Impact of Non-Adherence on Drug Development and Therapeutics

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Disclosures

- Between 2012 and 2015 I was an employee of the Bill and Melinda Gates Foundation
- For the past 8 years I have been on the Board of Directors of DURECT Corporation, a specialty pharmaceutical company focused on the development of drug delivery platform technologies
- I have worked with AARDEX and consulted for Proteus Digital Health, both involved in developing and marketing adherence technologies
- I agree to disclose approved and non-approved indications for medications in this presentation
- I agree to use generic names of medications in this presentation

Acknowledgements

- **Contributors to ideas presented today:**
  - John Urquhart
  - Bernard Vrijens
  - Lars Osterberg
  - Carl Peck
  - Lewis Sheiner
  - Bruce Thomas

“Adherence”

Definition(s) and Taxonomy

Definition of Adherence

The extent to which a person's behavior ... coincides with medical or health advice.

-- Haynes, 1979

Definition of Non-Adherence

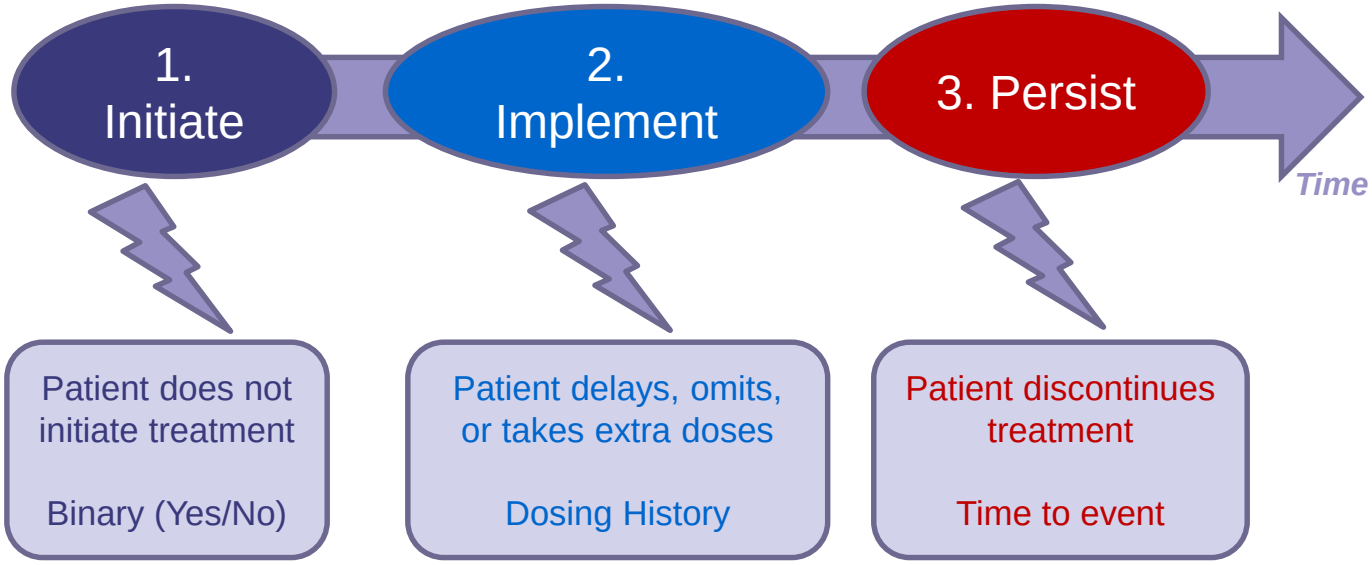
Non-Adherence is present when the actual treatment a subject receives is different from the nominal (intended) assignment

But…

- Adherence is not a dichotomous variable (“adherent” vs “non-adherent”)
- No single metric (e.g., percent of prescribed doses taken) can adequately describe actual patterns of adherence
- TIME is an important component of describing adherence
- We need to have a common taxonomy for describing adherence

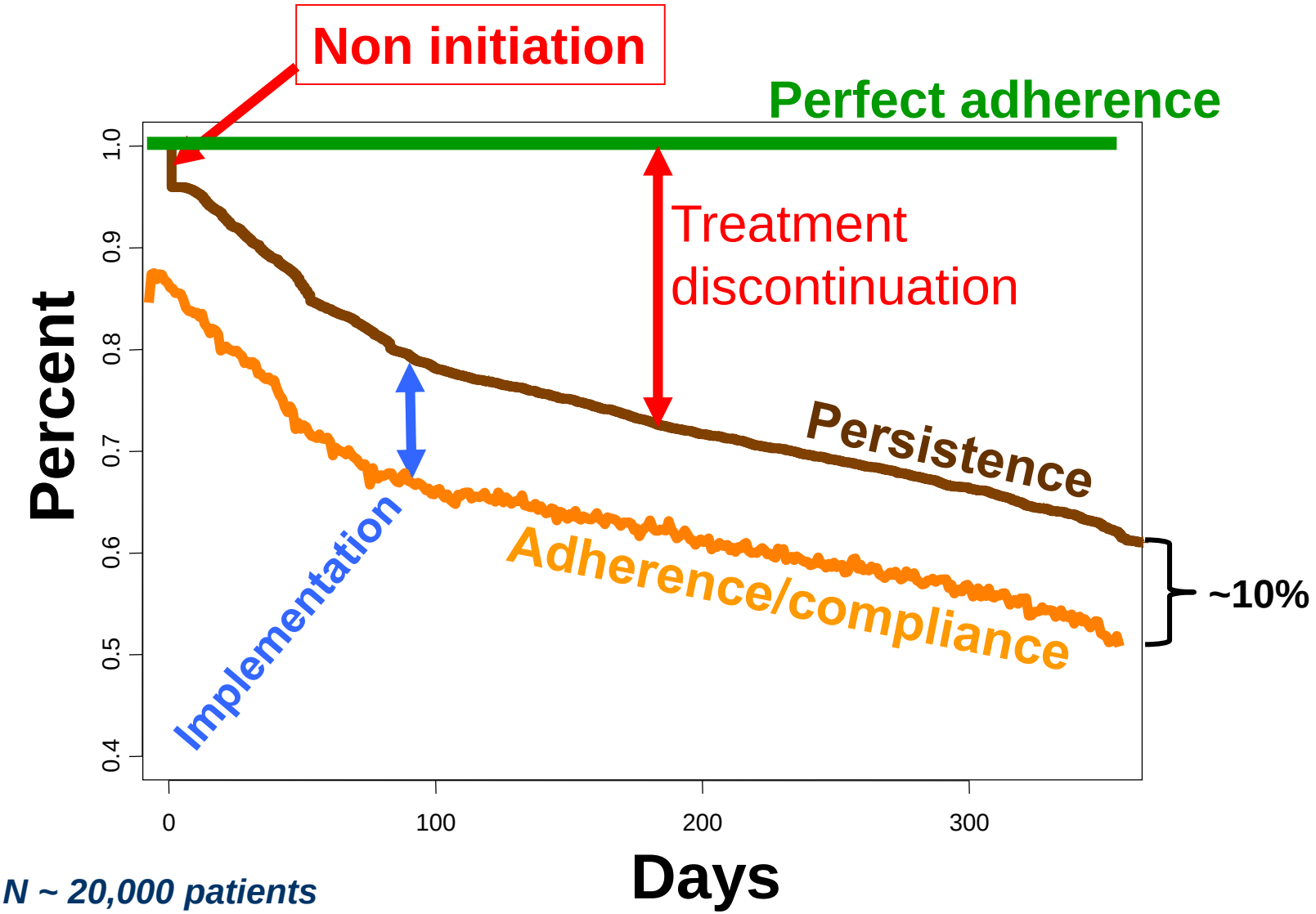
Medication Adherence

‘The process by which patients take their medications as prescribed’



Vrijens et al., BJCP, 2012.

