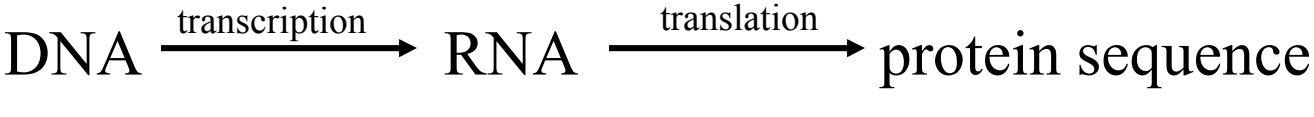
- Definitions, Background Information
- The R&D process:
  - ✓Discovery, Lead Identification
  - ✓Preclinical Development
  - ✓Clinical Development
- NDA Approval, Labeling
- Life-Cycle Management
- Summary Comments

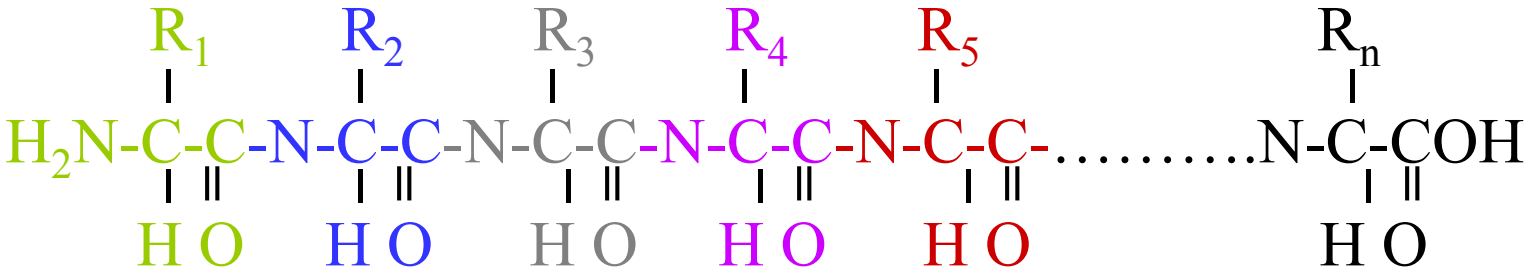
What is a protein?



amino acid

- A protein is a biopolymer made of amino acids joined end to end
- There are 20 kinds of amino acids (differing in structure at the R group), the sequence of which are encoded by:





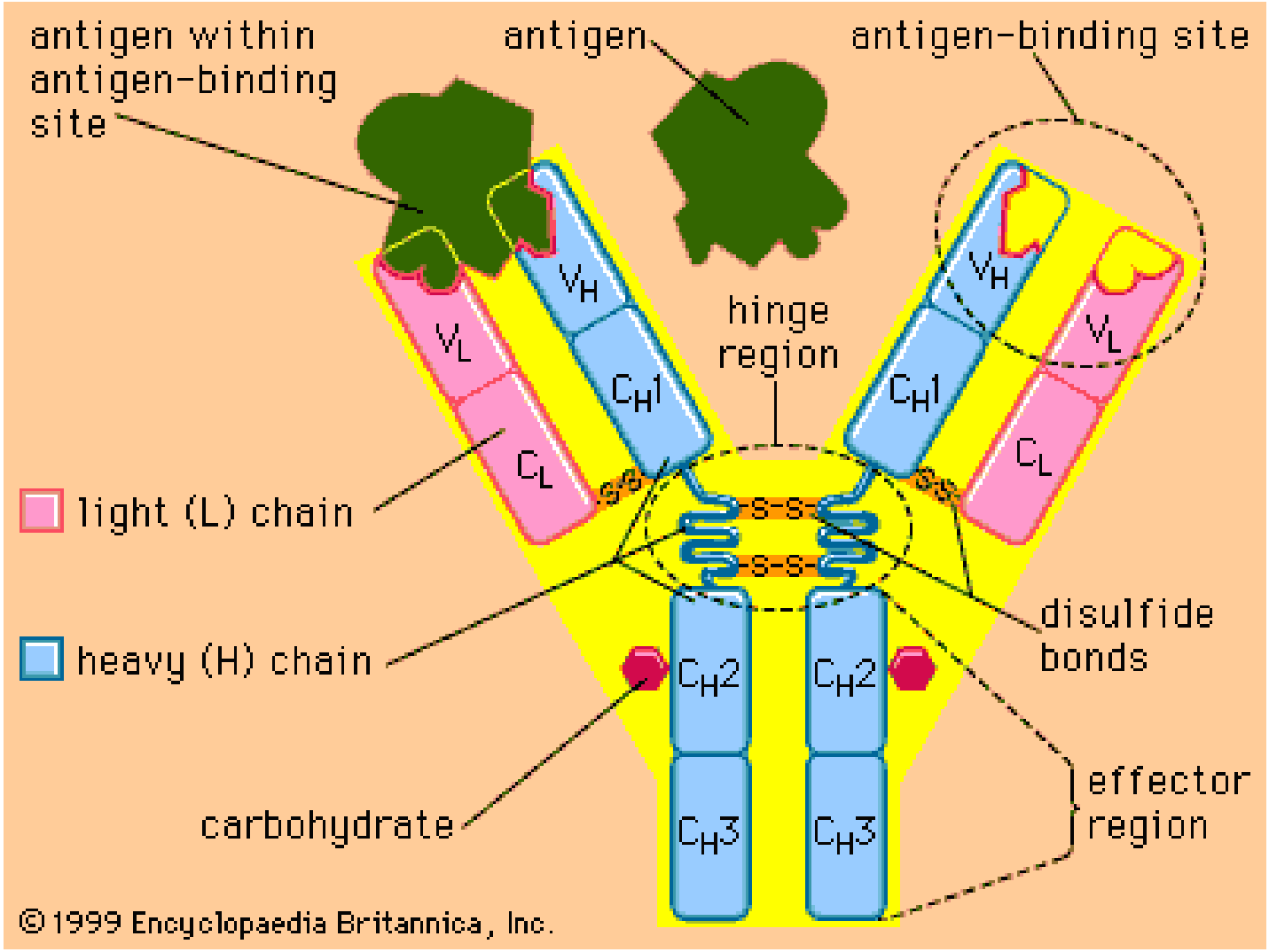
What is a protein?

Proteins perform a wide variety of biological functions:

- Enzymes (catalyze reactions)
- Enzyme inhibitors/modulators
- Carriers of small molecules
- Mediators – hormones
- Receptors/Signaling
- Antibodies
- Cellular structure components
- Many other functions

Monoclonal Antibodies

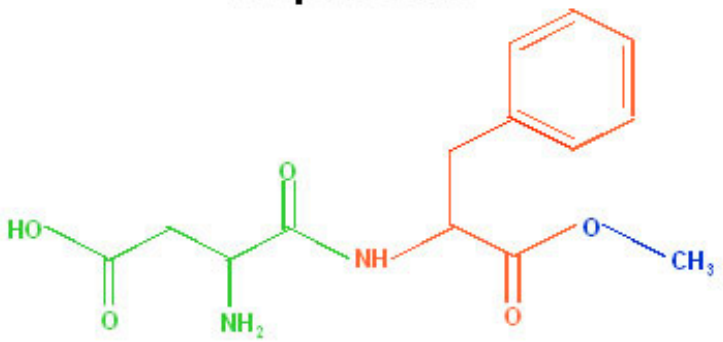
(substantial variety in specificity, many common features in physical properties)



Non-Monoclonal Antibodies
(substantial variety in size, structure, and other chemical and biological properties)

- Blood Factor VIII: up to 200k (glycoprotein)
- Cytokines: 10-70k (interferons, EPO, etc)
- Insulin: 5.8k, two chains (some assembly required)
- Dipeptides or even *single* amino acids can have potent bioactivity

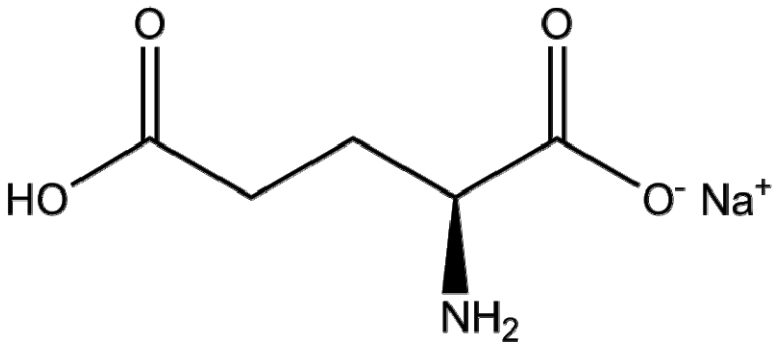
Aspartame



L-aspartyl-L-phenylalanine methyl ester

Aspartate Phenylalanine Methanol

MSG



One of the 20 natural amino acids

•Proteins can undergo natural post-translational modification:

- Large carbohydrate moieties attached (glycosylation)
- Phosphorylation
- Sulfation
- N or C-terminal modifications
- Proteolytic processing
- **Over 40 other modifications have been identified**

