CHALLENGES AND OPPORTUNITIES IN CLINICAL DRUG DEVELOPMENT

Arthur J. Atkinson, Jr., M.D.

Adjunct Professor

Department of Molecular Pharmacology and Biochemistry

Feinberg School of Medicine

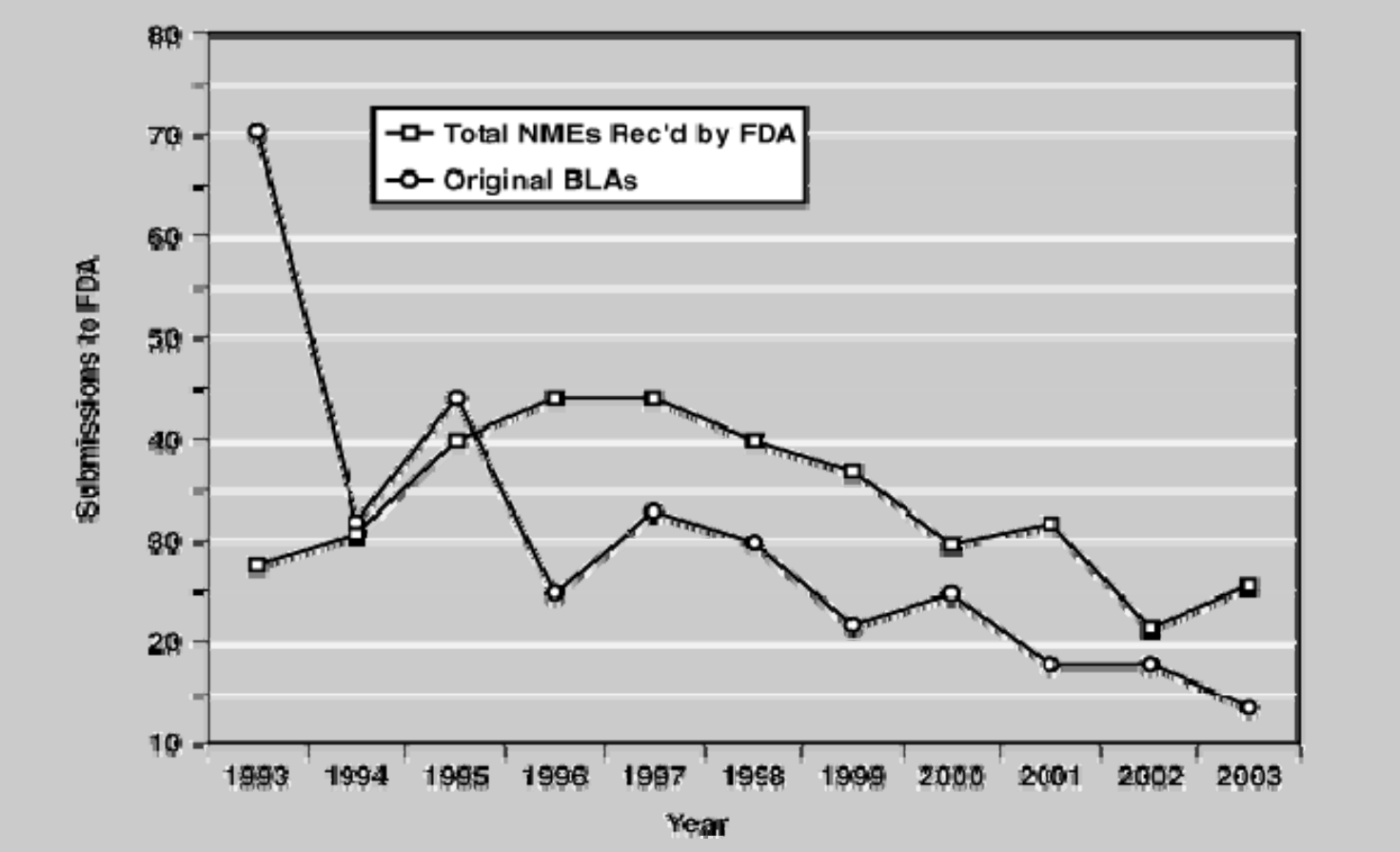
Northwestern University

April 16, 2009

GOALS OF CLINICAL DRUG DEVELOPMENT LECTURE

- CURRENT STATE ANALYSIS
- TARGETED APPROACH TO DRUG DEVELOPMENT
- INFORMATION TO BE OBTAINED DURING EACH DEVELOPMENT PHASE
- DECISION MAKING IN DRUG DEVELOPMENT