Let's look again at the components of adherence



PKC: N ~ 20,000 patients

Source: Urquhart & Vrijens*; Pharmacovigilance: Second Edition Edited by R.D. Mann and E.B Andrews* © 2007 John Wiley & Sons, Ltd

Variable Adherence in Clinical Trials

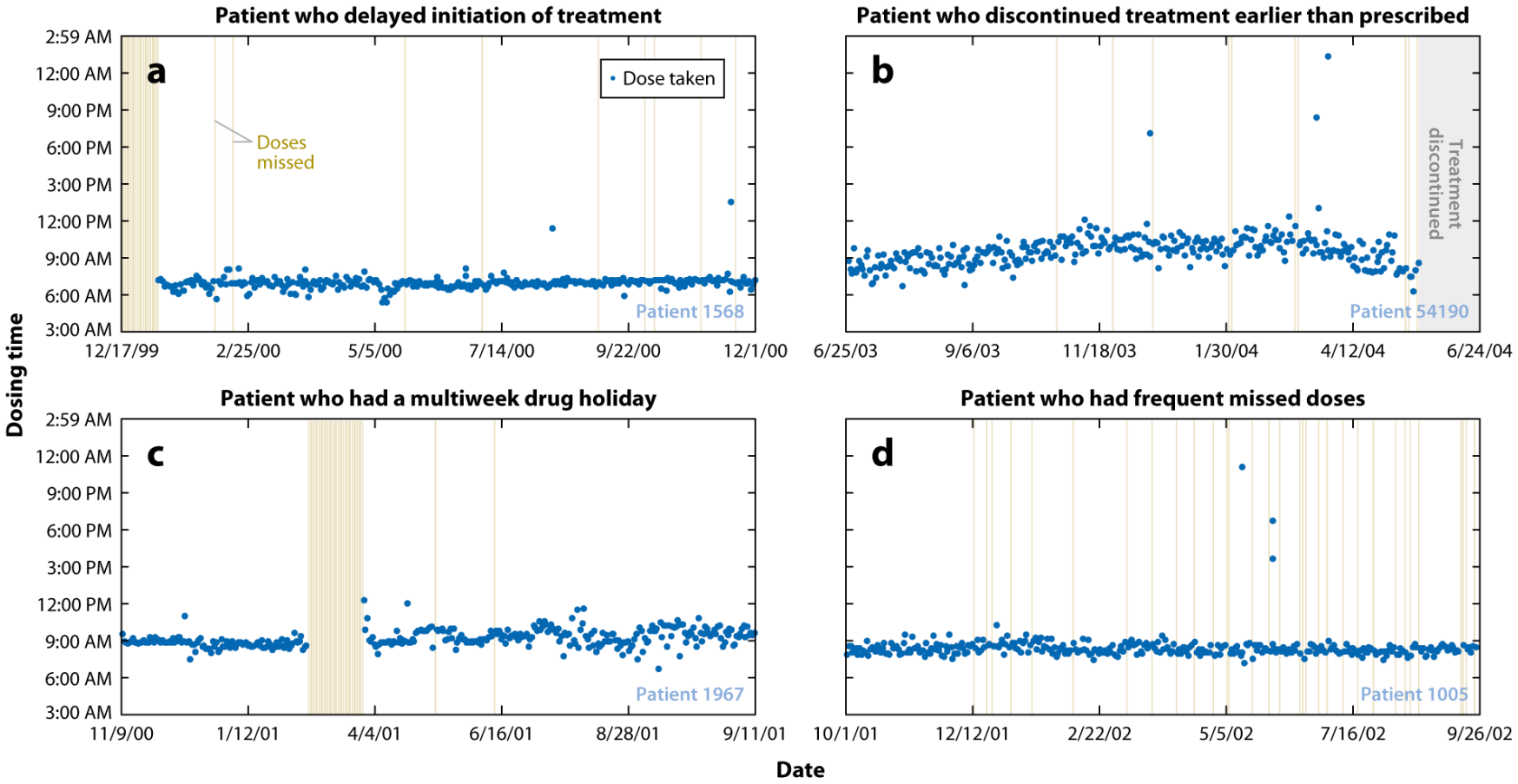
Is it a problem?

YES!

Source of information: The AARDEX Group

(see http://www.iadherence.org/)

“Execution” examples (from iAdherence database)



Blaschke TF, et al. 2012.
Annu. Rev. Pharmacol. Toxicol. 52:275–301

During the periods depicted above, each patient took 90–91% of prescribed doses, with the indicated wide variations in the temporal patterns of dose omissions.

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Group Selection

View tutorial

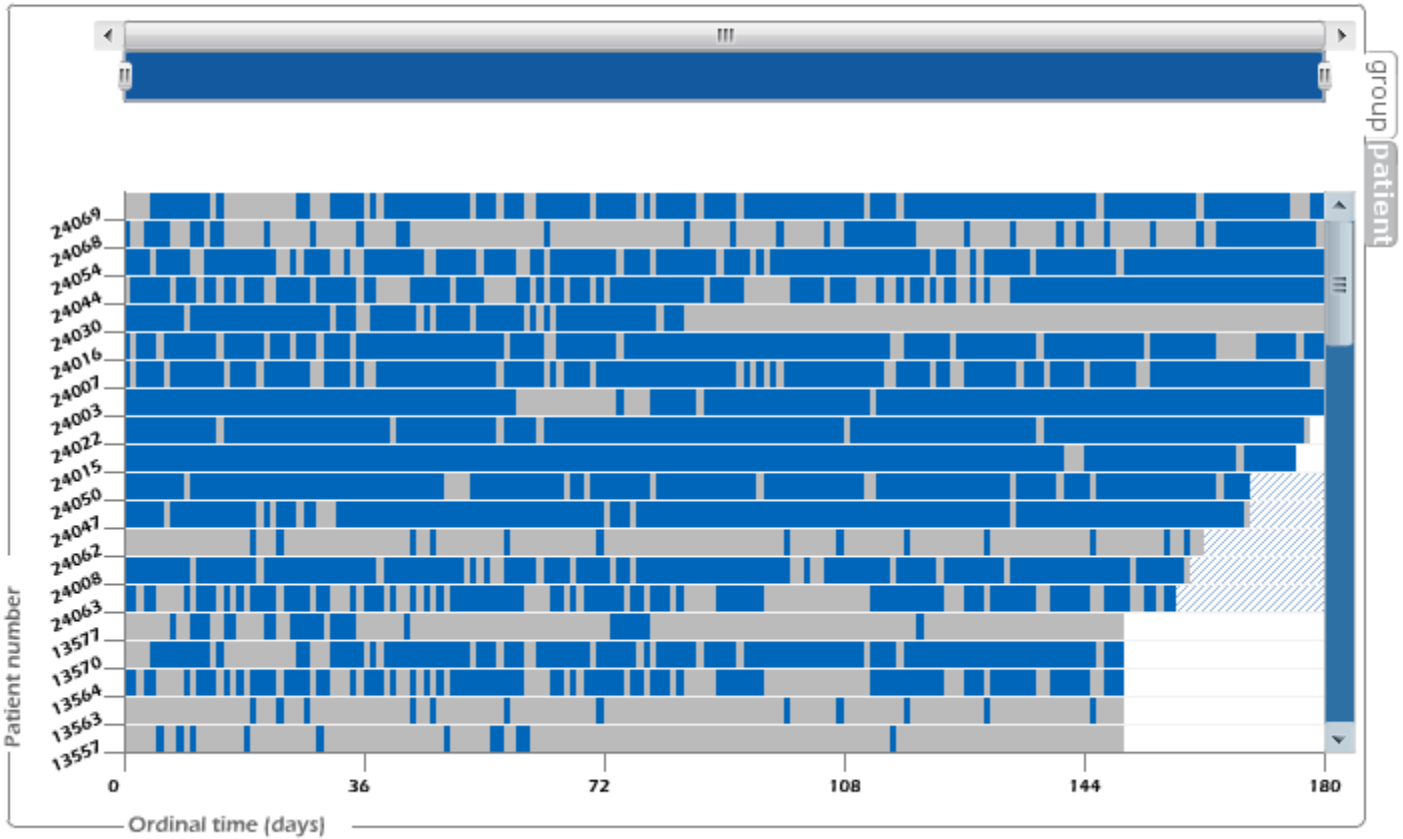
- ANGINA
- ANTICOAGULANTS
- BREAST CANCER
- CHRONIC VENOUS INSUFFICIENCY
- COLORECTAL POLYP
- COLOTIS ULCEROSA
- CROHNS DISEASE
- CYTOTOXIC DRUGS
- DEMENTIA
- DEPRESSION
- DIABETES
  - QD
  - BID
  - TID
- HEART FAILURE
- HIV
- HYPERCHOLESTEROLAEMIA
- HYPERTENSION
- LIPID METABOLISM DISEASE
- LIVER CIRRHOSIS
- MALARIA
- MIGRAINE
- OSTEOPOROSIS
- OTITIS
- PARKINSONISM
- PEPTIC DISEASE
- PHOSPHATE BINDERS
- REVERSIBLE OBSTRUCTIVE

80 patients for DIABETES in BID regimen

DIABETES (BID) 80 patients — 80 of 17625 patients (0%)

