Sheiner-Beal Award Lecture
ASCPT, March 17, 2017

Pharmacometrics @ 45

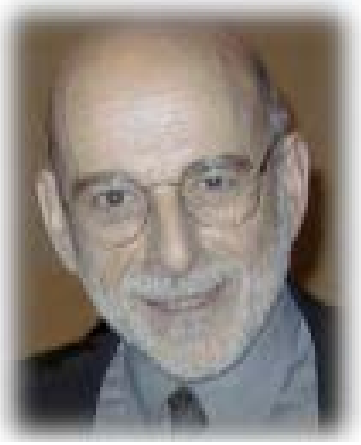
What Next ?

Carl Peck, MD

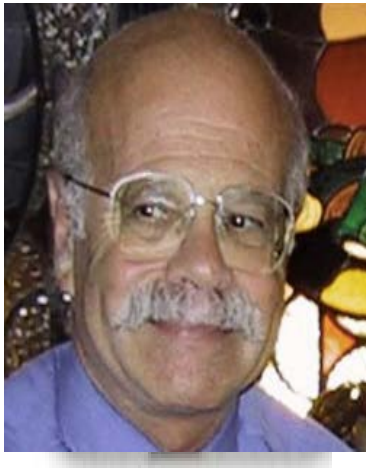
Department of Biopharmaceutical Sciences
School of Pharmacy,
University of California San Francisco

NDA Partners LLC

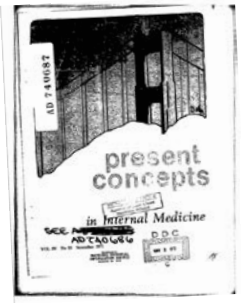
UCSF
University of California
San Francisco



Lewis Sheiner
Chemistry
Internal medicine
clinical Pharmacology



Stuart Beal
mathematics, logic
fine arts
biostatistics



Present Concepts in Internal Medicine. Volume 4.
Number 11. Medical Literature Symposium

October 1971

THE ALMIGHTY P-VALUE
OR THE SIGNIFICANCE OF "SIGNIFICANCE"

MAJ Carl C. Peck, MC

"Today a medical journal article can hardly be accepted for publication without the data being lavishly garnished with referrals to "p < 0.001"

These statements of statistical "significance" have obtained an almost mystical power, as if in themselves capable of establishing the "truth" of the data to which they pertain. The true *meaning and utility of these statistical maneuvers*, however, are *widely misunderstood, by authors, editors, and readers*. …"

Pharmacometrics @ 45

Why 1972 ?

1972 – 2017

What Next ?

"Pharmacometrics"

- **Science that quantifies drug actions in humans**
  - efficient drug development
  - regulatory decisions
  - therapeutic decisions in patients
- **Pharmaco-statistical simulation models**
  - Exposure-response variability
  - pharmacology, physiology, anatomy, genetics, disease
  - PK, PD, PG, disease progression, compliance (adherence), clinical trials

Why 1972 ?

Computers and Biomedical Research 5. 441-459 (1972)

COMPUTERS AND BIOMEDICAL RESEARCH 5, 441–459 (1972)

Modelling of Individual Pharmacokinetics for Computer-Aided Drug Dosage*

LEWIS B. SHEINER, BARR ROSENBERG,† AND KENNETH L. MELMON

Departments of Medicine and Pharmacology, Division of Clinical Pharmacology, University of California San Francisco Medical Center, San Francisco, California 94122

TABLE 1

THE CONCEPTUAL SCHEME

1. Observations (O) $\xrightarrow{T_1}$ Physiologic Variables (P)

Patient Factors

Example: Body Surface Area (BSA) = F (height, weight)

2. $P \xrightarrow{T_2}$ Pharmacokinetic Variables (Q)

PK Parameters

Example: Volume of Distribution (V_D) = F (BSA)

3. $Q \xrightarrow{T_3}$ Pharmacokinetic Parameters (K)

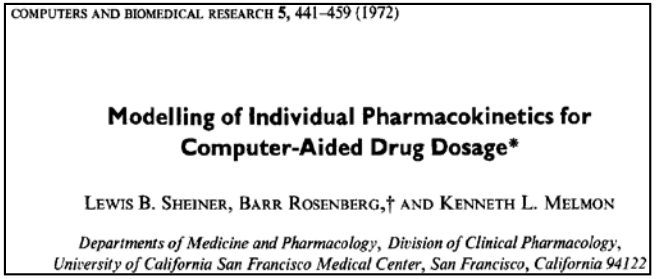
Model Parameters

Example: Rate Constant of Elimination (K_{el}) = Clearance/V_D

4. $K \xrightarrow{M}$ Blood Level Predictions

PK Model

Example: one compartment model with first order absorption



COMPUTERS AND BIOMEDICAL RESEARCH 5, 441–459 (1972)

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- **Estimation of Population PK**

$$\mathbf{l} = M(\mathbf{d}, \mathbf{td}, \{T_3(\mathbf{BP}_i + \boldsymbol{\eta})\}, \mathbf{tl}) + \mathbf{u}. \qquad (3.4)$$

Model enabling estimation of *population PK distributions*

- **Individual PK predictions**

$$\tilde{\mathbf{l}} = M(\mathbf{d}, \mathbf{td}, \{T_3(\mathbf{BP}_i + \hat{\boldsymbol{\eta}})\}, \mathbf{tl}), \qquad (3.13)$$

Model enabling *Bayesian* prediction of individual drug levels

Computer-*algorithm* vs Clinician vs Dose-table

(NEJM 289:441-446, 1973)

COMPUTER-ASSISTED DIGOXIN THERAPY

CARL C. PECK, M.D., LEWIS B. SHEINER, M.D., CARROL M. MARTIN, M.D., DARREL T. COMBS, M.D., AND KENNETH L. MELMON, M.D.

Abstract In 42 patients requiring digitalis, and randomly divided into two groups, the performance of a computer program using patient size and renal function to compute digoxin dosage was compared to that of unaided physician judgment. Serum digoxin concentrations were measured repeatedly. Efficacy was measured by changes in the manifestations of heart failure, and toxicity by electrocardiographic criteria. For each patient, physicians specified a desired serum digoxin concentration and predicted this concentration at each visit. For one group, the computer program suggested the dosage needed to achieve the desired digoxin concentration.