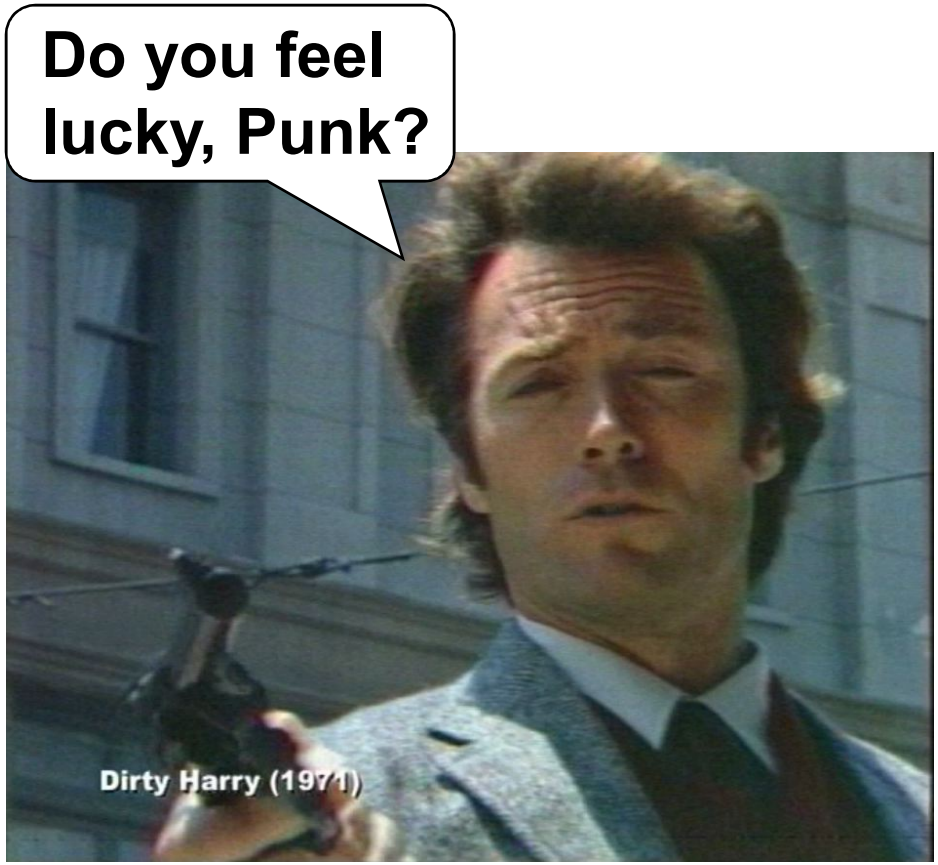
•If such modifications are required for activity, the means of production by genetically engineered cells may be limited – for example, engineered *E. coli* cells will not glycoslyate proteins

•In addition, bioprocess engineers and chemists can chemically modify peptides (peptidomimetics) and proteins in the laboratory to improve pharmaceutical properties such as solubility, stability, activity, safety, and others (for example, polyethylene glycol (PEG) conjugates)

Bottom line – All "pure" protein preparations are actually mixtures with varying degrees of micro-heterogeneity

Drug R&D “stages” and the role of the DMPK Scientist

Data Driven Decisions vs Guessing



A team informed by data

The "good" old days of drug R&D

Discovery

- Chemistry
- Pharmacology
- Molecular biology
- Cell biology

Preclinical

- Toxicology/pathology
- ADME/PK
- Pharmaceutical science
- Process development

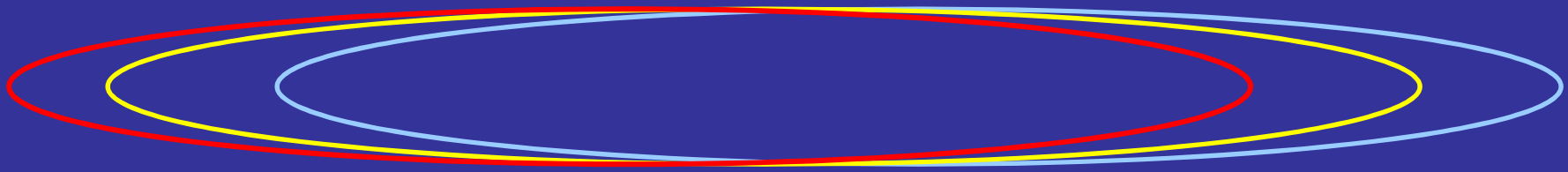
Clinical

- Clinical pharmacology
- Trial design
- Clinical statistics

Input from Business Development,
Regulatory Affairs, Project Management

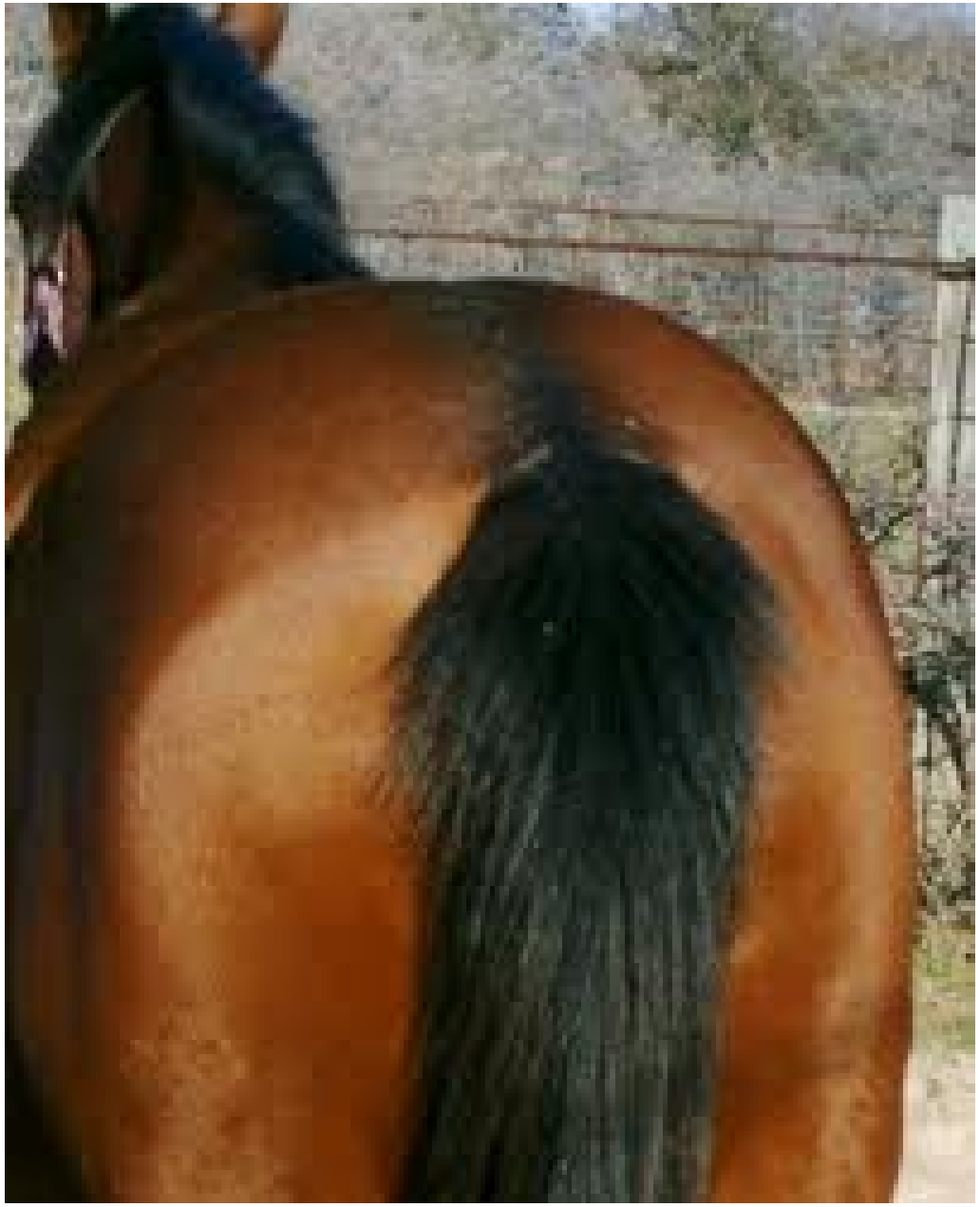
The new paradigm for drug R&D

- **Integration of skills**
- **Joint ownership/responsibility**



Discovery **Preclinical** **Clinical**

Input from Business Development, Regulatory Affairs, Project Management



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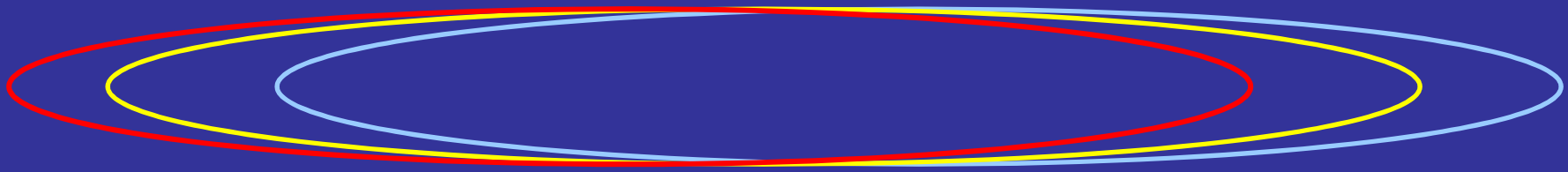

Discovery **Preclinical** **Clinical**

Input from Business Development, Regulatory Affairs, Project Management, Patent

Generic Candidate Testing Scheme

Set The Goal:
Pre-determine a *target candidate profile* based upon the following:
- Efficacy
- Selectivity
- ADME
- Safety
- Pharmaceutical
- Ease of synthesis
- Other properties

New Target

↓

HITS

↓

Med Chem SAR (*in vitro* potency and selectivity)

↓

***in vivo* PK in PD species (BA, CL, V, $t_{1/2}$)**

↓

PD proof of efficacy in one or more species

↓

PK/PD, TK/TD evaluation

↓

Multi-species ADME/safety

DOES THE CANDIDATE MEET ALL THE CRITERIA??