13407	13416	13504	13511	13522	13538	13547	13556
13408	13417	13507	13515	13528	13540	13550	13557
13414	13418	13508	13516	13534	13541	13552	13558
13415	13503	13509	13520	13535	13544	13555	13561

1 / 3 13407→13561 | 2 / 3 13563→24053 | 3 / 3 24054→68511

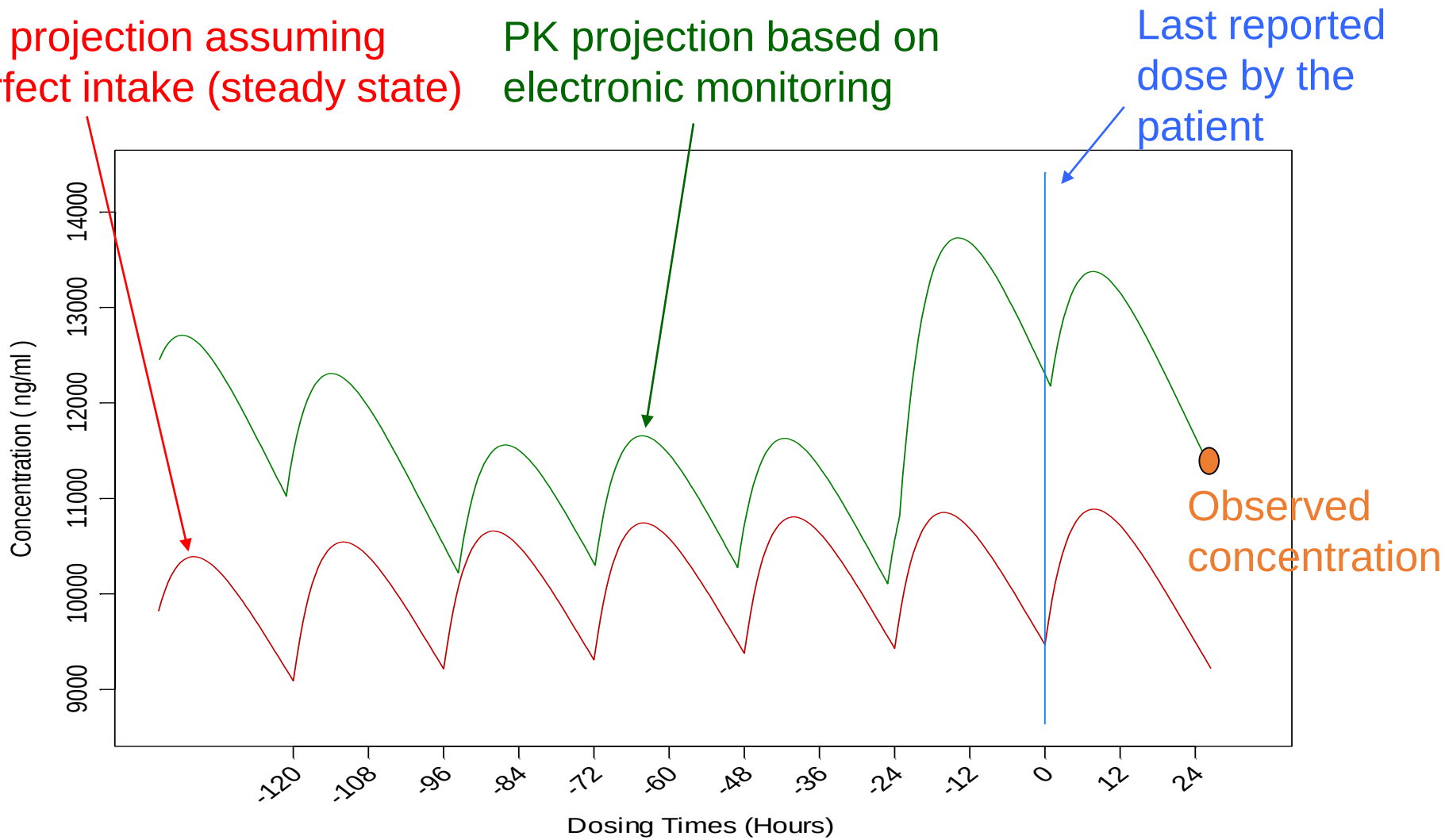


Successful Projection of the Time Course of Drug Concentration in Plasma During a 1-Year Period From Electronically Compiled Dosing-Time Data Used as Input to Individually Parameterized Pharmacokinetic Models

Bernard Vrijens, Eric Tousset, Richard Rode, Richard Bertz, Steve Mayer, and John Urquhart

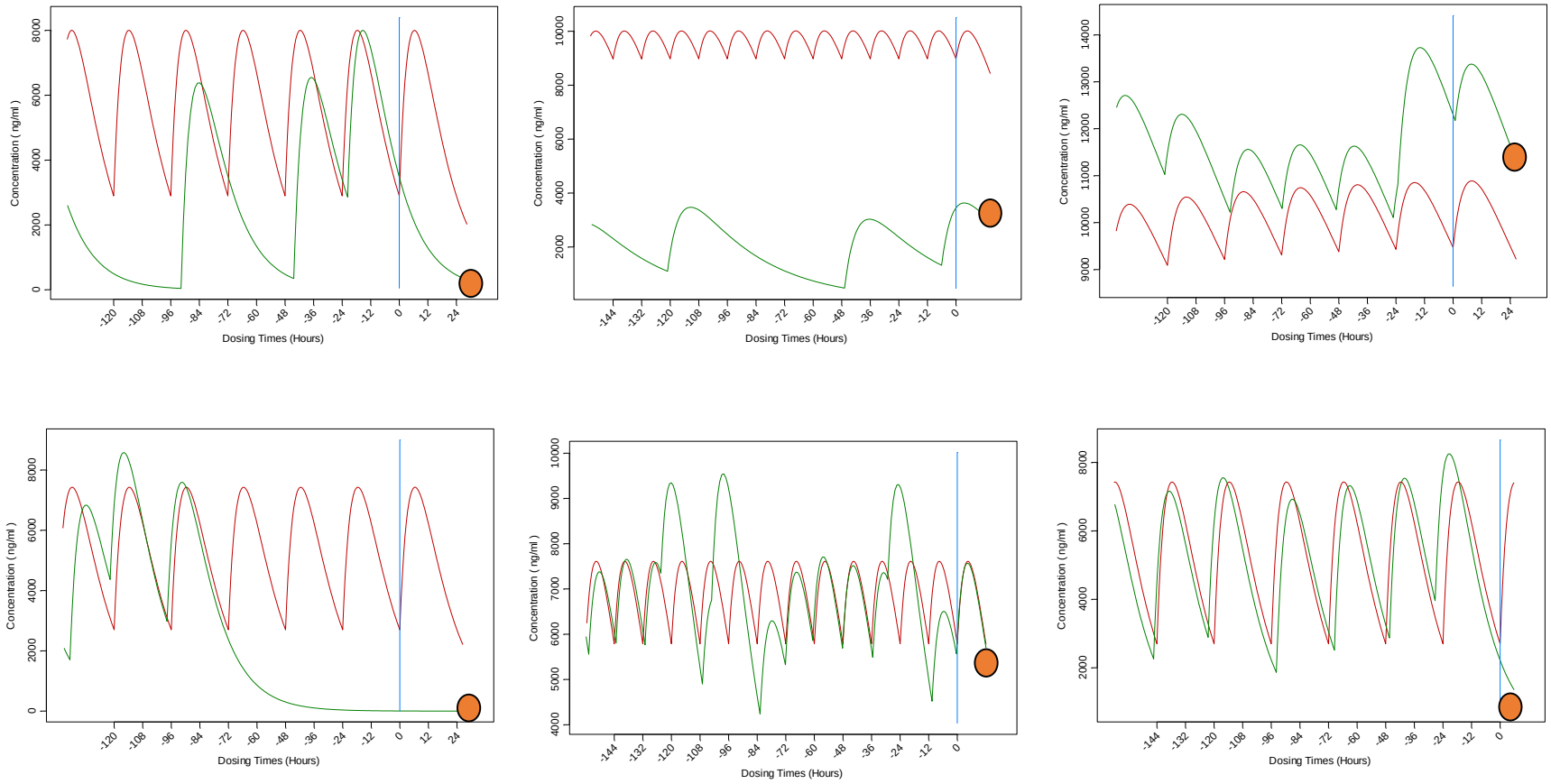
Journal of Clinical Pharmacology, 2005;45:461-467