Efficacy was the same in both groups, and there was no toxicity. Although the computer slightly outperformed the physicians, prediction and achievement errors were unacceptably large. Hence, much between-patient variability in serum digoxin concentrations remains unexplained after adjustments for dose, body size and renal function. This argues for measurement of digoxin concentrations and their use for feedback dosage adjustment. (N Engl J Med 289:441-446, 1973)

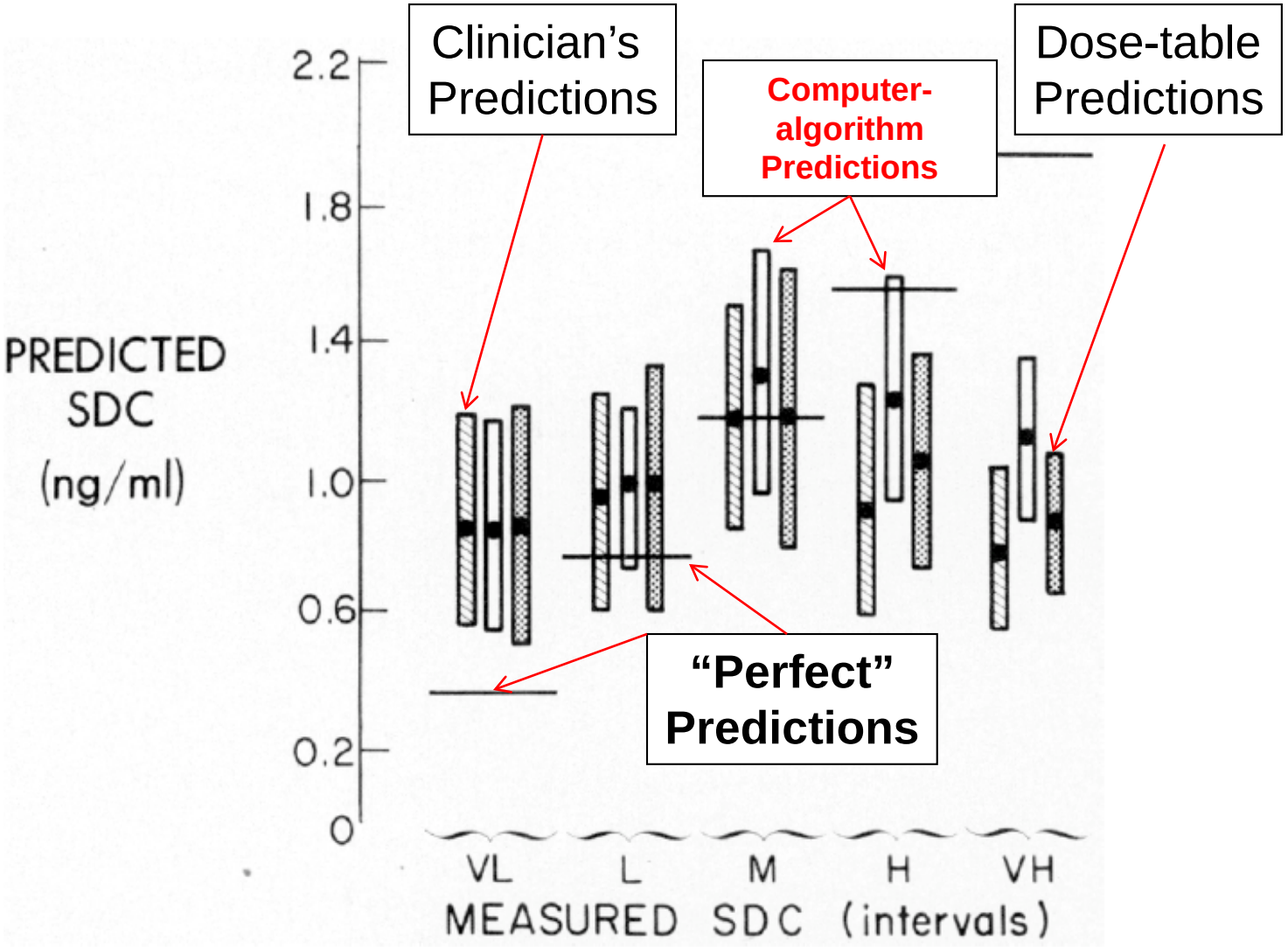
Findings

Prediction *errors* of computer-*algorithm* & achieved digoxin levels *too high*

computer-*algorithm* *not better* than *clinician's predictions*

Measured [digoxin] needed* for *feedback dosage adjustment

NEJM, 289:441-446, 1973



Early Pharmacometric Learnings

- **Sheiner**, **Peck**: Differences in serum digoxin concentrations between outpatients and inpatients - an effect of ***compliance***? Clin Pharm Ther, **1974**

- **Peck**, **Sheiner**, Melmon: ***Practical application*** of ***computer aided drug therapy***. Proc SD Biomed Symp, **1974**

- **Halkin**, **Sheiner**, **Peck**: "***Determinants of the renal clearance of digoxin***. Clin Pharm Ther, **1975**

Improved Computer-Assisted Digoxin Therapy

A Method Using Feedback of Measured Serum Digoxin Concentrations

LEWIS B. SHEINER, M.D., HILLEL HALKIN, M.D., CARL PECK, M.D., BARR ROSENBERG, Ph.D., and KENNETH L. MELMON, M.D., F.A.C.P., San Francisco and Berkeley, California