High throughput chem/phys, ADME, and safety screening:
- *In silico – rule of 5, clogP*
- *DEREK/TOPKAT*
- *ID/Purity/stability*
- *Solubility*
- *Pharmaceutical properties*
- *Electrophilicity*
- *Metabolic stability*
- *Permeability/Efflux*
- *Protein binding*

Lower throughput ADME/safety tests:
- *CL mechanism(s)*
- *Metabolite profiling*
- *Metabolite ID*
- *In vitro* ➡ *in vivo prediction*
- *Cross species comparison*
- *P450 inhibition/characterization*
- *Safety profiling in vitro*
- *Safety issues resolution*
- *Allometric scaling, PBPK*

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- *Protein binding*

↓

***in vivo* PK in PD species**
(BA, CL, V, $t_{1/2}$)

↓

PD proof of efficacy in one or more species

Lower throughput ADME/safety tests:
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↓

PK/PD, TK/TD evaluation

↓

Multi-species ADME/safety

DOES THE CANDIDATE MEET ALL THE CRITERIA??

Integrated R&D model has shifted the reasons why drug candidates fail in development – fewer failures due to poor ADME properties largely due to better screening pre-R2D

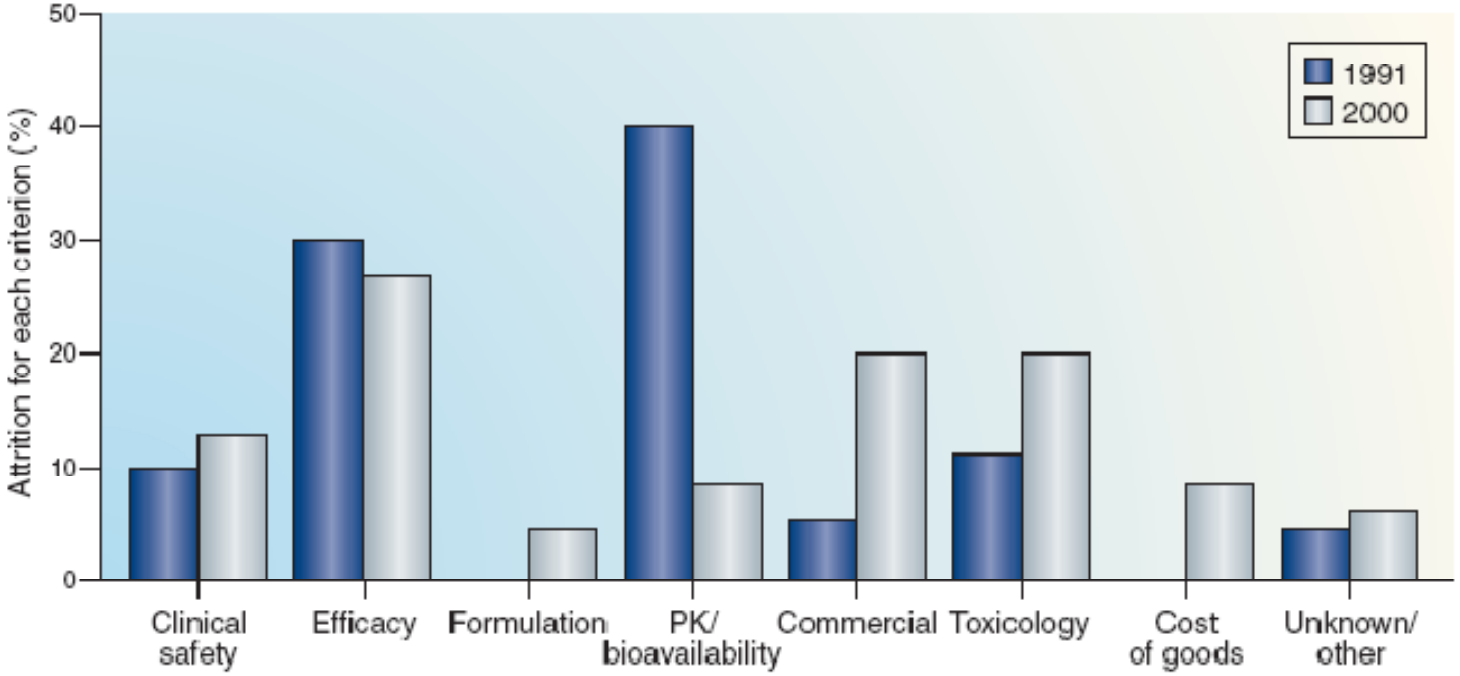
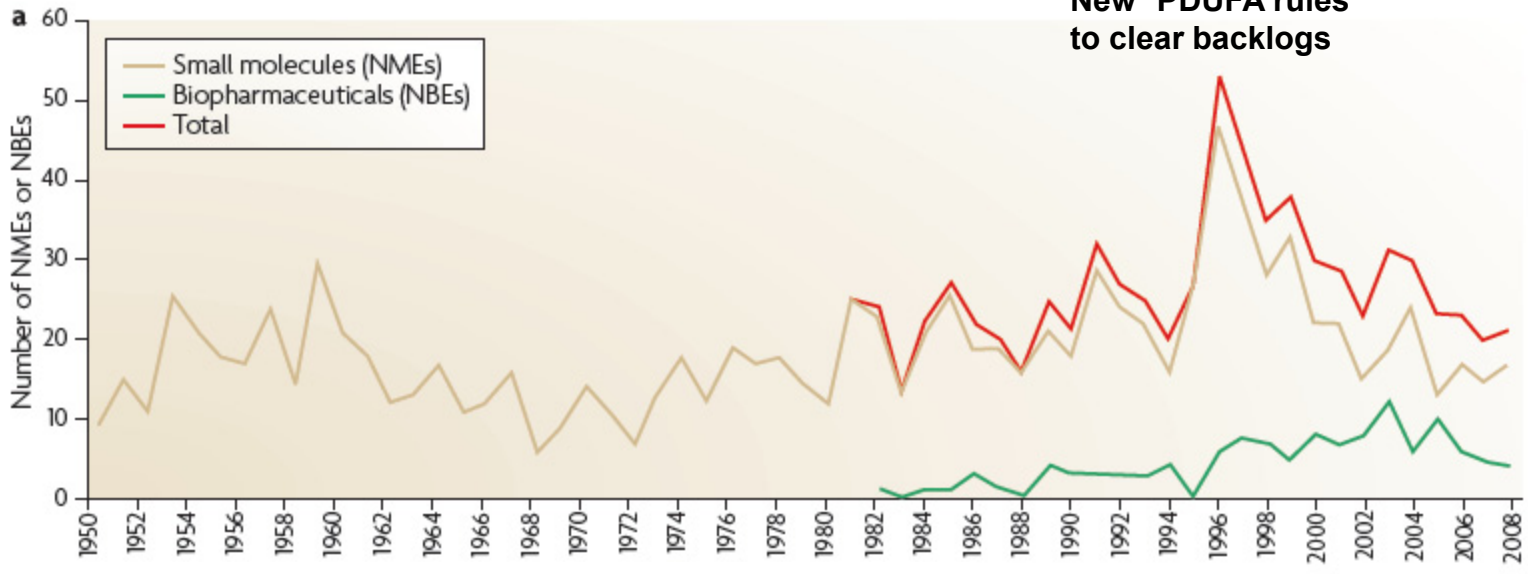


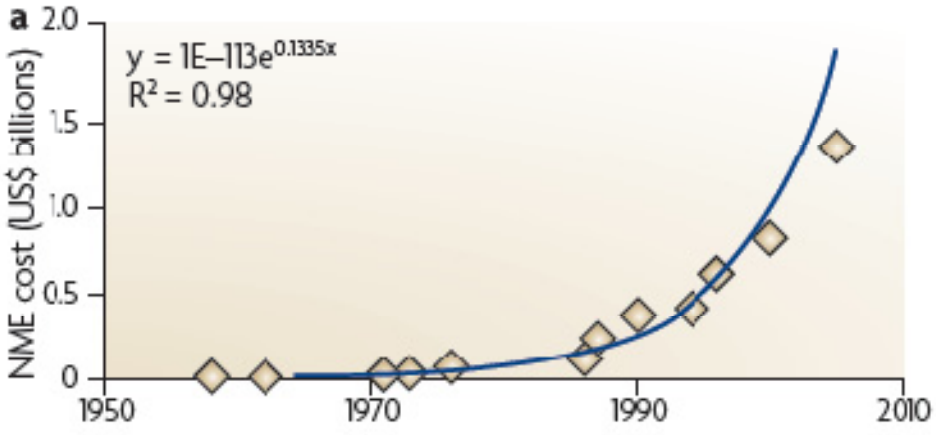
Figure 1 Reasons for attrition in drug development from 1991 to 2000. Attrition due to pharmacokinetics (PK) and bioavailability significantly decreased during this period whereas other causes of attrition became relatively more common. (Reproduced from ref. 1 with permission.)

R. Boyd, R. Lalonde
Clinical Pharmacology and Therapeutics
January 2007

Why do we need to make better use of pharmacometrics?