EM enables long term PK projections



Vrijens & al., Journal of Clinical Pharmacology, 2005

55% of residual PK variability is explained by EM



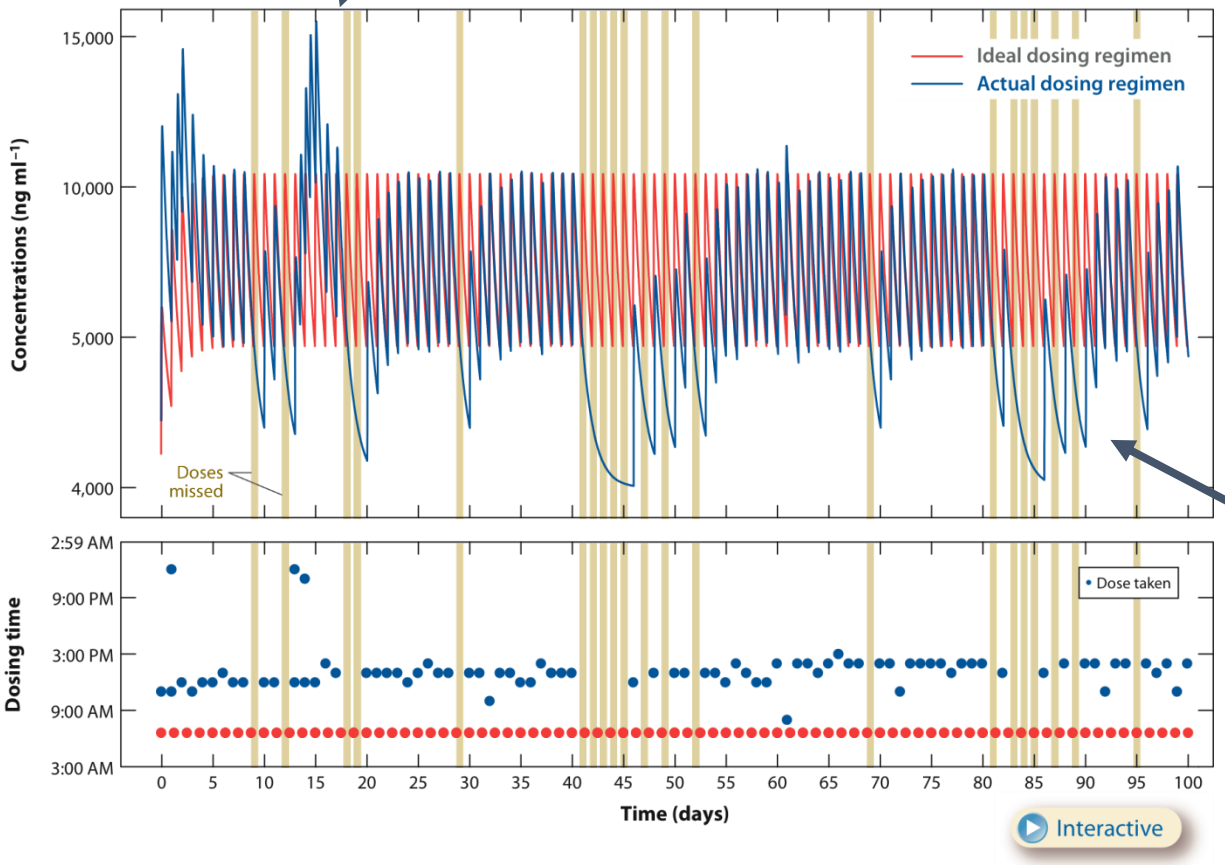
Vrijens et al. – IAS Paris 2003

What is the value of (detailed) dosing histories in clinical trials?

- When combined with pharmacodynamic measures (clinical or biomarkers) provides insights as to causes of failure and to appropriate dosing regimens (dose and dosing intervals)
- Especially useful in proof-of-concept studies when go- no go and Phase 2b or Phase 3 regimens are decided

Patients Vary Dosing Intervals and Keep the Dose Constant

Occasional toxicity



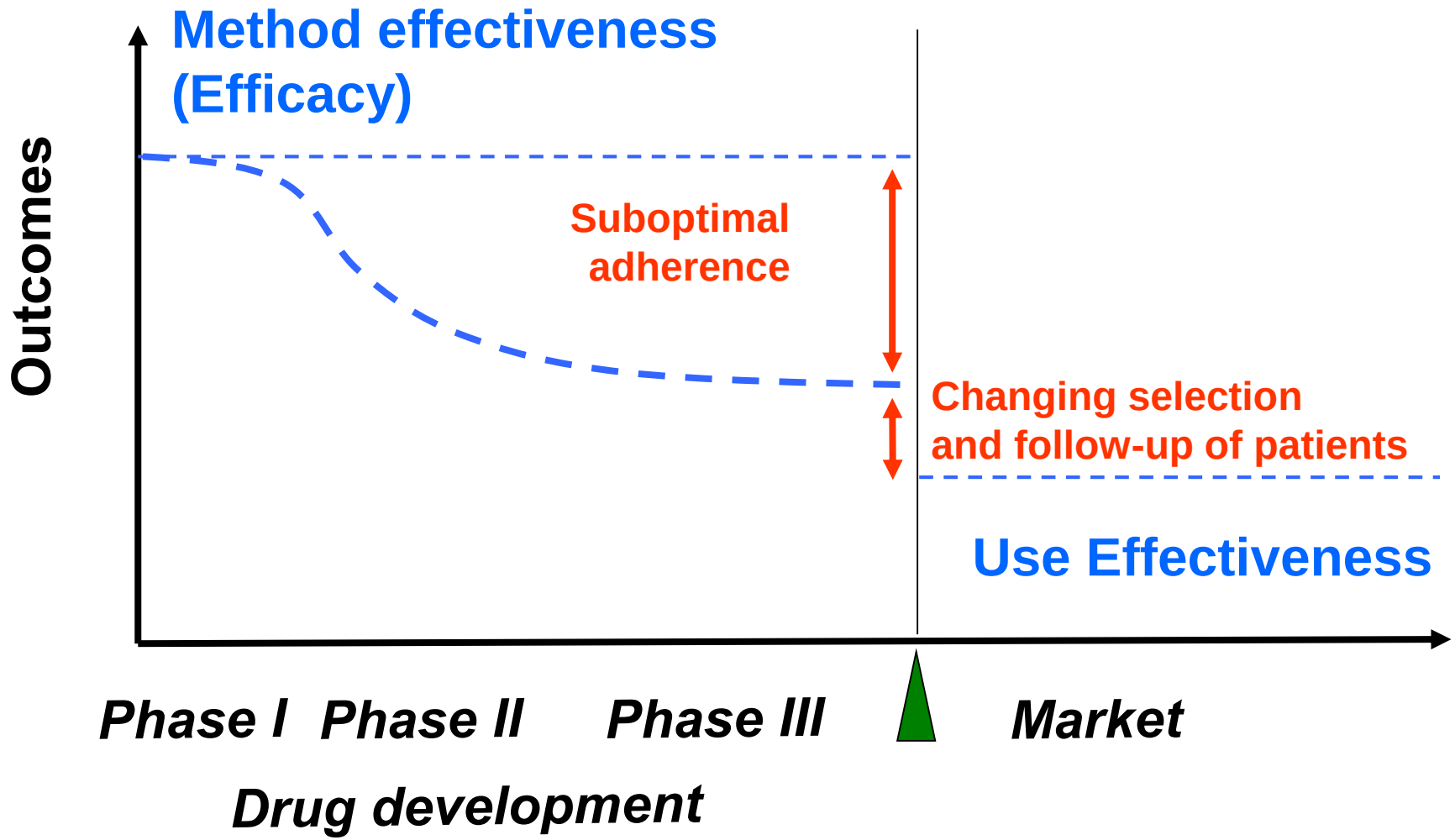
Periodic loss of effectiveness & emergence of drug resistance (HIV)

Blaschke, Osterberg, Vrijens, Urquhart. Ann Rev of Pharmacol and Toxicol 2012. 52:275-301.