Ann Int Med 82:619-727, 1975

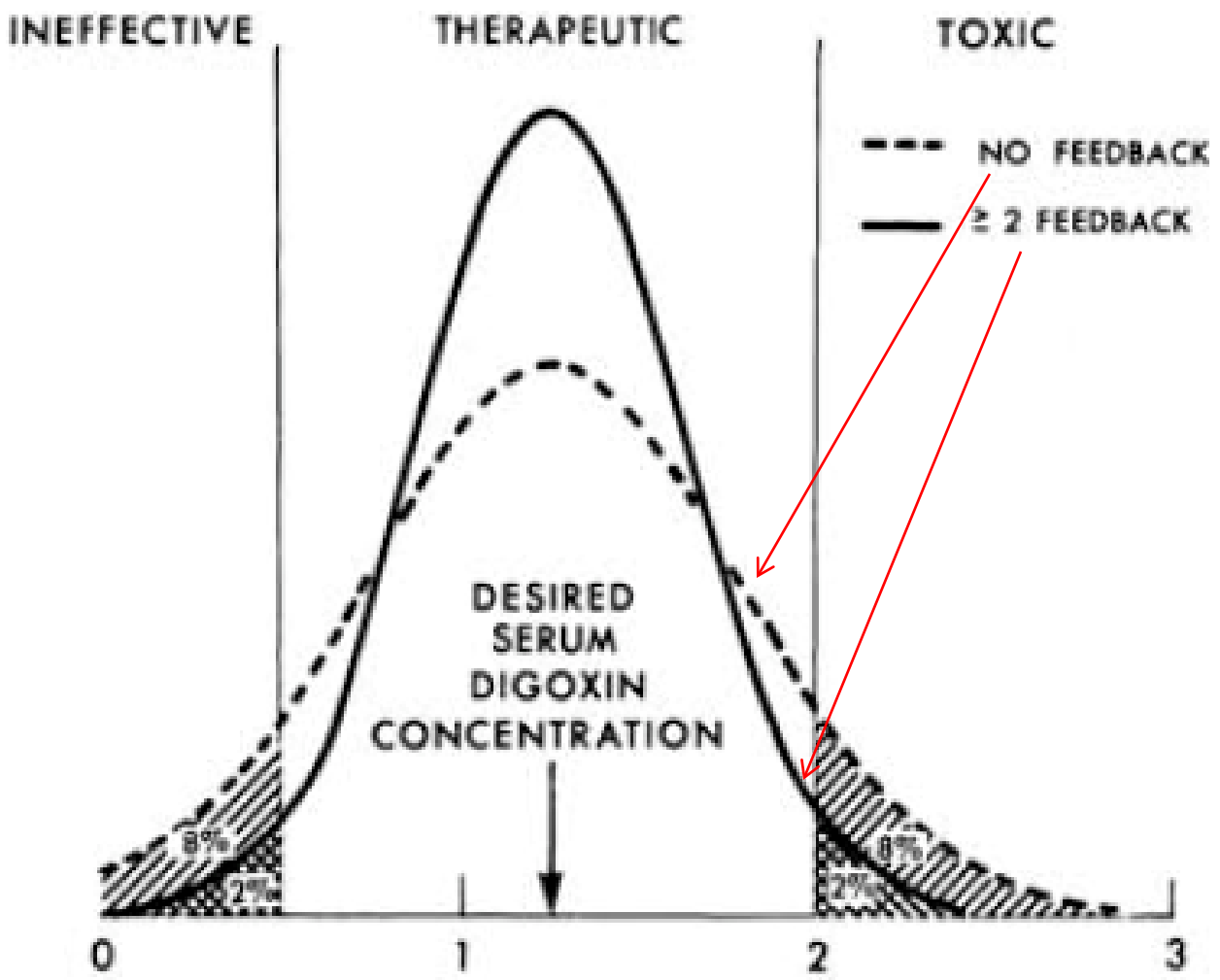
Findings

Measured [digoxin]'s + Bayesian estimation resulted in lower prediction errors vs computer-algorithm predictions

Better predictions than those of clinicians, unaided by* computer-*predictions

Measured [digoxin]'s + Bayesian estimation enabled better predictions, & potentially safer & more effective digoxin therapy

Ann Int Med 82:619-727, 1975



J Pharmacokin Pharmacodyn 5: 445-479 (1977)

"Estimation of population characteristics of pharmacokinetic parameters from routine clinical data."

Sheiner LB, Beal S., Marathe VV

Estimation of *population PK*

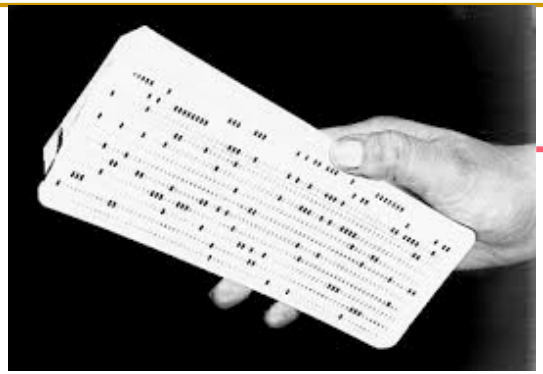
Provides

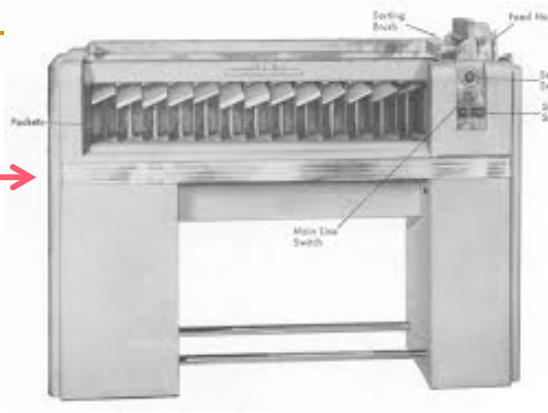
"priors" for *Bayesian* predictions

Clin Pharmacol Ther 26: 294-305 (1979)

"Forecasting individual pharmacokinetics"