10-YEAR TRENDS IN MAJOR DRUG AND BIOLOGICAL SUBMISSIONS TO FDA

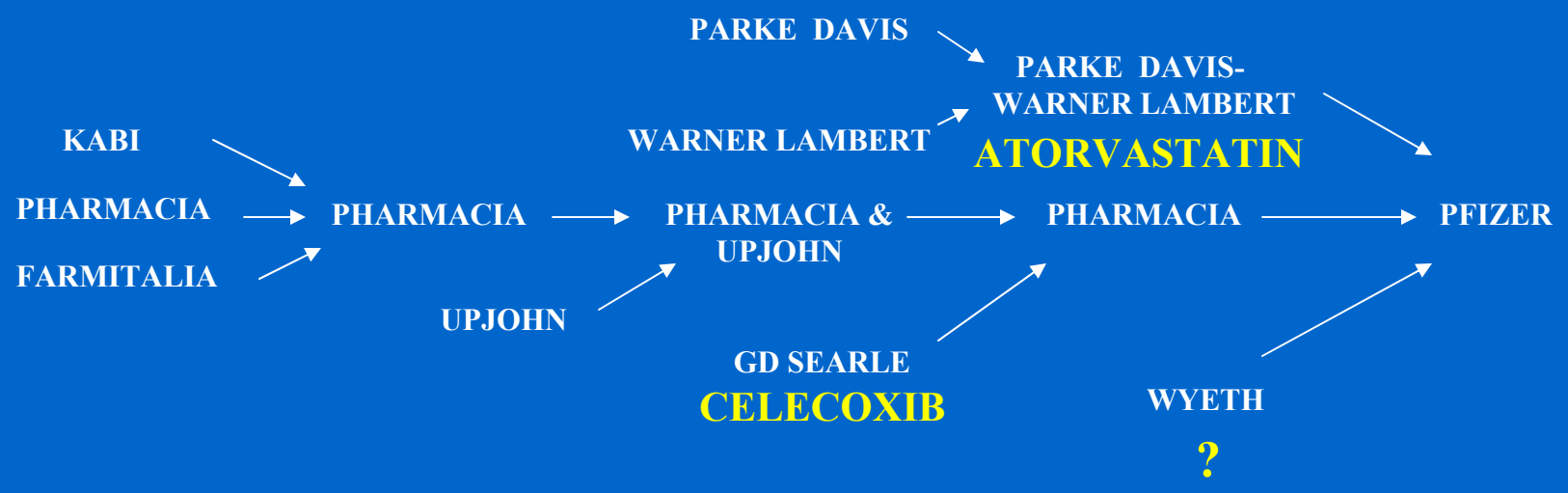


http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

REASONS FOR DECLINE IN NDA SUBMISSIONS

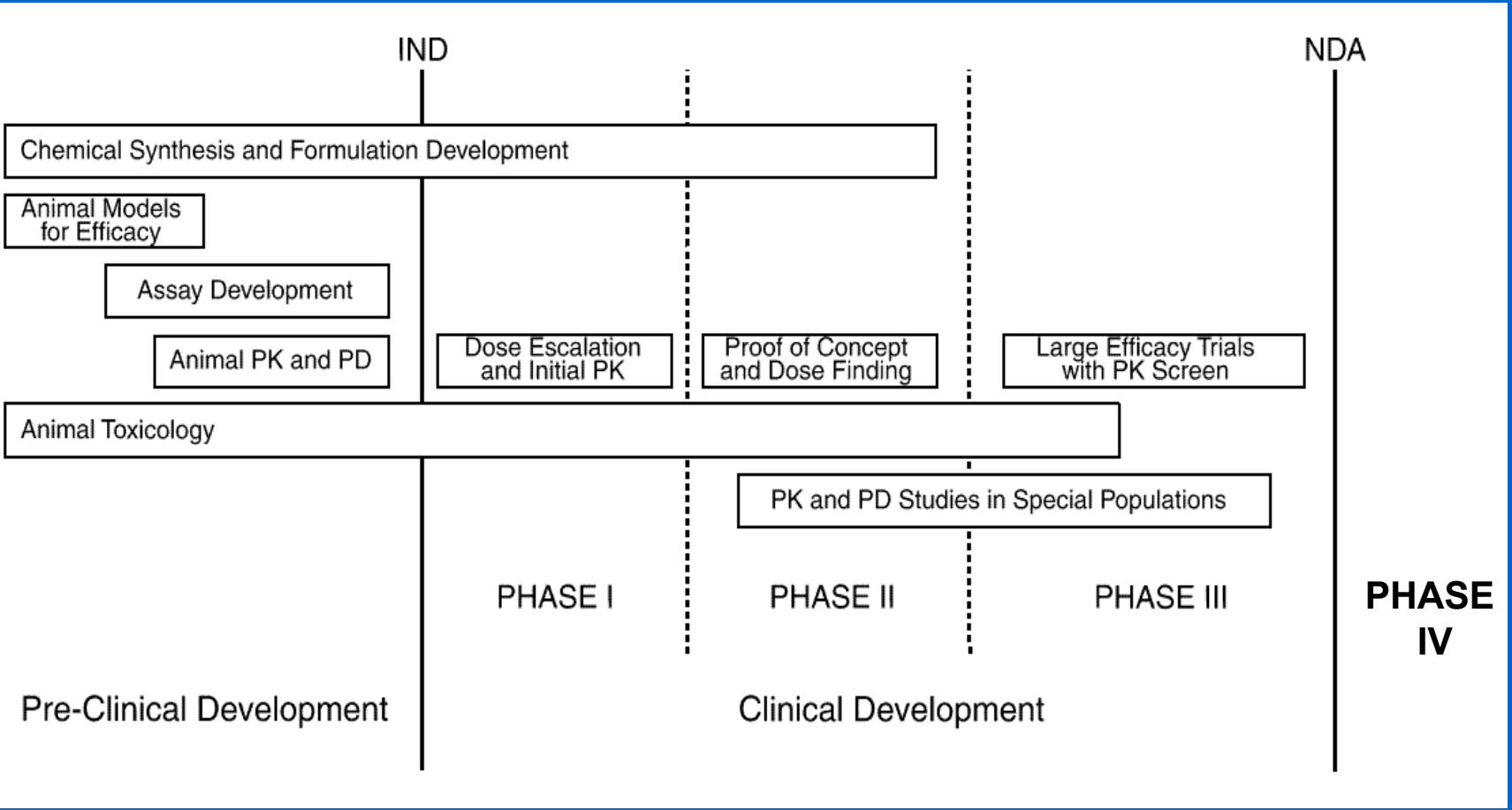
- ↓ "LOW HANGING FRUIT"
- ↓ MAJOR PHARMACEUTICAL COMPANIES
- ↑ REGULATORY BURDEN & COST
- INEFFICIENCIES IN DEVELOPMENT PROCESS