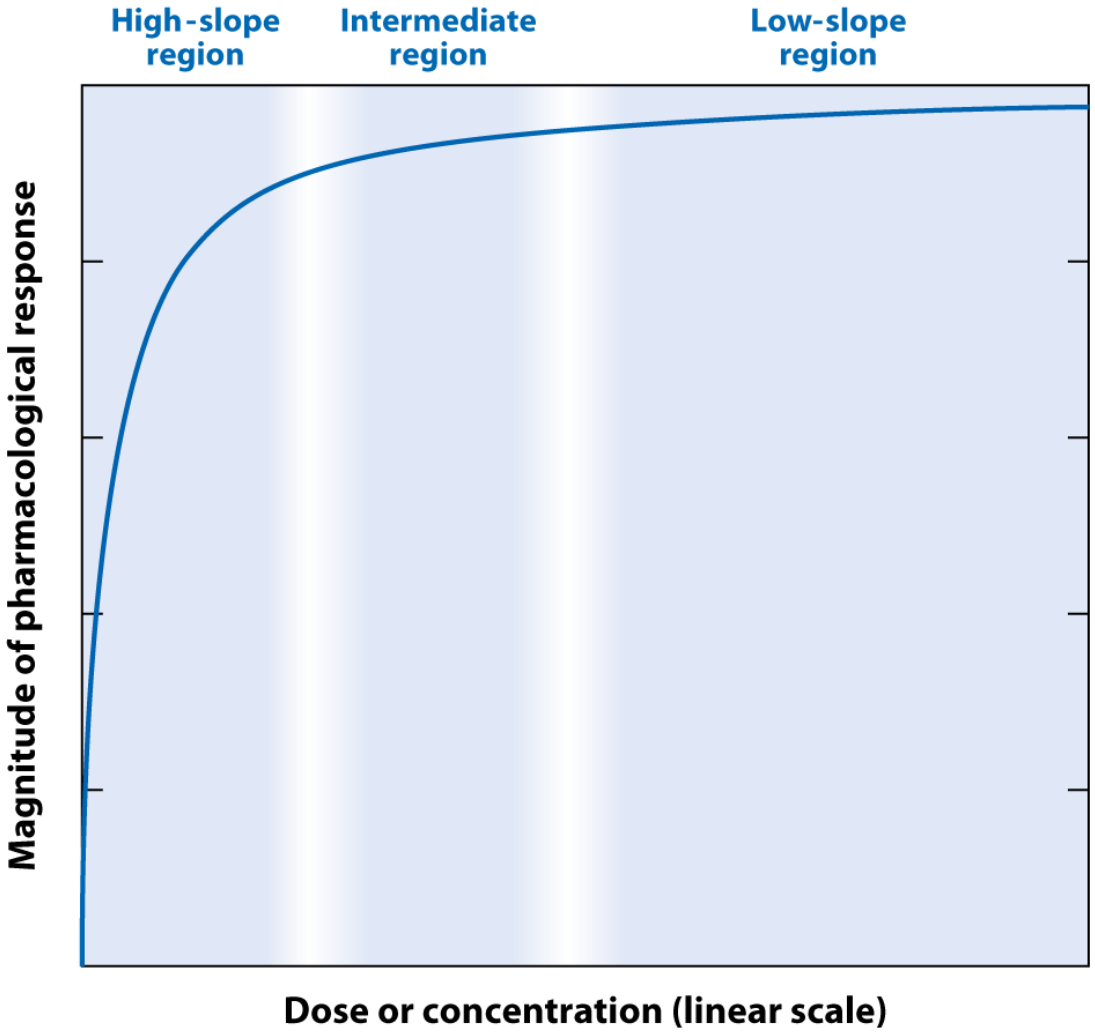
Problems with ITT Analysis when there is no adherence information

- ITT underestimates true efficacy of the regimen
- ITT decreases study power, risking the possibility of a Type II error during development
- Therefore, consider in addition to ITT an as-treated analysis and/or instrumental variables
  - (see Sheiner LB, Rubin DB Intention-to-treat analysis and the goals of clinical trials Clin Pharmacol Ther. 1995 Jan;57(1):6-15.

Drug effectiveness over different phases of drug development and in the market place



Source: Ann Rev Pharm Tox, 2012



Blaschke TF, et al. 2012.
Annu. Rev. Pharmacol. Toxicol. 52:275–301

Type II errors

A **type II error** occurs when the wrong decision is made because a statistical test (e.g., ITT analysis) accepts a false null hypothesis. A type II error may be compared with a so-called *false negative* in other test situations.

Possible recent examples of Type II Errors during drug development

- Fem-PrEP study
- Hepatitis C therapy

BIOWORLD®
The Daily Biopharmaceutical News Source

HCV Relapses Short Circuit Gilead's ELECTRON Study

By Catherine Shaffer
Staff Writer

Disappointing results from Gilead Sciences Inc.'s Phase II ELECTRON study of nucleotide analogue polymerase inhibitor GS-7977 showed that six out of eight patients with a prior null response to an interferon regimen relapsed within four weeks of completing a course of GS-7977 plus ribavirin.

With analysts still picking apart the big biotech's recent acquisition of GS-7977 through its $11 billion buyout of Pharmasset Inc., the news sent Gilead stock's (NASDAQ: GILD) plummeting $7.81, or 14 percent, to close Friday at $46.82. (See *BioWorld Today*, Nov. 22, 2011.)

FEM-PrEP – Update, June 2011

Components

- Randomized clinical trial
- Socio-behavioral and community (SBC) activities
- Seroconverter sub-study

Variable Adherence in Clinical Medicine

Variable Adherence:

A neglected source of variation in response

Chronobiology[a]

Suggestions for Integrating It into Drug Development

JOHN G. HARTER AND CARL C. PECK

Division of Oncology
Food and Drug Administration
5600 Fishers Lane, Room 9B-45
Rockville, Maryland 20857

ANNALS NEW YORK ACADEMY OF SCIENCES[1991]

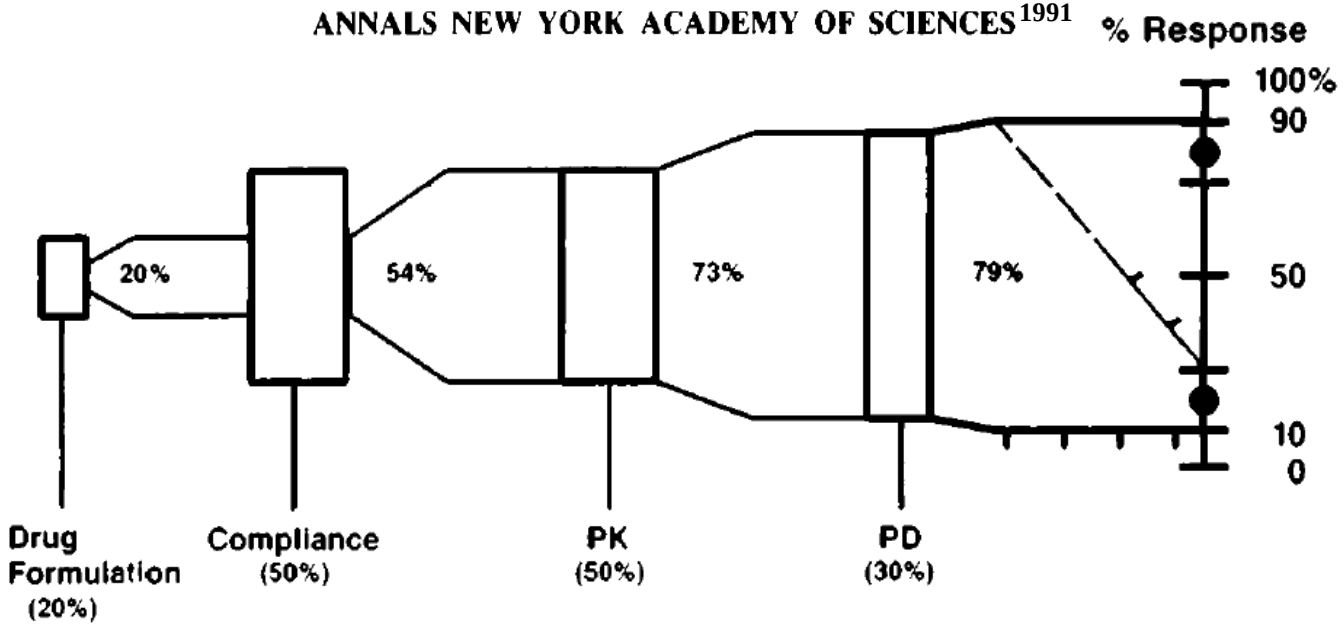
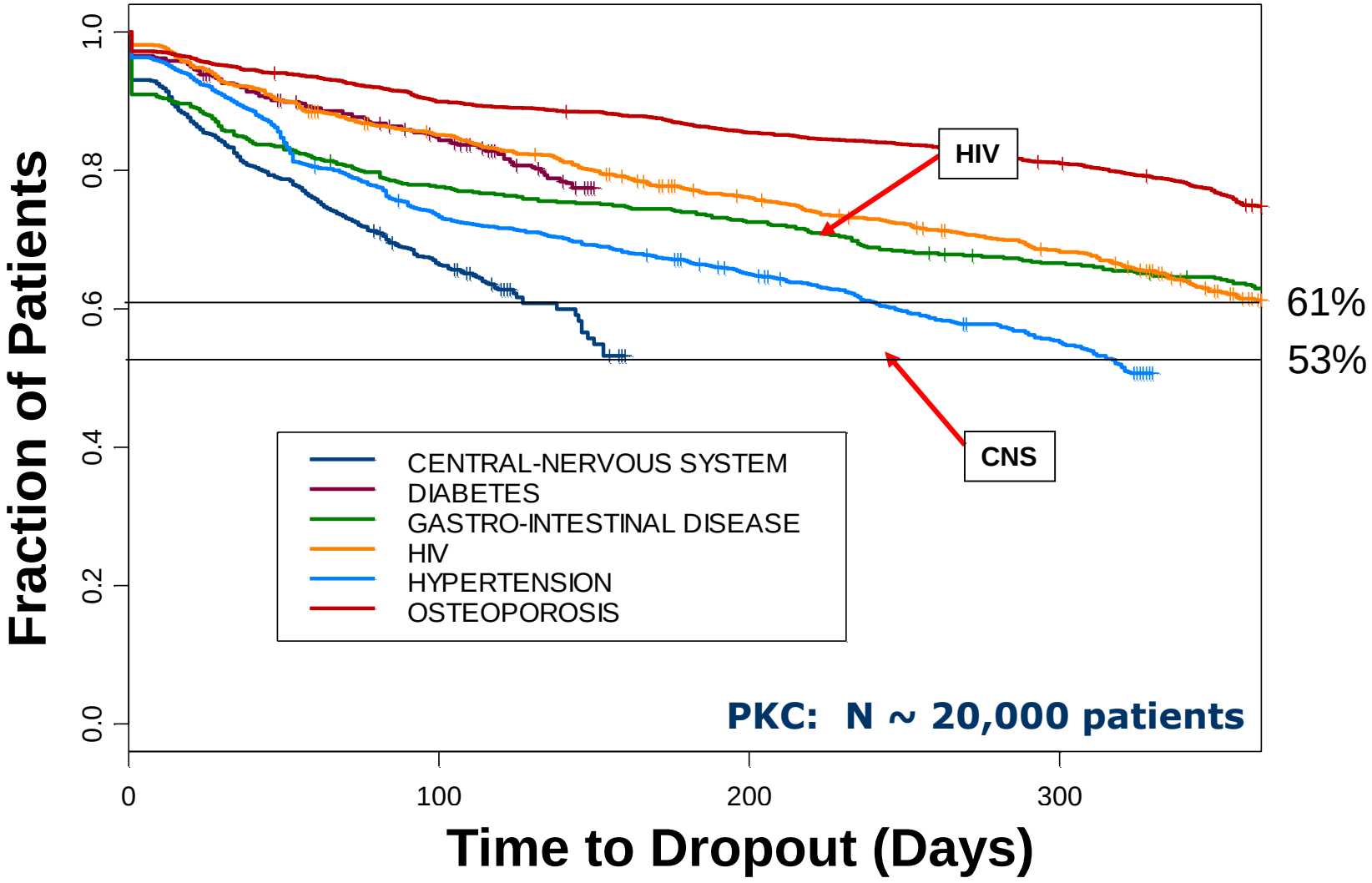