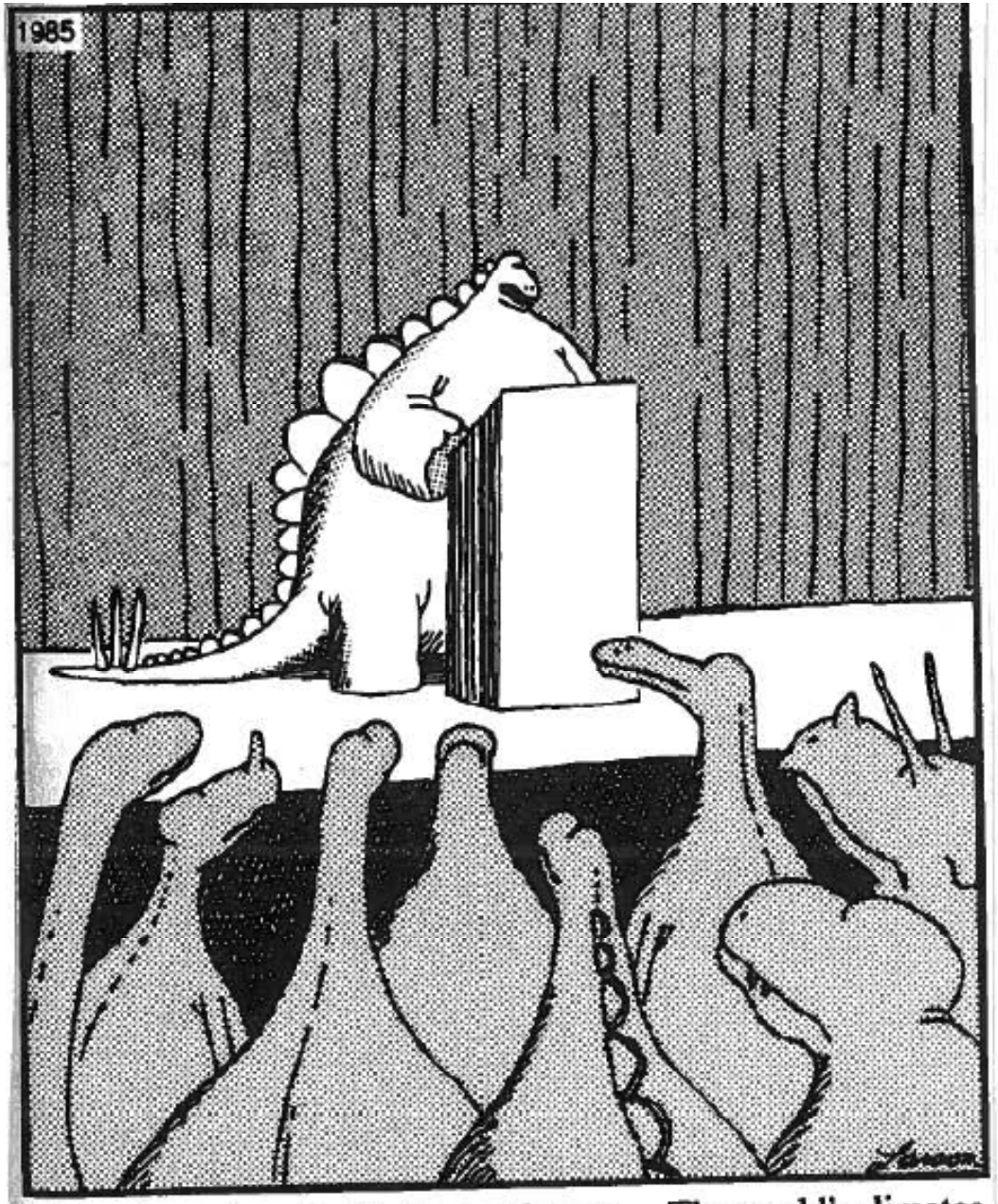


New *PDUFA rules to clear backlogs



***PDUFA: prescription drug user fee act**

Bernard Munos
Nature Reviews/Drug Discovery
December 2009



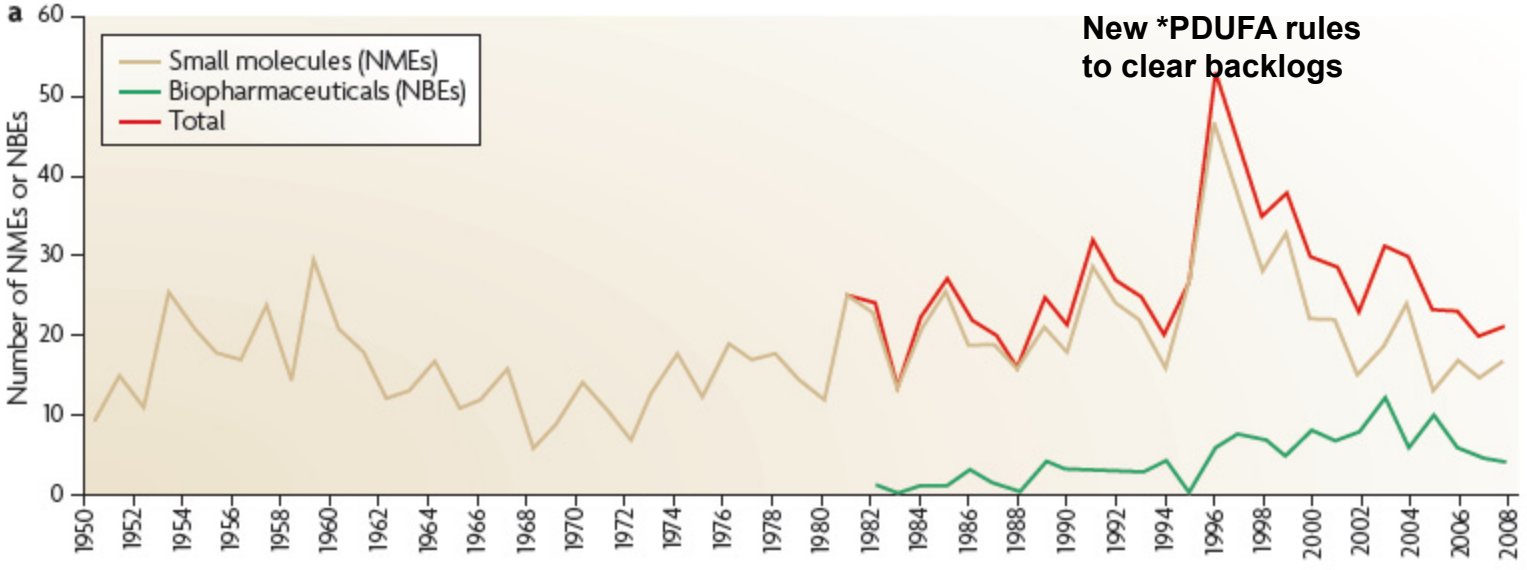
"The picture's pretty bleak, gentlemen.... The world's climates are changing, the mammals are taking over, and we all have a brain about the size of a walnut."

Why do we need to make better use of pharmacometrics?

Waning productivity in drug R&D is not a new observation. There have been a number of innovative attempts to improve R&D output including:

- Investment in science and technology -
  - Recombinant DNA technology/Site-directed mutagenesis
  - Hybridomas
  - Genomics (genomics, proteomics, metabolomics, you-name-it-omics)
  - Gene knockouts
  - Expanded chemical diversity
  - High throughput screening
  - etc
- Partnerships and consortia to de-risk and/or synergize expertise
- Mergers and Acquistions (bigger is better…….NOT!)
- Shift from bucket brigade to functionally integrated R&D teams

Why do we need to make better use of pharmacometrics?



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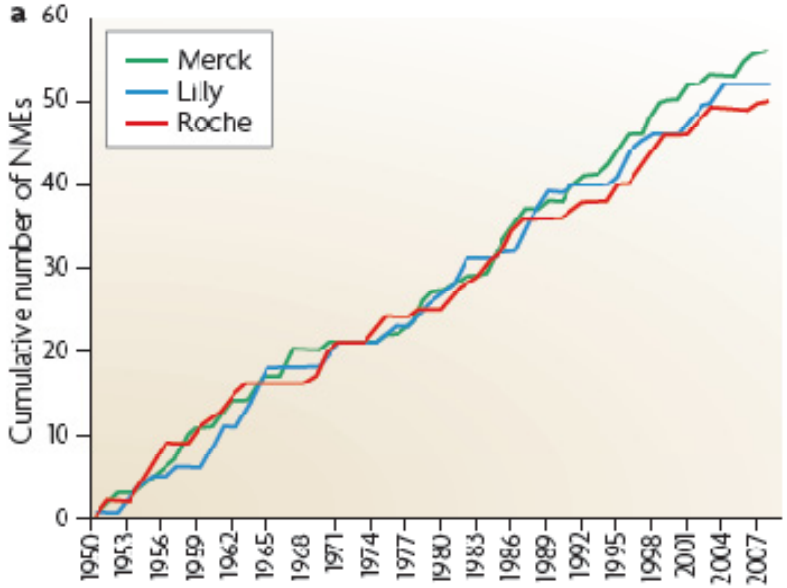


Bernard Munos
Nature Reviews/Drug Discovery
December 2009

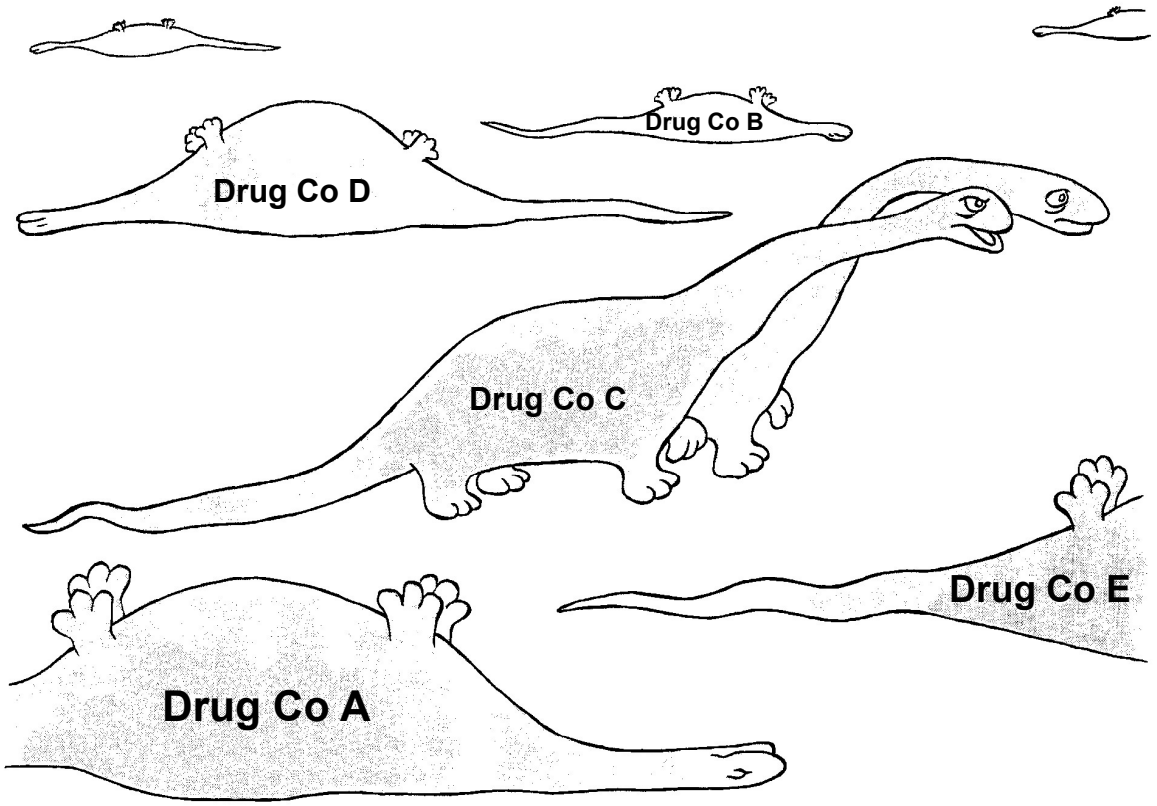
The R&D model that has powered that success, however, is showing signs of fatigue: costs are skyrocketing, breakthrough innovation is ebbing, competition is intense and sales growth is flattening. This cluster of symptoms has often foretold major disruption in other industries[39,40].