Sheiner LB, Beal S, Rosenberg B, Marathe VV






commodore
PET
2001 Series
personal
computer

Methodological Applications

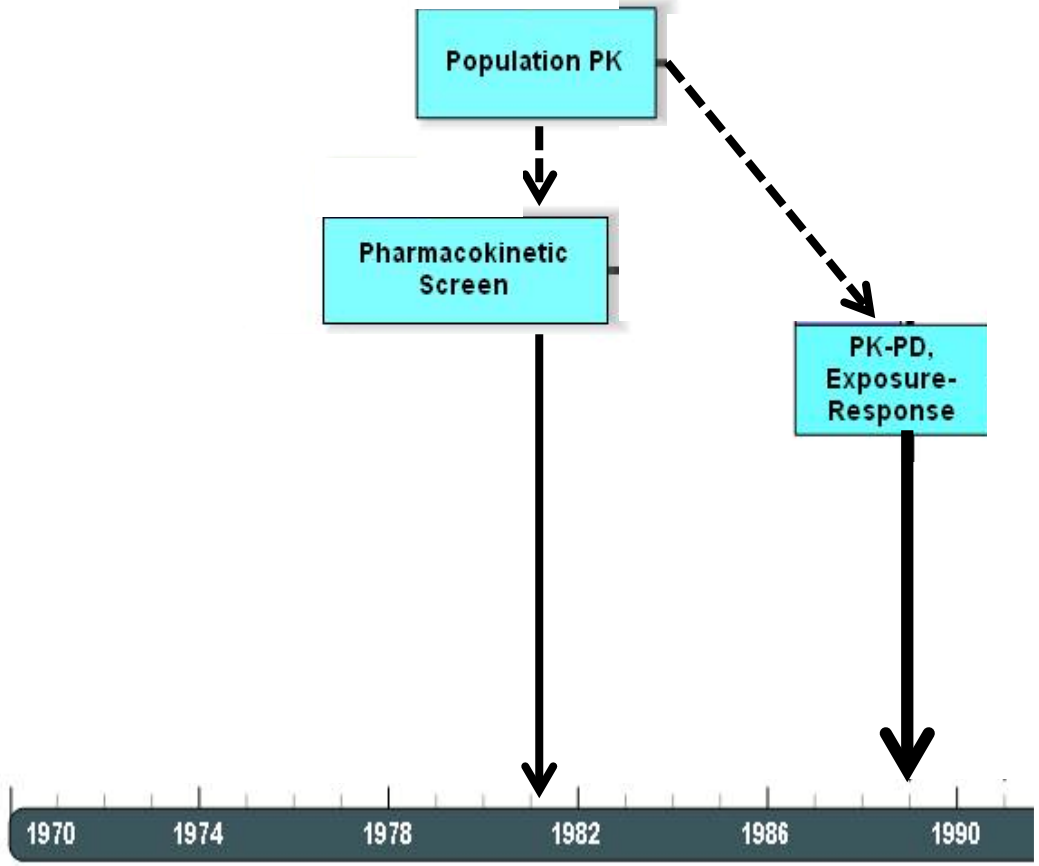
- **Peck**, Barrett: ***Nonlinear least-square regression*** programs for ***microcomputers***. J. Pharmacokin Biopharm **1979**

- **Peck**, Brown, **Sheiner**: A ***microcomputer*** drug (theophylline***)*** ***Bayesian dosing program*** which assists and teaches physicians". Proc 4th Annl Symp Comp Appli Med Care, **1980**

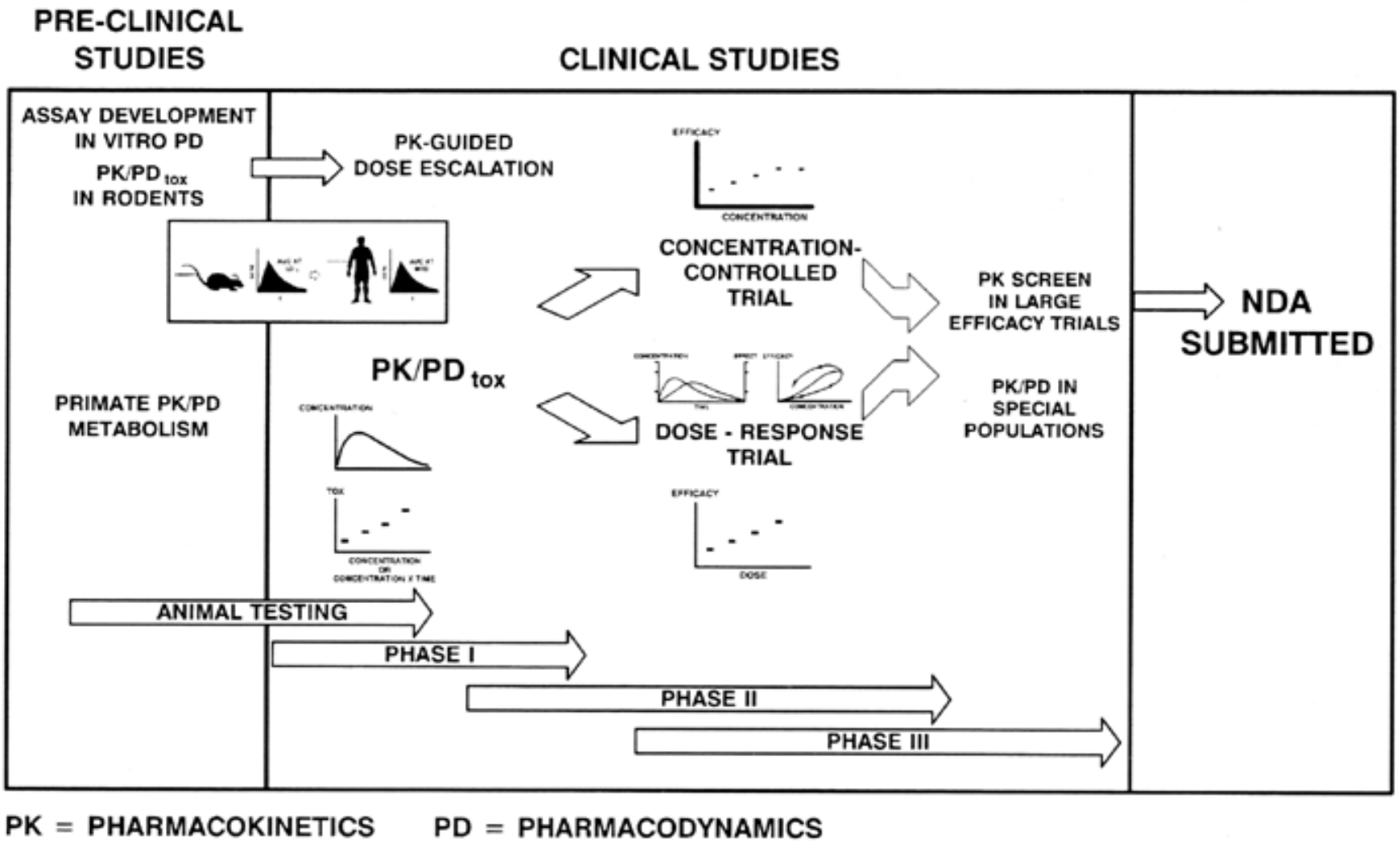
- Perlin, **Peck**, Nichols: An aminoglycoside ***dosing program*** using a ***Bayesian algorithm***. Proc 5th Ann Symp Comp App Med Care,**1981**