FIGURE 3. Sources of variability in drug response in the individual patient.

Persistence: time to treatment discontinuation

Overall, ~40% of patients with HIV will have discontinued the prescribed drug after 12 months



Adapted from: Vrijens et al., Clinical Pharmacology and Therapeutics 2005

Adherence Rates

- Acute Conditions- adherence much better and readily achievable by giving clear instructions[1]

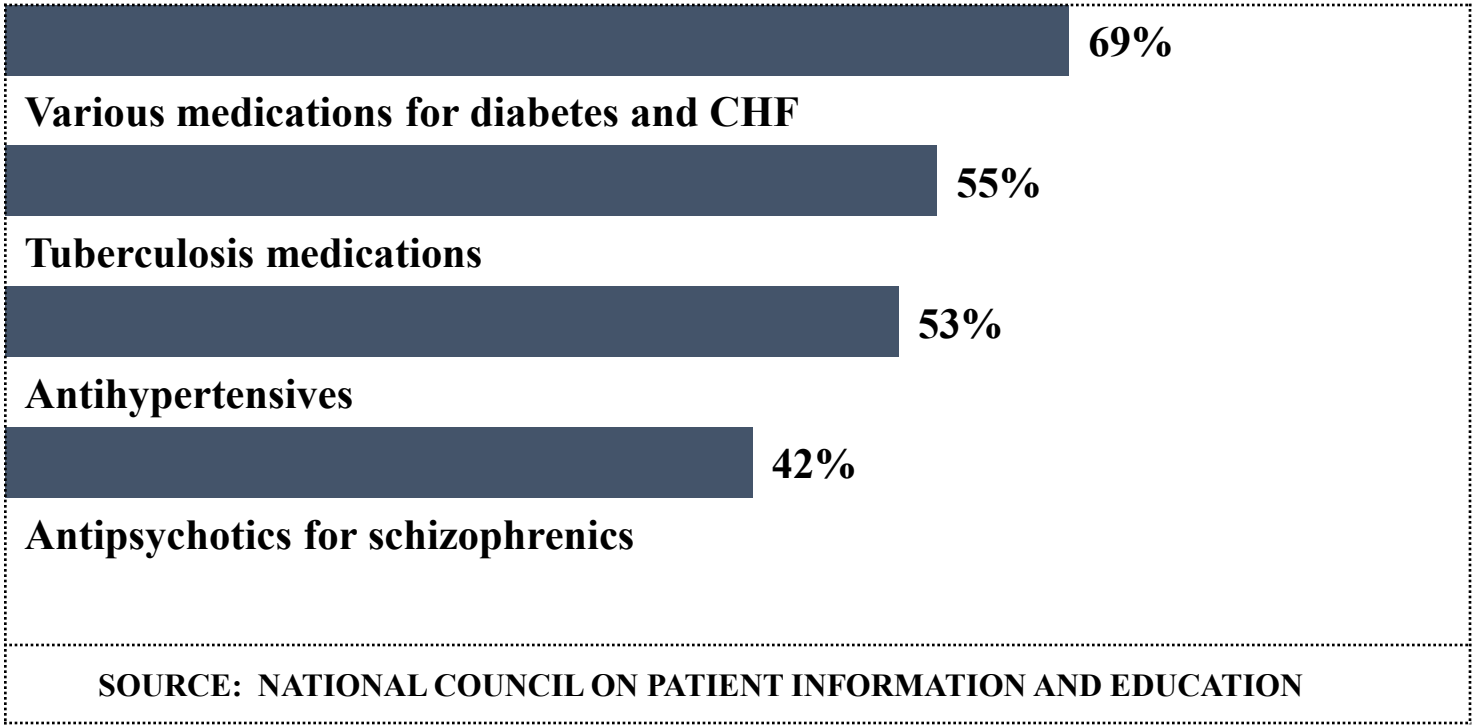
- Chronic Conditions
  - ~40-60% of patients abandon medications by 1 year[2,3]

  - Typical adherence rates: 50-60% [1,5]

1. **JAMA 2002; 288: 2880-3**
2. **JAMA 2002; 288:455-61**
3. **NEJM 1995; 332: 1125-1131**
4. **J Hypertens 1997; 10: 697-704**
5. **Sackett DL. Compliance in Health Care c. 1979**

Slide courtesy of Lars Osterberg

Medication Adherence Rates for Selected Illnesses



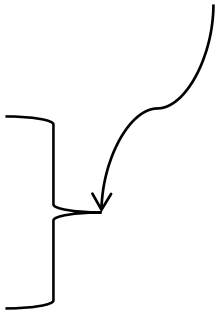
Severity of Disease does not correlate with better adherence!

Slide courtesy of Lars Osterberg

Why Patients Don't Take Their Medications

- Unintentional
  - Forget
  - Ineffective physician-patient communication (eg. symptoms disappeared,…)
  - Couldn't afford/obtain them
- Intentional
  - Wanted to save money
  - Didn't need them anymore
  - Perceived higher risk/benefit- eg. side effects
  - Other- "emotional factors": beliefs, mistrust, social, ...