Bernard Munos
Nature Reviews/Drug Discovery
December 2009

Sounds a lot like:

"The picture's pretty bleak, gentlemen. ... The world's climates are changing, the mammals are taking over, and we all have a brain about the size of a walnut."

How Do We Improve?



"Frankly, I don't like the way things are going."

http://www.fda.gov/oc/initiatives/criticalpath/stanski/stanski.html

DMPK Role in Discovery Research:

- Identify strong development candidates based on quantitative criteria (Product Candidate Criteria – eg. Acceptable BA, sufficient PK to drive response *safely*, etc.)
- Provide critical information to the development team regarding clinical dosing strategy based on early PK/PD, formulation, choice of route, device, biomarkers (good and bad), populations (what to expect in humans)

The Discovery period for a biological candidate is about the same as that for a small molecule – about 1-3 years

DMPK Role in Process and Formulation Development

- Select final formulation for preclinical safety and clinical evaluation
  - **Must support systemic exposure requirements**

- Protein therapeutic agents are always heterogeneous (contain by-products of both the fermentation and purification process). Assessing the impact of contaminants and defining release specifications is challenging especially as process and/or formulation changes are made during scale up
  - **Defining comparability/bioequivalence involves PK/PD analysis**

- Hitting commercially feasible cost-of-goods targets can be an issue for products requiring high dose levels
  - **Crucial to "tailor" dose strategy (not overdose, choose the right population)**

DMPK Role in Preclinical Research:

- Assess toxicokinetics to support safety studies
- Evaluate anti-drug antibody formation and impact on bioactivity (ADA)
- Perform allometric scaling to human PK
- Further refine PK/PD understanding, including site of action distribution, clearance pathways, linearity
- Begin thinking about drug-drug interaction strategy (yes, I said drug-drug interactions!)
- Begin thinking about special populations, eg. renal insufficiency, pediatrics, etc.

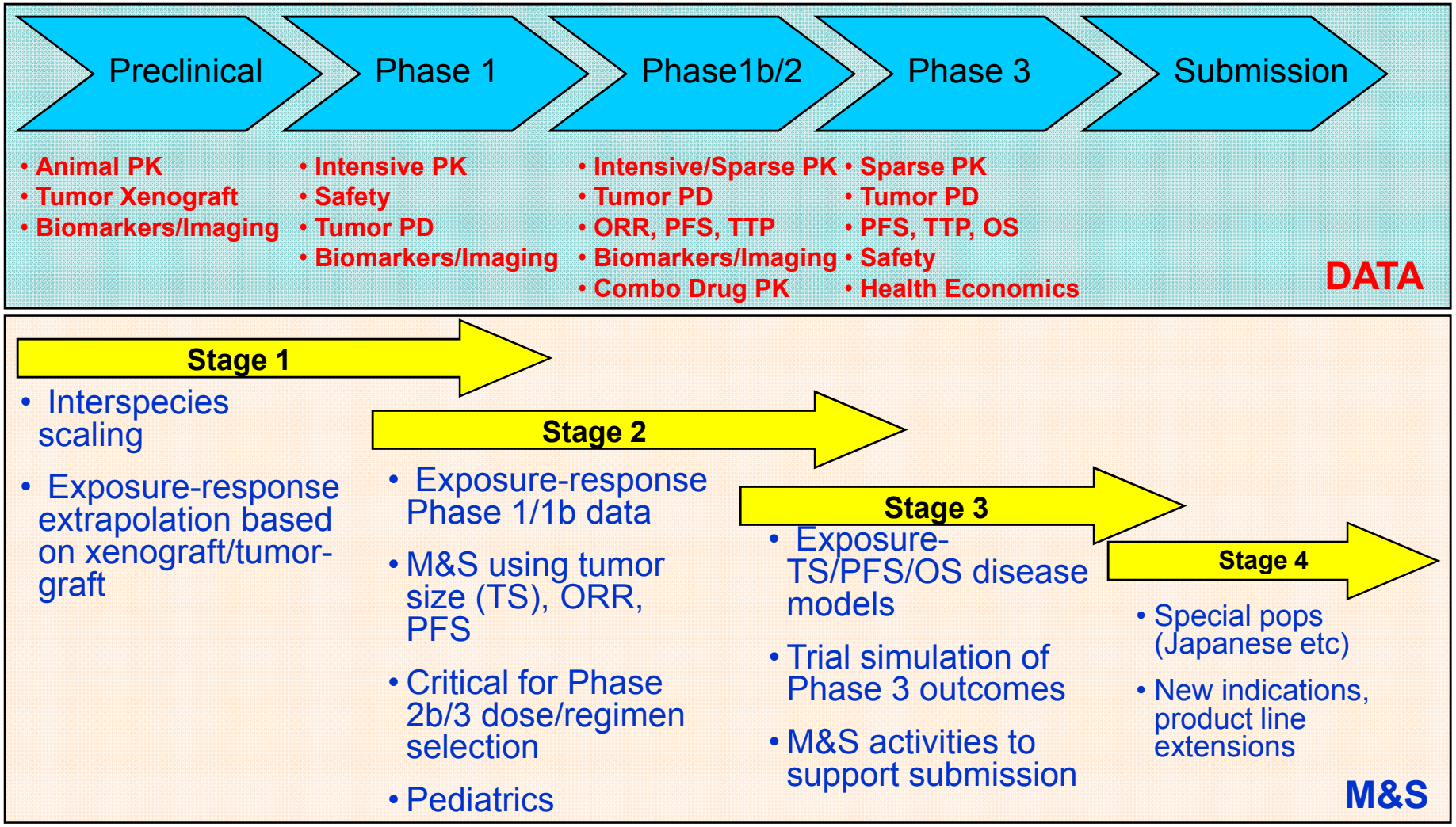
DMPK Role in Early Clinical Research:

- Establish clinical pharmacology strategy as part of the clinical development plan – what do you want to know and when
- Combining classical NOAEL/STD10 with PK/PD knowledge to set initial dose in humans
- Real-time assessment of clinical data to refine dosing strategy as needed
- Assessment of anti-drug antibody formation and impact on PD
- Design phase 1/2 trials to generate robust data sets which simulate probable outcomes in Phase 3
- Further refine PK/PD understanding to ultimately give the right dose to the right patients in the right amount and at the right time

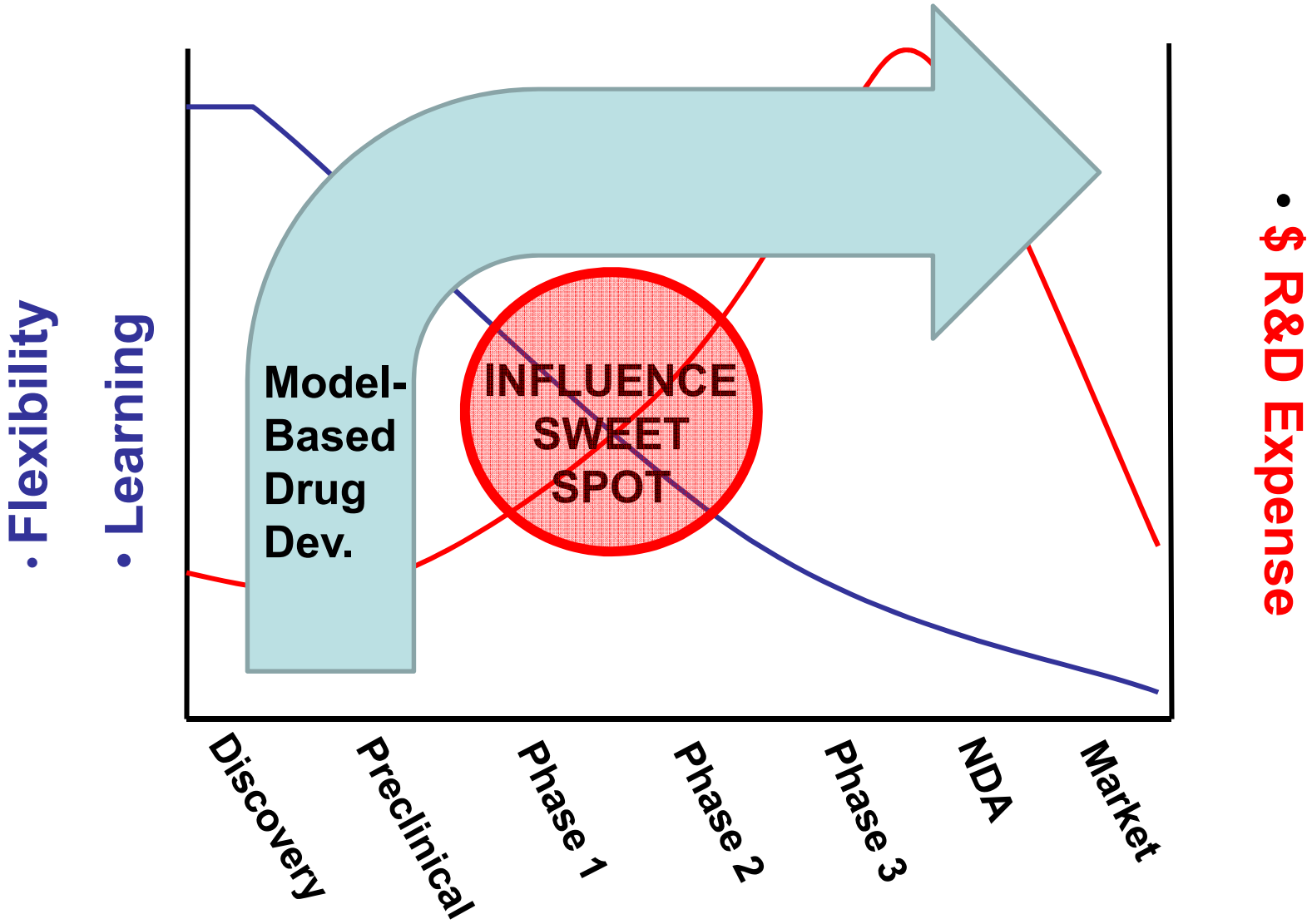
The terms Phase 1, 2, and 3 are slowing giving way to Lew Shiner's terms: Learn and Confirm