- **Peck**, **Beal**, **Sheiner**, Nichols: ***Extended Least Squares Nonlinear Regression***: A Possible Solution to the 'Choice of ***Weights***' Problem in Analysis of Individual Pharmacokinetic Dat", J Pharmacokin Biopharm, **1984**

Early applications of pharmacometrics in drug in development & regulation



Incorporating PK/PD in Drug Development[1]



1 Opportunities for Integration of PK/PD/TK in Rational Drug Development AAPS,FDA, ASCPT, Arlington, VA April 24-26, 1991. Clin Pharm Ther 51:467, 1991

Pharmacometrics in Drug Development

- Sanathanan, **Peck**: The Randomized ***Concentration-Controlled*** Trial: Evaluation of its Sample Size Efficiency: Cont. Clin. Trials 12:780-794, **1991**

- **Holford**, **Peck** et al: "***Simulation of Clinical Trials***". Ann Rev Pharm Tox, **2000**.

- Kimko, **Peck** (Eds). ***Clinical Trial Simulations***: Applications and Trends. AAPS Adv Pharm Sci, **2011**

- Lesko, Rowland, **Peck**, **Blaschke**; ***Optimizing the Science of Drug Development***: opportunities for better candidate selection and accelerated evaluation in humans. J Clin Pharm **2000**

Pharmacometrics in Regulation

- **Peck**: ***Population Approach in Pharmacokinetics and Pharmacodynamics***: ***FDA View***. Commission Europ Commun**1992**

- **Peck**, Benet et al: Opportunities for ***integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development***. Clin Pharm Ther **1992**

- **Peck**. ***Quantitative clinical pharmacology*** is ***transforming drug regulation***. JPharmacokin Pharmacodyn **2011**

Pharmacometrics and FDA

Modernization Act of 1997

Section 115a

Population PK

Pharmacokinetic Screen

PK-PD, Exposure-Response

Clinical

Committee

2003

End-of-Phase 2a Meeting

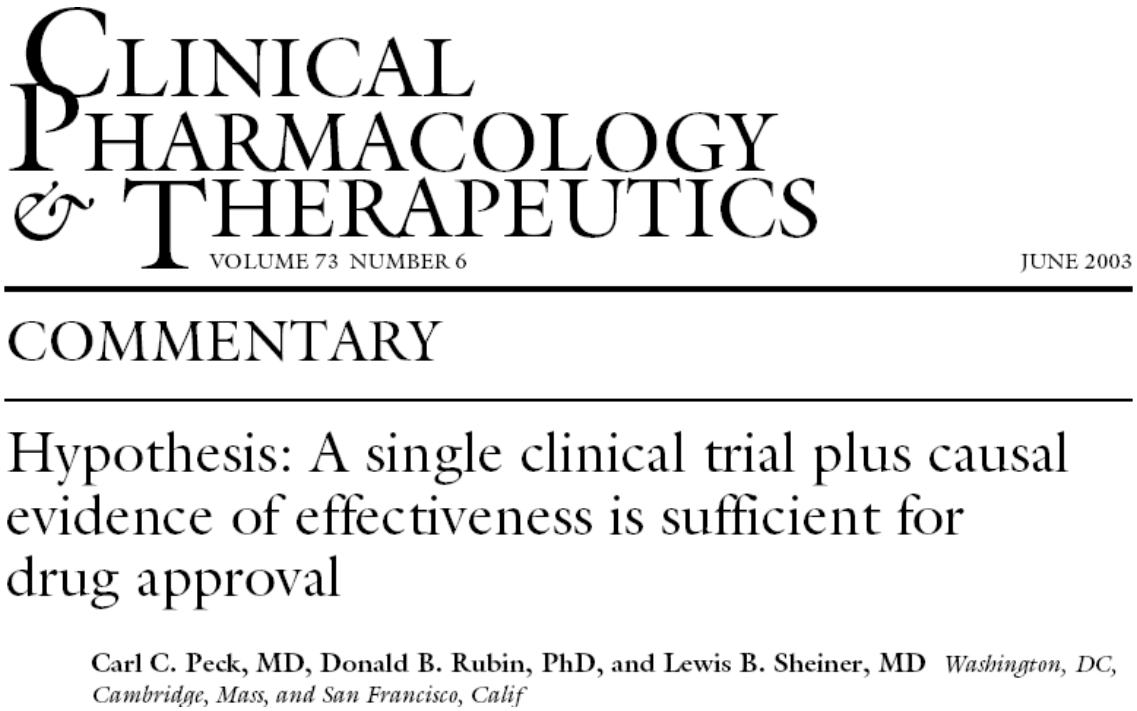
1997

FDAMA Section 115a

1970 1974 1978 1982 1986 1990 1994 1998 2002 2006 2010

Pharmacometrics in Drug Regulation

- **Peck,** Wechsler. Workshop on ***Confirmatory Evidence to Support a Single Clinical Trial as a Basis for New Drug Approval***. Drug Inf J **2002**



CLINICAL PHARMACOLOGY & THERAPEUTICS

VOLUME 73 NUMBER 6 JUNE 2003

COMMENTARY

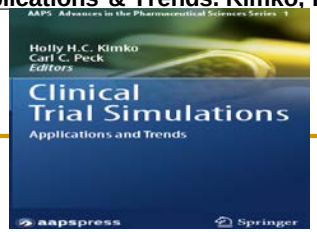
Hypothesis: A single clinical trial plus causal evidence of effectiveness is sufficient for drug approval