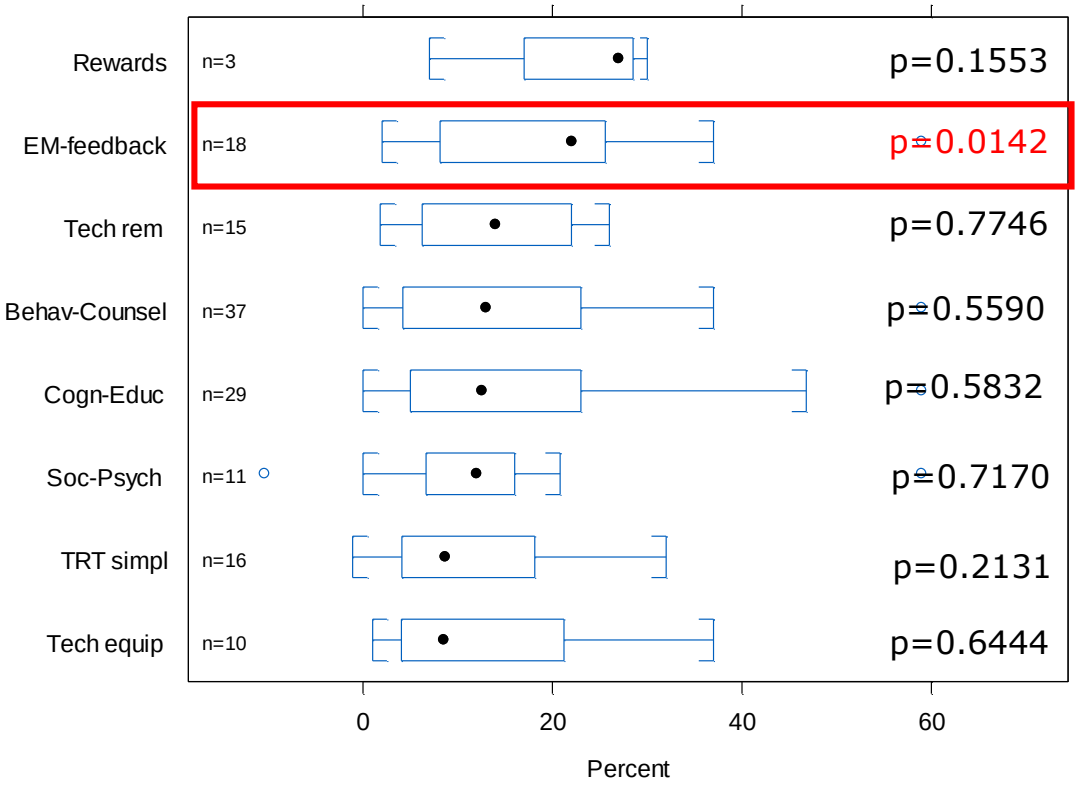
Ineffective physician-patient communication?



IDENTIFICATION AND ASSESSMENT OF ADHERENCE-ENHANCING INTERVENTIONS: SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

J.Demonceau[1], T. Ruppar[2,3], P. Kristanto[1], D. A. Hughes[4], E. Fargher[4], P. Kardas[5], S. De Geest[2,6], F. Dobbels[2], P. Lewek[5], J. Urquhart[1,7], B. Vrijens[1,8], for the ABC project team

67 RCT identified with electronic compilation of drug dosing histories (1979-2010) N = 9057 patients



Effect sizes in EM-feedback studies **20.90%** [9.85; 31.96] vs non-EM-feedback studies **9.67%** [6.65; 12.69]

One solution– “Forgiving” drugs or drug formulations

“Forgiveness” (1)

Forgiveness can be defined as how long drug action continues at therapeutically effective levels after a last-taken dose

or

The post-dose duration of effective action minus its recommended dosing interval.

“Forgiveness” (2)

- Forgiveness is dose-dependent, also exemplified by the high- vs low-dose OC’s
  - One approach to extend forgiveness is dose-escalation, but that approach is often limited by dose-dependent toxicity.
  - **The impact of early discontinuation, however, is not offset by a few days of forgiveness**

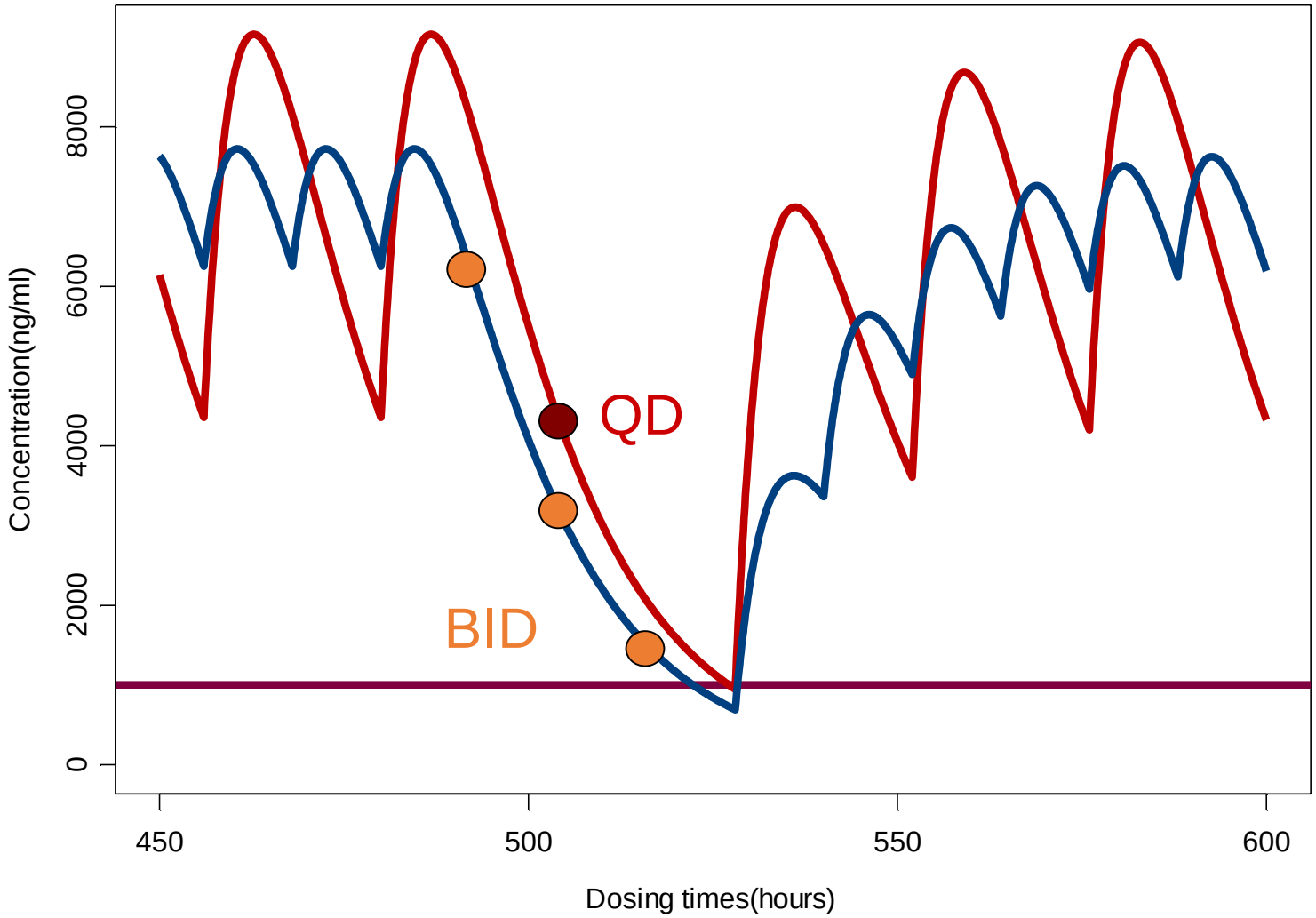
Example: Lack of forgiveness of protease inhibitors

J Pharmacokinet Pharmacodyn
DOI 10.1007/s10928-007-9058-0

Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based on integrated analysis of dosing history data and pharmacokinetics