The Learning window essentially closes when a sponsor advances a drug candidate into Phase 3 to Confirm efficacy/safety. Therefore, it is pivotal to design and execute Phase 1/2 studies which provide

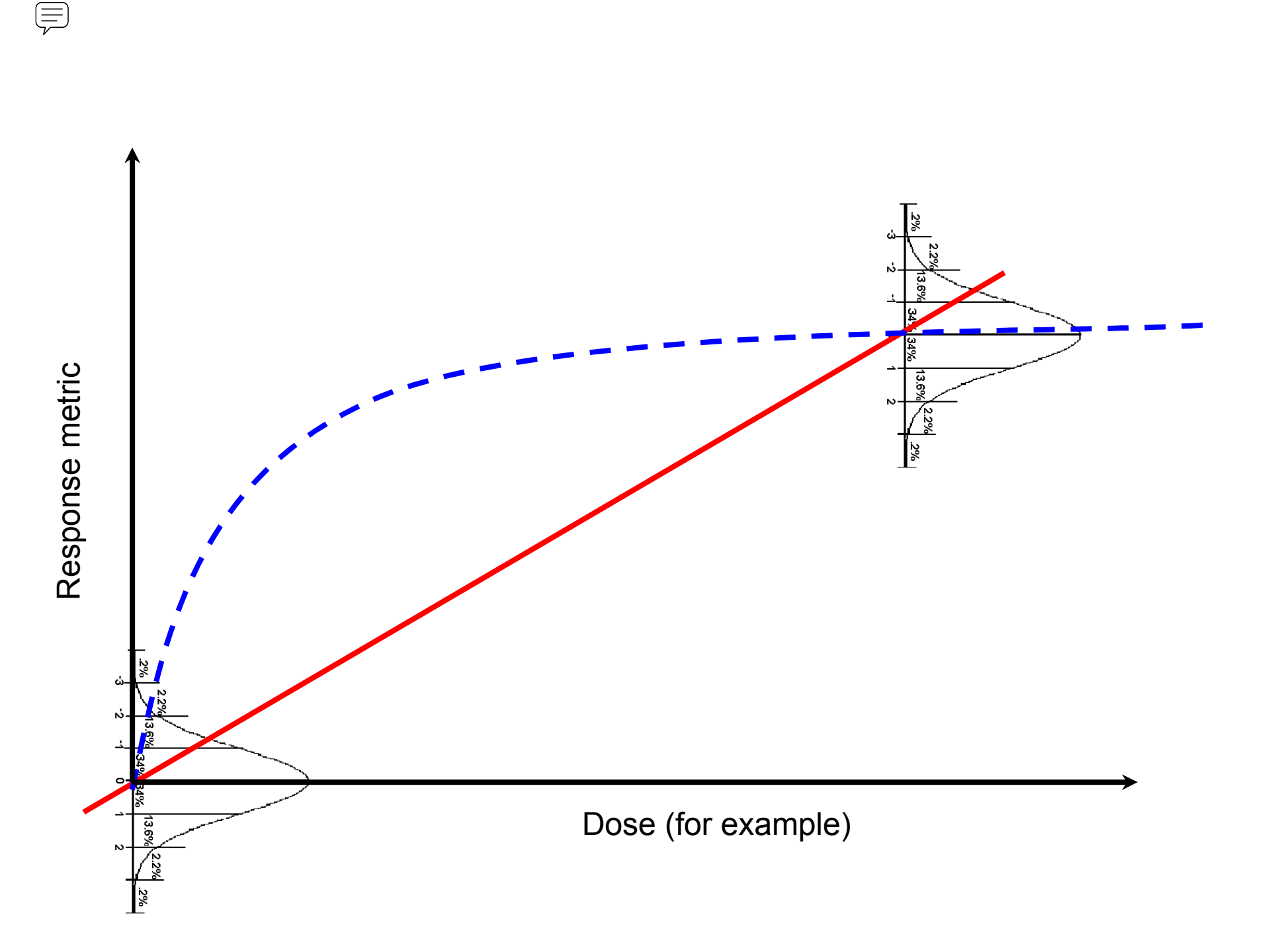
Modeling and Simulation in Oncology Therapy – Overlapping Stages Approach

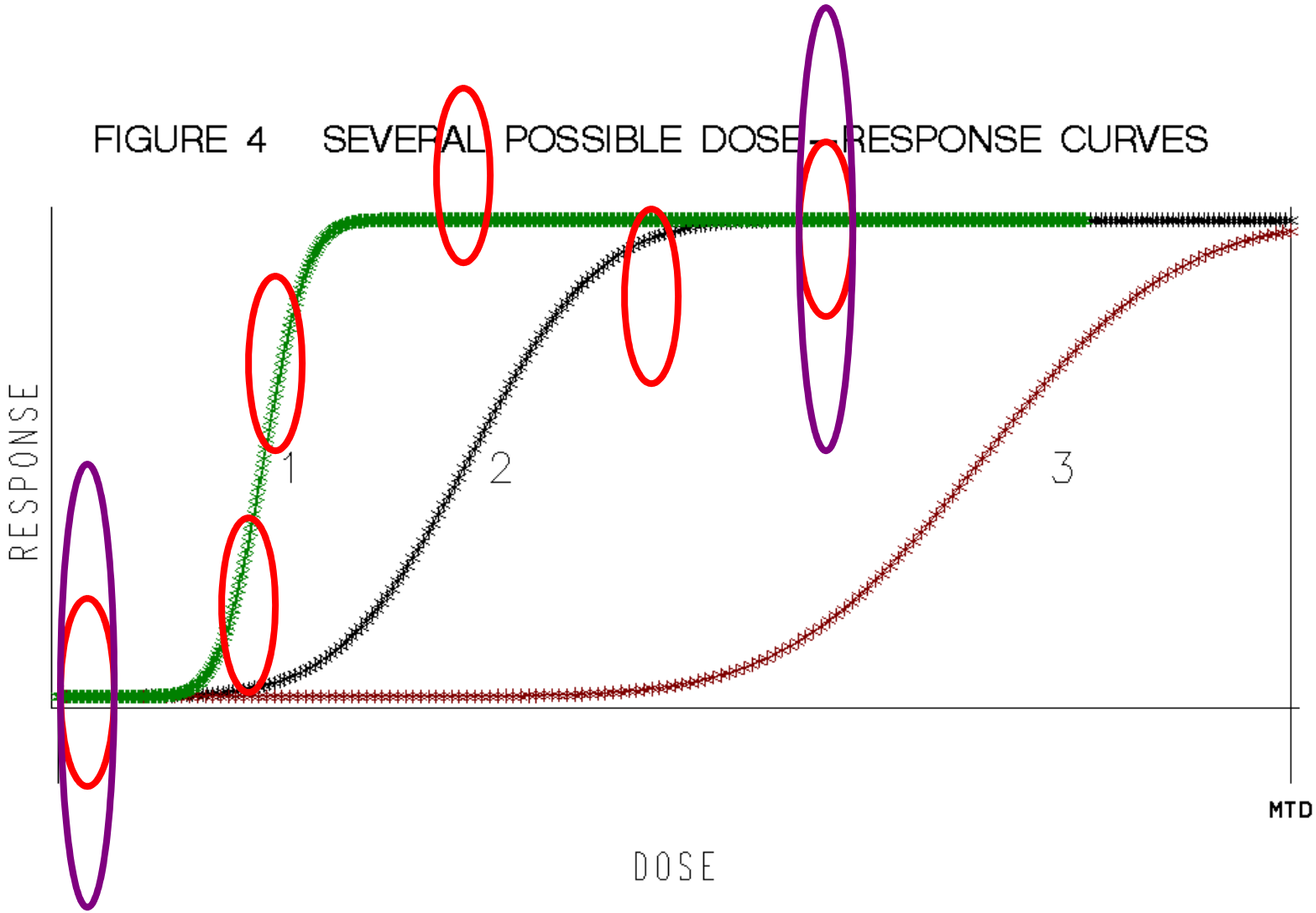


When Model-Based Drug Development is of Most Value



Adapted from D.Mitchell's personal communication with Robert Powell


Response metric
Dose (for example)
.2%
2.2%
13.6%
34%
34%
13.6%
2.2%
.2%
-3
-2
-1
0
1
2