Carl C. Peck, MD, Donald B. Rubin, PhD, and Lewis B. Sheiner, MD *Washington, DC, Cambridge, Mass, and San Francisco, Calif*

U.S. FDA Perspective: *Impact Of Modeling & Simulation on Regulatory Decision Making,* * Garnett, Gobburu

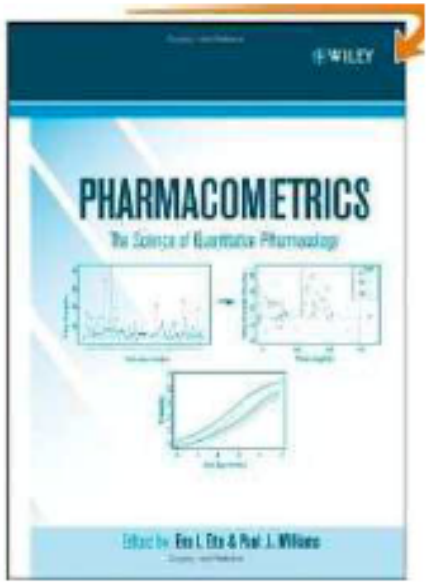
- PM Reviews of 198 IND/NDA/BLA (‘00-’08)
  - Trial designs, QT, EOP2a
  - popPK, E-R, Peds (38)
  - Impacted >60% APP, labeling
  - Evidence of effectiveness (9) & APP unstudied doses (21)
- Research & Policy
  - TQT design & E-R analyses
  - Disease models (2+5)
- > 30 NDA’s approved w/1 clinical trial

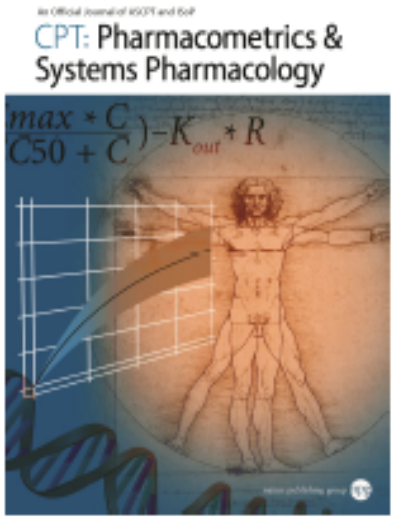
*** Chapter 3, Clinical Trial Simulations: Applications & Trends. Kimko, Peck**



Pharmacometrics in the world (1)

- **Conferences**
  - PAGE (1992-)
  - ACOP (2005-)
  - WCOP (2012-)
    PAGANZ (2000)
    PASIPHIC (‘11-15)
- **Book**
  - Pharmacometrics (2007)
    SIMULATION OF CLINICAL TRIALS (2011)
- **Journal**
  - CPT: PSP (2012-)
- **Society**
  - ISOP (2012-)
    WCOP (2014)





Adapted from Mentre 2013

Pharmacometrics @ 45

What Next ?

Next

PM can play a crucial role in the

disruptive reinvention of DD&R

by

Replacement of the *p-value tradition*

with

Bayesian probabilities

A work in progress

Why Reinvent DD&R ?

- DD costs too much and takes too long

- An imperfect criterion is used for regulatory approval decisions:

  - 2 Phase III trials @ $p < 0.05$ via frequentist null-hypothesis “significance” testing,

    or

  - 1- Phase III trial @ $p <<< 0.05$ (eg < 0.0025)

Evolution of Reporting *P* Values in the Biomedical Literature, 1990-2015

David Chavalarias, PhD; Joshua David Wallach, BA; Alvin Ho Ting Li, BHSc; John P. A. Ioannidis, MD, DSc

JAMA. 2016;315(11):1141-1148.

- **4,572,043 P values in 1,608,736 MEDLINE abstracts (~ 3/abstract)**
- **3,438,299 P values in 385,393 PMC full-text articles (~ 9/article)**

CONCLUSIONS AND RELEVANCE In this analysis of *P* values reported in MEDLINE abstracts and in PMC articles from 1990-2015, more MEDLINE abstracts and articles reported *P* values over time, almost all abstracts and articles with *P* values reported statistically significant results, and, in a subgroup analysis, few articles included confidence intervals, Bayes factors, or effect sizes. Rather than reporting isolated *P* values, articles should include effect sizes and uncertainty metrics.

The ASA's statement on p-values: context, process and purpose

American Statistician 2016;70:129-33.

- "**Science News (2010)**: "*It's* ***science's dirtiest secret***: The *'scientific method' of* ***testing hypotheses*** *by* ***statistical analysis stands*** *on a* ***flimsy foundation***."

- **Science (2014):** "*statistical techniques for* ***testing hypotheses****…have* ***more flaws than Facebook's privacy policies***."

- **FALLACIES: P-values**
  - ***Do not measure the probability that the hypothesis is true***
  - ***Do not provide a good measure of evidence of a hypothesis***
  - ***Do not measure the size or importance of an effect***

1962
Substantial evidence of effectiveness

"*substantial evidence*" means evidence consisting of *adequate and well-controlled investigationS*, including clinical investigations, by experts qualified by scientific training and experience to *evaluate* the *effectiveness* of the drug involved, on the basis of which it could fairly and responsibly be *concluded* by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from *one adequate and well-controlled clinical investigation* and *confirmatory evidence* (obtained prior to or after such investigation) are *sufficient to establish effectiveness*

No statutory requirement to rely solely on *Phase III data,*

Nor to *reject the null-hypothesis @ p < 0.05*

Flaws of the traditional p-value criterion for substantial evidence

- **Relies on *low frequentist probability*, (p-value<0.05), based *solely on 1-2 phase III clinical trials*:**
  - **Does not provide the probability of effectiveness**
  - **Ignores pre-phase III evidence of *effectiveness*** from **randomized, blinded trials** trials, including ***dose-*** ***and exposure-response trials***
  - **Leads to the "*p-value fallacies*"**
  - **Power-reducing penalties for multiple analyses**
  - **Risks failure to confirm effective drugs**

Disruptive alternative criterion for drug approval

- Base drug approval on a ***high probability of effectiveness*** **(> 90% ?)** utilizing evidence of **all reliable sources of effectiveness data**
  - **Requires *Bayesian statistics***