Laetitia Comté · Bernard Vrijens · Eric Tousset · Paul Gérard · John Urquhart

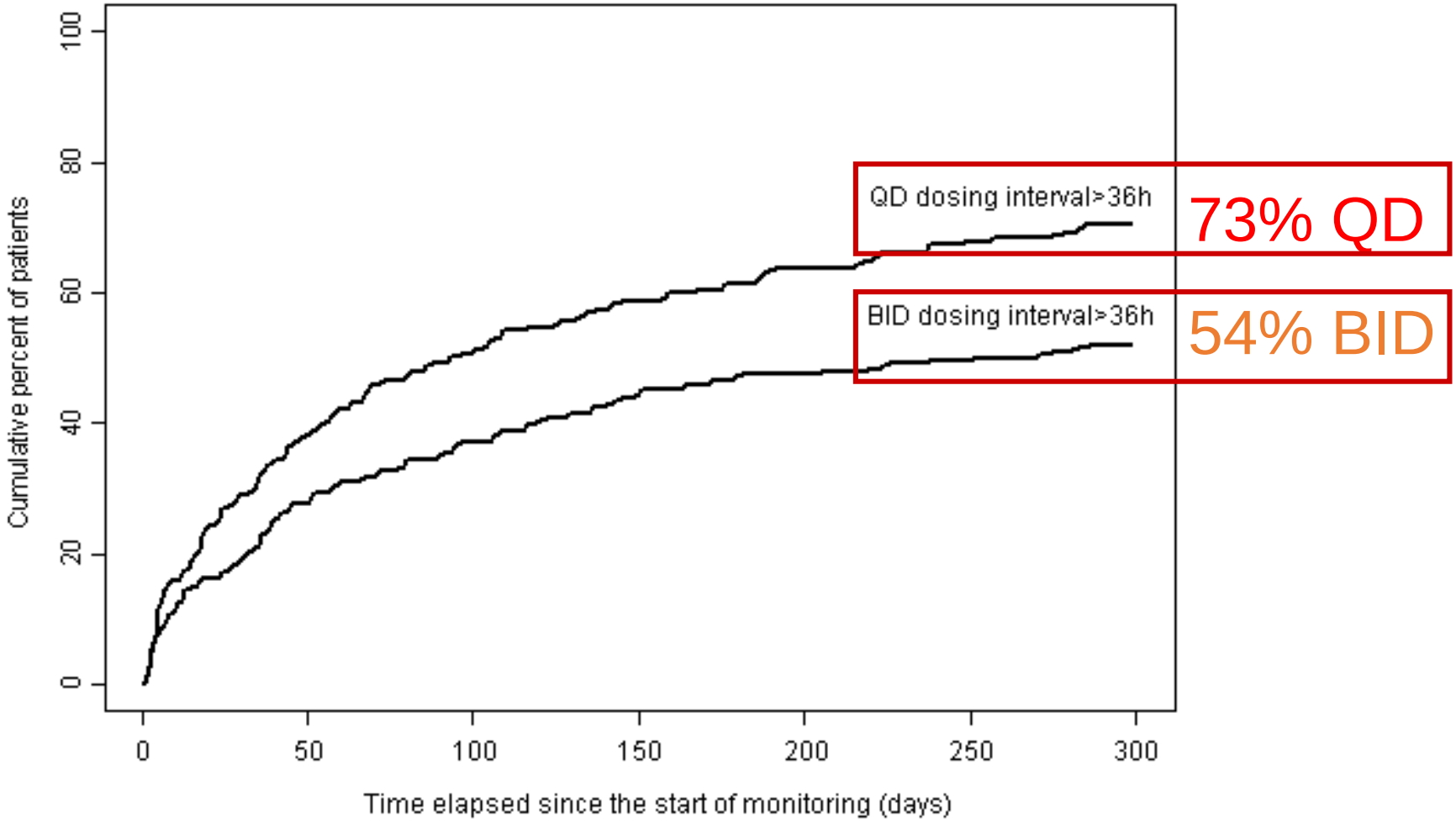
PK considerations



Pharmacokinetic projections of representative patients during a QD or BID dosing regimen assuming that the patients maintain pharmacokinetic steady state. The *y*-axis shows the concentration of PI as a function of time. The consequences of missing one QD or three BID doses are illustrated. The time to reach a critical concentration of 1000 ng/ml is 42.3 h and 47.2 h, respectively, for a BID and a QD regimen when the drug is lopinavir/ritonavir

Slide courtesy of Bernard Vrijens, AARDEX and Pharmionic Research Centre, Visé, Belgium

How frequent are those errors?

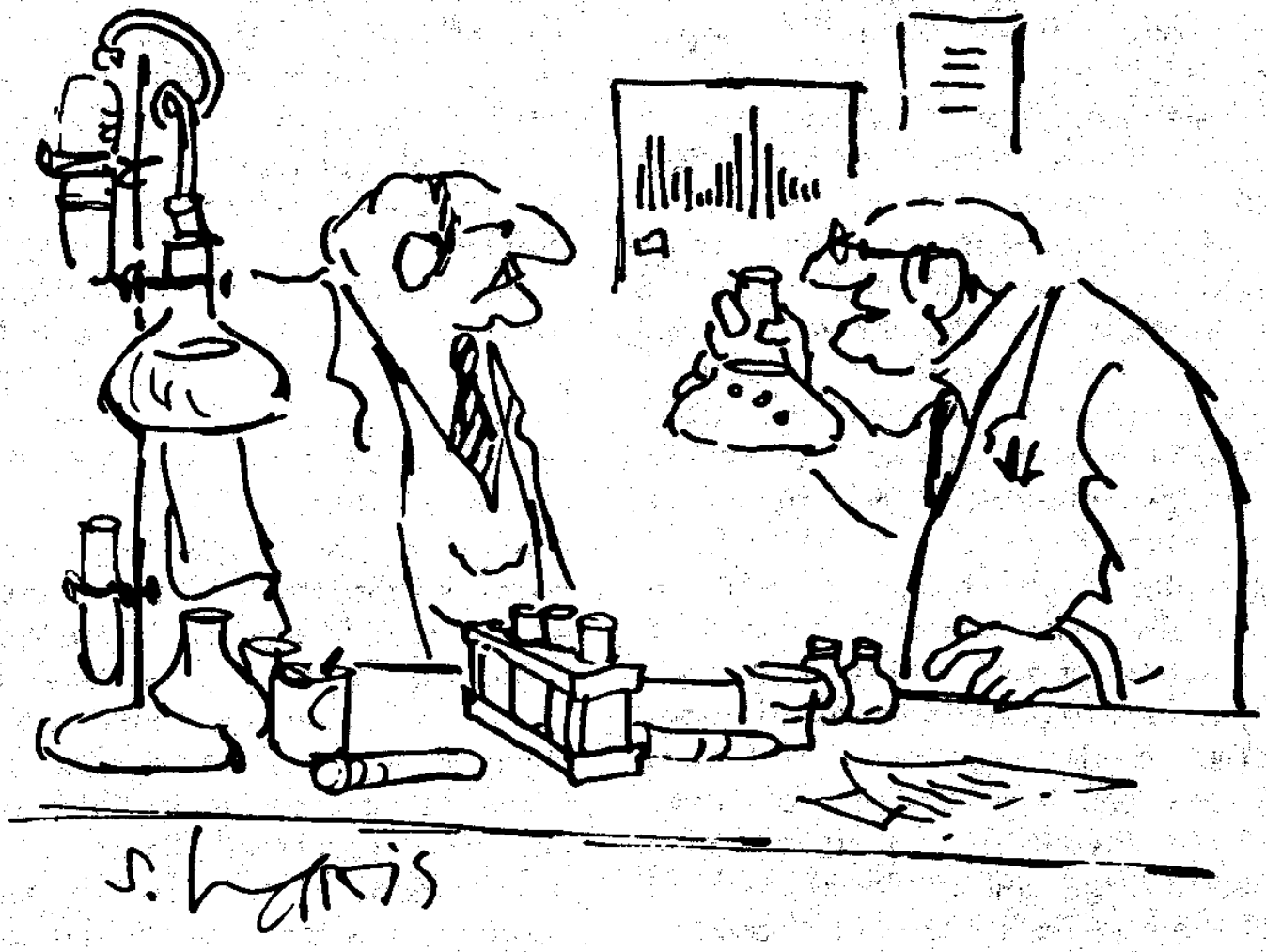


The cumulative percentage of QD and BID patients with dosing intervals greater than 36 h

Slide courtesy of Bernard Vrijens, AARDEX and Pharmionic Research Centre, Visé, Belgium

Take-home Points

- Partial- or non-adherence is the rule, rather than the exception, in clinical trials
  - If adherence is not monitored, results may be misinterpreted and could impact development decisions
  - Investigating drug action following discontinuation, drug holidays and reinstitution of therapy would be of clinical value in the labeling
- Partial- or non-adherence is the rule, rather than the exception, in clinical medicine
  - Is the most important determinant of drug exposure and thus, drug response
  - Improving persistence with treatment is critical to efficacy in long-term, chronic conditions
  - Inadequate communication between the prescriber and the patient is a major cause of adherence problems
- Ascertainment of dosing histories is an essential tool for interventions designed to improve adherence in clinical trials and in clinical medicine



"It may very well bring about immortality, but it will take forever to test it."

Questions and Discussion?