Curve 1 = desired response

Curve 3 = adverse response

Underlying figure: http://www.amstat.org/Chapters/boston/Ting.ppt

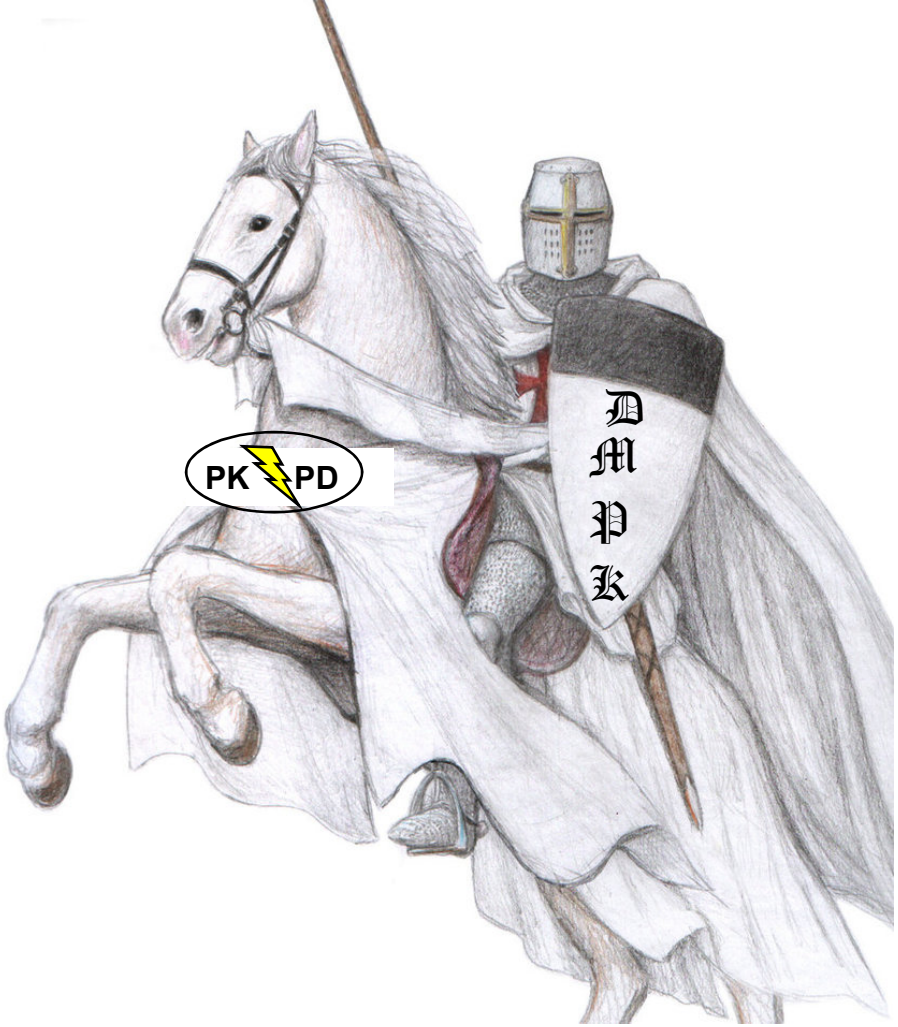
The Single Biggest Threat to the Pharmaceutical Industry

Failed Phase III Clinical Trails

Hundreds of Millions of Dollars Wasted

Current Cost ($1-2 Billion) per NDA is Unsustainable

Failed Phase III Clinical Trails



Failed Phase III Clinical Trails

Regulatory Guidances to Consider

- **FDA Guidance Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications**

- **FDA Guidance for Industry Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format**

- **ICH Topic E4 - Dose Response Information to Support Drug Registration**

- **FDA Guidance End-Of-Phase-2A Meetings With Sponsors Regarding Exposure-Response of IND and NDA Products**

> "… use all prior knowledge (including data and analyses, quantification of disease variability, subgroup heterogeneity, and dose (concentration)-response models in the development of computer simulations) to make more informed drug development decisions on trial design and dosage regimen selection."

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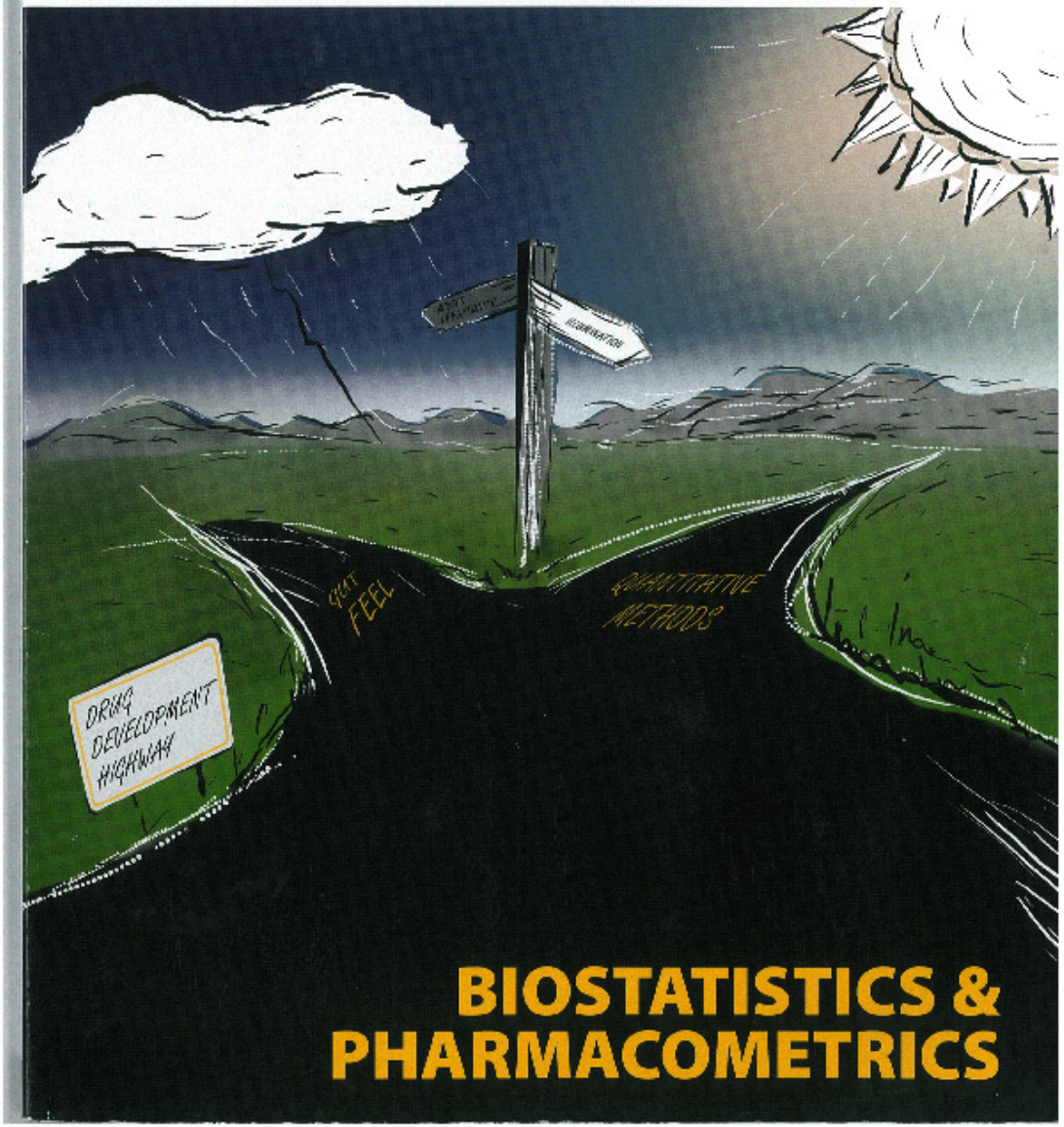

BIOSTATISTICS & PHARMACOMETRICS

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SUPPLEMENT 1

Supplement to
The Journal of

Clinical Pharmacology

Official Publication of the American College of Clinical Pharmacology

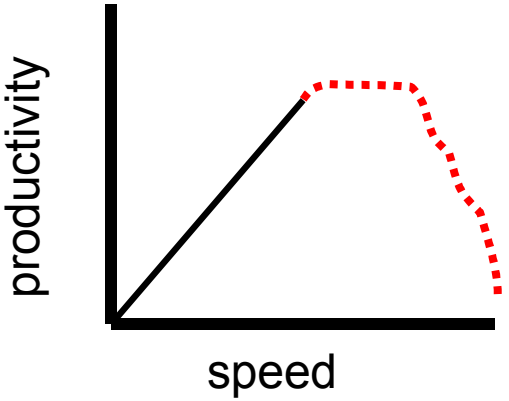
THE EMERGING SCIENTIFIC DISCIPLINE OF PHARMACOMETRICS

Guest Editors:
Marc Pfister and David Z. D'Argenio

This all sounds perfectly reasonable. So why haven't we been applying model-based drug development in all the programs??

The False Economy of Taking Shortcuts (where perceived constraints meet [defeat] noble intentions)

- Decreasing trial sizes and execution time will win the horse race to market; **faster is *always* better**



These false drivers persist in drug development and likely contribute to the high failure rate in the clinic; they also hinder the application of model-based drug development

The False Economy of Taking Shortcuts (where perceived constraints meet [defeat] noble intentions)

- The **competitors** will succeed; therefore we need to take shortcuts

These false drivers persist in drug development and likely contribute to the high failure rate in the clinic; they also hinder the application of model-based drug development

The False Economy of Taking Shortcuts (where perceived constraints meet [defeat] noble intentions)

- We'll build a thorough data set **later**

FOR SALE!!