Bayesian Decision Analytic Approach

Historical Data

Publications

Expert Knowledge

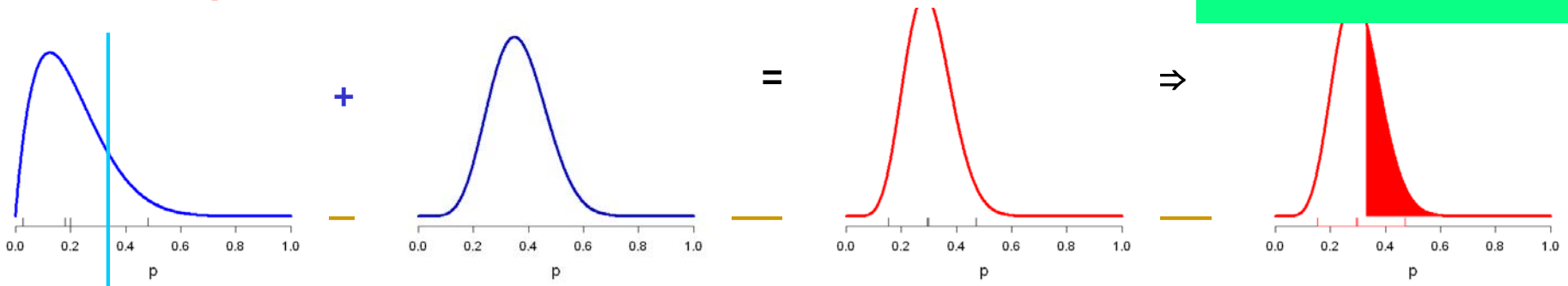
***Bayes Theorem*: Posterior ∝ Likelihood × Prior**

"Bayes" (probability calculus)

+

Evidence from pre-Phase III trials **+** ***Phase III trial Data*** **=** ***Probability of Effectiveness*** ⇒ ***Regulatory Decision Calculus***

'Prior' ***''Likelihood'*** ***'Posterior'***



Reconciling p-value and Bayesian approaches*

- "**Bayes Factor**" (BF) **calculation** permits recasting frequentist p-values test of ***ineffectiveness*** into a **probability that the drug** is ***effective***
  - Takes into account
    - the pre-confirmatory trial probability of ***effectiveness*** and confirmatory trial p-values

- $\mathbf{BF = [-e \cdot p_{value} \cdot \ln(p_{value})]}$
- $\mathbf{Prob_{Eff} = [1 + PriorOdds_{H_o:H_1} \cdot BF]^{-1}}$

- Steve Ruberg, Lilly, based on Sellke et al (2001) Calibration
- of p Values for Testing Precise Null Hypotheses. Am Stat, 2001.

P-value vs Bayes applied to Two Trial Paradigm

- **Example 1**: pre-phase III effectiveness probability = 0.5
  - One phase II trial @ p = 0.05, yields **71% Bayesian probability** of **effectiveness**
  - two phase III trials @ p = 0.05, yield ***86% prob*** of ***effectiveness***
    - ***APPROVED per traditional approach***

- **Example 2**: pre-phase III effectiveness probability = 0.8
  - two phase III trials @ p = 0.05, yield ***96 % probability*** of ***effectiveness***
    - ***APPROVED per traditional approach***

- **Example 3**: pre-phase III effectiveness probability = 0.8
  - two phase III trials @ p = 0.01 and p = 0.08, yield ***98% probability of effectiveness***
    - ***NOT APPROVED per traditional approach, despite 98% effectiveness !!***

*** due to *Steve Ruberg*, Lilly, based on Sellke et al (2001)**

P-value vs Bayes applied to Single Clinical Trial Paradigm

- **Traditional p-value approach (prior = 50%):**
  - single trial + "confirmatory evidence"
- @ **$p < 0.0025 \rightarrow 96\%\ Prob_{effectiveness}$**

- **Bayesian framework:**
  - if "prior" probability of effectiveness is 80%
- ***single trial $p < 0.02$*** **$\rightarrow 95\%\ Prob_{effectiveness}$!!!**

* **Steve Ruberg, "Strength of Evidence for clinical Trials and Biomarkera in Tailored Therapeutics", PaSiPHIC Conference, 27 Feb, 2014**

CDRH Experience

"valid scientific evidence"

reasonable assurance that the device is safe and effective

Guidance
for Industry and FDA Staff

Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials

Document issued on: February 5, 2010

The draft of this document was issued on 5/23/2006

For questions regarding this document, contact Dr. Greg Campbell (CDRH) at 301-796-5750 or greg.campbell@fda.hhs.gov or the Office of Communication, Outreach and Development, (CBER) at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Biostatistics
Office of Surveillance and Biometrics

Center for Biologics Evaluation and Research

DIA Bayesian Scientific Working Group (BSWG)

Special Workshop

Substantial Evidence in 21st Century Regulatory Science

Borrowing Strength from Accumulating Data

April 21, 2016

University of California Washington Center, DC

21st Century Cures Act

UCSF
University of California
San Francisco

Points to Consider

- **D*ose-response & exposure-response* RCT's** yield ***causal evidence*** **of effectiveness**

- These data can inform the ***prior*** **likelihood of *effectiveness***

- ***Prior effectiveness probabilities*** may be employed in a combined ***Bayesian statistical* framework** to improve efficiency & informativeness of demonstrating ***substantial evidence of effectiveness***