The Brooklyn Bridge

These false drivers persist in drug development and likely contribute to the high failure rate in the clinic; they also hinder the application of model-based drug development

The False Economy of Taking Shortcuts
(where perceived constraints meet [defeat] noble intentions)

- We **can't afford** to collect *extra* data in phase 1/2; therefore only test one dose level versus control

CORPORATE FINANCE

"You wanna spend WHAT?!?"

These false drivers persist in drug development and likely contribute to the high failure rate in the clinic; they also hinder the application of model-based drug development

The False Economy of Taking Shortcuts (where perceived constraints meet [defeat] noble intentions)

- The *only* question in phase 2 is “does the drug work?”, eg. **Signal Seeking**; only test one dose level versus control
  - Answering this alone leaves us ill-prepared to make a strong go/no-go for a registration trial; must do phase 2b next
  - We also need to understand the therapeutic window to recommend the *right* dose for phase 3
- **More drug is always better** and MAbs are very safe; therefore dose as high as feasible
  - Not true, we still need to define *both* the efficacy curve and the tolerability curve; a single data point (one dose level) is insufficient to define either curve
  - Reaching the market with a single dose level later found to be toxic is not winning the game

---

These false drivers persist in drug development and likely contribute to the high failure rate in the clinic; they also hinder the application of model-based drug development

The False Economy of Taking Shortcuts (where perceived constraints meet [defeat] noble intentions)

- Increasing cohort sizes and elucidating the response curves is **unethical and unnecessary**
  - Trial designs are predicated on the robustness of prior data
  - Executing a phase 3 with an inappropriate dose *is* unethical, but we often do this as we have not gathered sufficient data to substantiate our dose/regimen selection
  - We are conducting clinical research, not therapy

- Statistical readouts (**p value**) from single-arm active-control trials correctly inform the probability of success in the registration trial
  - P-value does in phase 2 is not a Bayesian statistic and does not predict future probabilities – only data supported models and Bayesian analyses can provide these statistics
  - Experience tells us phase 2 p values alone do not accurately predict phase 3 outcomes

---

These false drivers persist in drug development and likely contribute to the high failure rate in the clinic; they also hinder the application of model-based drug development

The False Economy of Taking Shortcuts (where perceived constraints meet [defeat] noble intentions)

- "**FDA is not asking** for this"

These false drivers persist in drug development and likely contribute to the high failure rate in the clinic; they also hinder the application of model-based drug development

The science and technology for model-based drug development are in existence. We just need the data, the resources, and the patience to fully exploit the benefits.

This can happen NOW

DMPK Role at Drug Approval and Labeling:

- New FDA Guidance for Clinical Pharmacology section of a drug label *suggests* including a detailed description of PK/PD and dose justification

  FDA - "If you don't model the data, we will do it for you"

- New draft FDA Guidance *recommends* evaluation of PK for proteins <69 kD in subjects with renal insufficiency (based on reported decreased renal CL of some cytokines in subjects with renal impairment)
- Emerging regulatory expectation that sponsors will evaluate the potential for drug-drug interactions between therapeutic proteins and concomitant medications

Drug-drug interactions are most commonly due to one drug (the perpetrator) modulating the PK of another drug (the victim), usually by inhibiting the P450 enzyme responsible for clearing the latter. Initial example: terfenadine/ketoconazole

There are other types of drug-drug interactions, in which one drug indirectly affects the PK or PD of another


grand
theft
auto IV


Perpetrators and Victims

Understanding Consequences of Concurrent Therapies

In 1989, the occurrence of a rare, life-threatening ventricular arrhythmia (torsades de pointes) in an otherwise healthy young woman led alert clinicians at the Naval Hospital in Bethesda, Md, to consider the possibility that the patient's near-fatal arrhythmia was triggered by a drug-drug interaction involving her antihistamine (terfenadine) and her antifungal (ketoconazole) medications.[1] Consulting clinical pharmacologists from the Uniformed Services University of the Health Sciences and the US Food and Drug Administration (FDA) suggested that ketoconazole inhibited the oxidative metabolism of terfenadine. Analysis of blood samples revealed that the patient had high levels of unmetabolized terfenadine, a compound not usually detectable in blood because it is metabolized so quickly. Review of reports to the FDA's spontaneous reporting system revealed that among additional cases of torsades de pointes in patients receiving terfenadine, many were also receiving ketoconazole. This evidence led the FDA to ask Marion Merrill Dow, Kansas City, Mo, manufacturers of terfenadine, to issue a "Dear Doctor" letter warning physicians about the terfenadine-ketoconazole interaction in August 1990. The articles by Honig et al[2] and Woosley et al[3] in this issue, as well as an earlier article by Honig, Woosley, and coworkers[4] describing the terfenadine-erythromycin interaction, now provide a more complete explanation of this important mechanism of drug-induced variability in drug action and show clearly that the increased levels of parent terfenadine provoked by inhibitors of cytochrome P-450 3A4 inhibit the cardiac potassium slow channel, leading to prolongation of the QT interval and torsades de pointes.

See also pp 1513 and 1532.

This new information was made available to the FDA last summer and, coupled with more reports of arrhythmias, led to further revision of labeling of terfenadine to contraindicate its coadministration with the antifungal agents ketoconazole and itraconazole and with macrolide antibiotics such as erythromycin and troleandomycin. Shortly thereafter, similar labeling revisions were required by the FDA for another an-

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Carl C. Peck, Robert Temple, Jerry M. Collins

Possible mechanisms for interactions between therapeutic proteins and small molecule drugs:

- Modulation of expression of drug metabolizing enzymes by the therapeutic protein
- NF-κB mediated CYPs (or drug transporters) suppression
  - Cytokines (e.g. interferon)
- Inhibition of renal excretion transporters
- Alteration in plasma protein binding

Therapeutic Protein–Drug Interactions and Implications for Drug Development

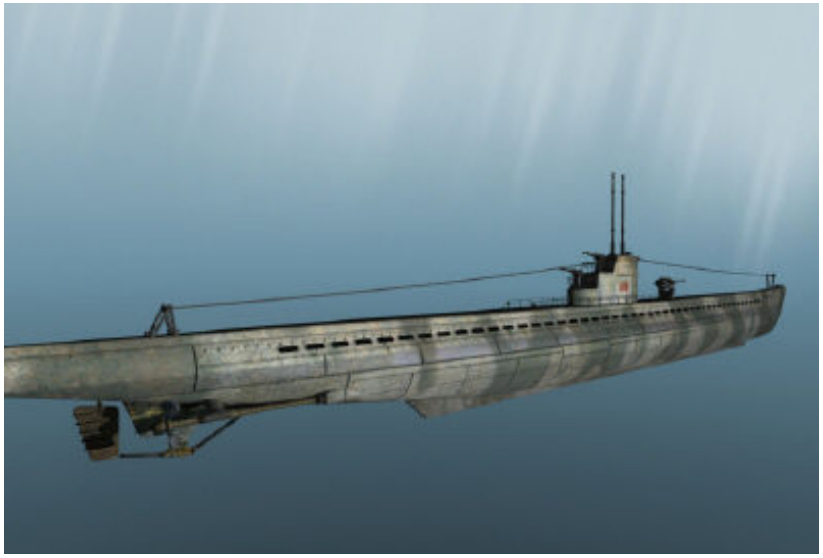
S-M Huang[1], H Zhao[1], J-I Lee[1], K Reynolds[1], L Zhang[1], R Temple[2] and LJ Lesko[1]

Clinical Pharmacology and Therapeutics, 2010

After 10 long years, your Biological License Application (BLA) was finally approved. Is it time to relax and enjoy??

NO !!!!!

Marketed drugs are under constant pressures, some visible and others lurking



DMPK Role in Life Cycle Management:

- Label expansion – clinical trial aided by PK/PD knowledge; Enbrel in pediatrics
- Safety issue resolution
- New or changing Regulatory policies
- Obamacare – more cost justification needed?
- Competition/Biosimilars (generic equivalent for protein drugs)

ISSUE RESOLUTION

Thinly designed studies during development leave a sponsor vulnerable when unexpected problems occur with a marketed drug. Mitigation strategy is severely restricted if little is known about alternate dose regimens, etc.

Deer in headlights = Unprepared Sponsor

WILLKIE FARR & GALLAGHER LLP

CLIENT MEMORANDUM

DRUG APPROVAL PATHWAY ESTABLISHED FOR BIOSIMILAR DRUGS

On March 23, 2010, President Obama signed the Patient Protection and Affordable Care Act (the "Act") — health care legislation that includes the establishment of an abbreviated biosimilar biologic drug approval pathway.[1] The term "biosimilar" is often used to describe biologic drugs that are similar, but not identical, to previously approved biologic drugs. Abbreviated biosimilar biologic drug approval is now governed by the provisions set forth in a subtitle of the Act, the Biologics Price Competition and Innovation Act of 2009 (the "BPCIA").[2]

The BPCIA stems from years of industry and legislative debate focused on facilitating the introduction of cheaper alternatives to biologic drugs previously approved in the United States. Biosimilar biologic drug applicants and holders of previously approved biologics license

A. Application Requirements

The BPCIA requires biosimilar applicants to provide, among other things, analytical studies demonstrating that the biological product is highly similar to the reference product, animal studies (including an assessment of toxicity), and a clinical study or studies (including an assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are "sufficient to demonstrate safety, purity, and potency" of the applicant's proposed product.[3]

SUMMARY

DMPK scientists are making significant contributions to the development of therapeutic proteins. Continued application of the data → information → knowledge → wisdom pathway via well-designed studies will help slay the dragon

Drug Development Failures