Summary

Pharmacometrics @ 45

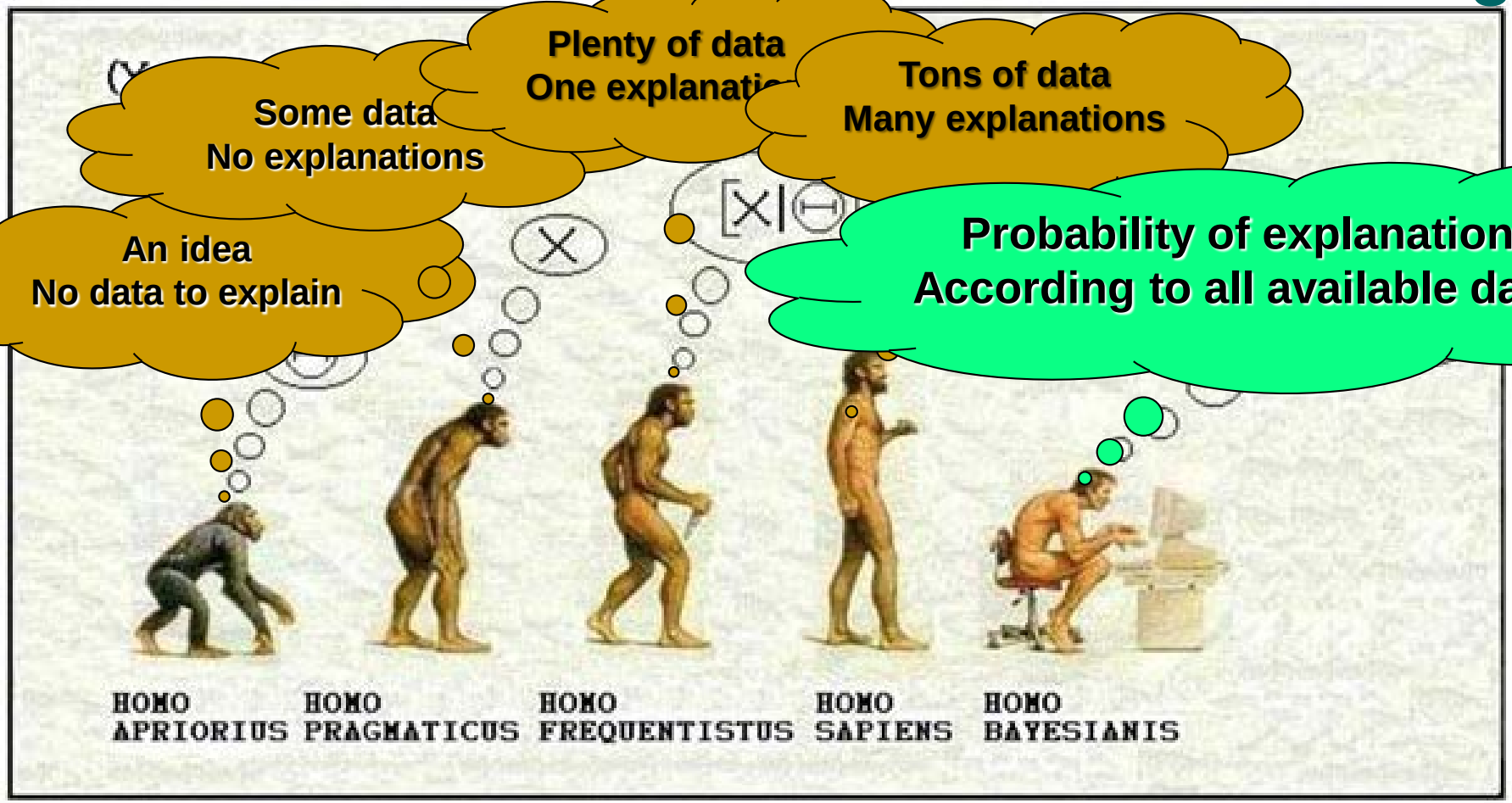
1972 – 2017 +

- PM has ***transformed*** Drug Development & Regulation (DD&R)
  - From ***rank empiricism*** to a ***quantitative, model-based framework***
  - Leading to ***more efficient/informed DD&R, drug labels & market approvals***

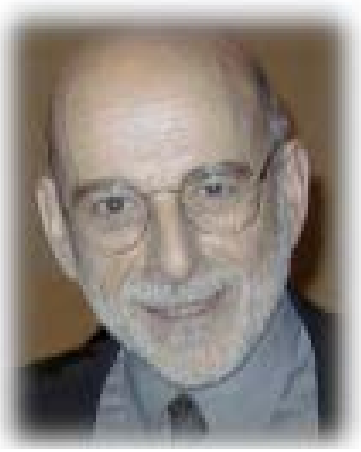
- ***NEXT:*** PM can play a crucial role in the ***reinvention*** of DD&R by
  - ~~***frequentist (p-value) tradition***~~ + ***decision-analytic framework,*** informed by ***Bayesian probabilities***

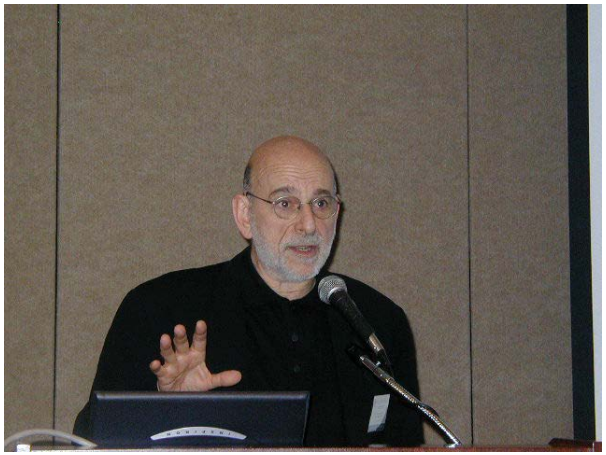
Eng's Law:

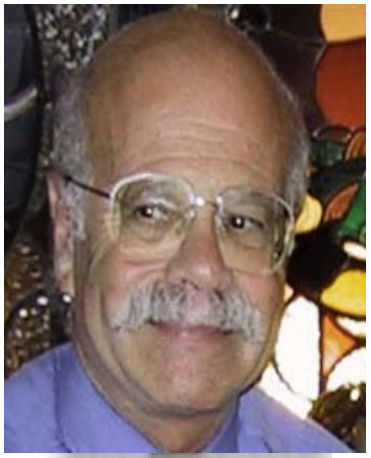
The easier it is to do, the harder it is to change.



Mike West, Department of Statistics, Duke University
http://www.brera.mi.astro.it/~andreon/inference/Inference.html







Lewis Sheiner

Chemistry
Internal medicine
clinical Pharmacology

Stuart Beal

mathematics, logic
fine arts
biostatistics

END