PHARMA SYNERGY: N = 9 → N = 1

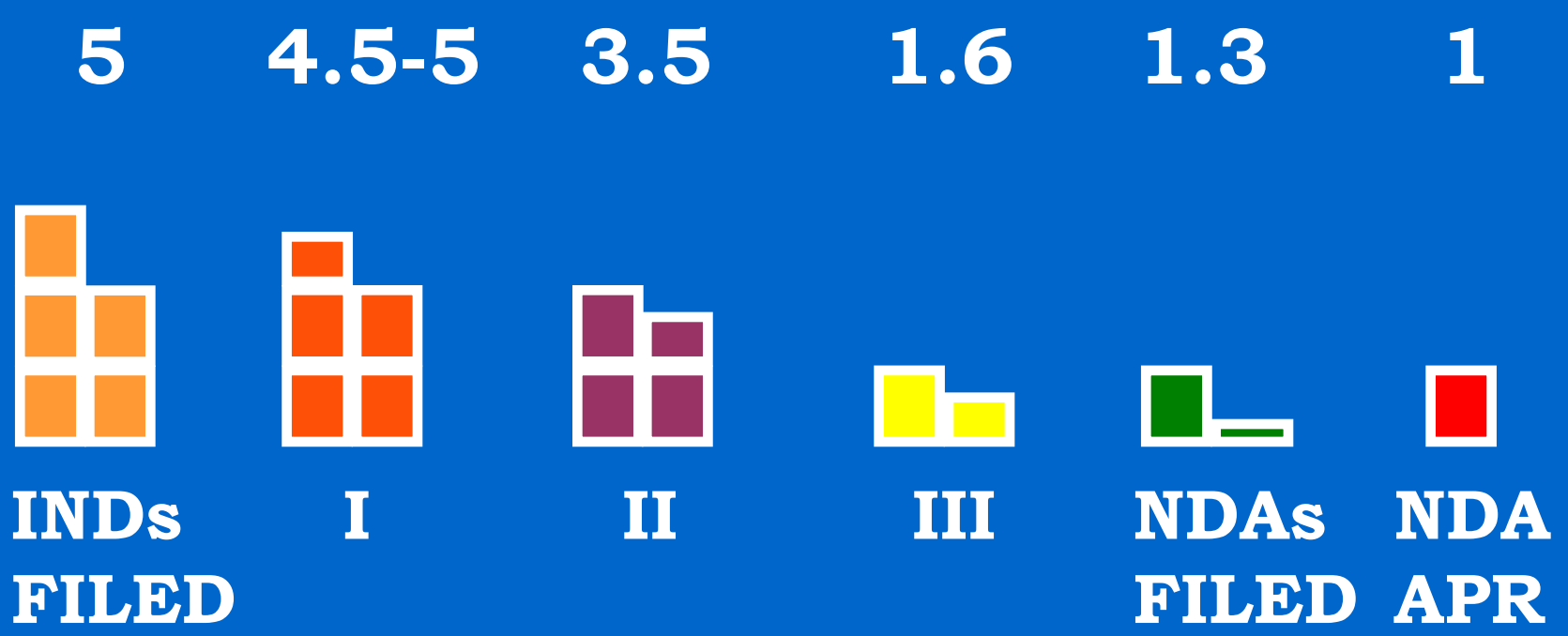


DO MERGERS AFFECT THE RATE OF NEW DRUG DEVELOPMENT ?

POST-DISCOVERY PHASES OF DRUG DEVELOPMENT

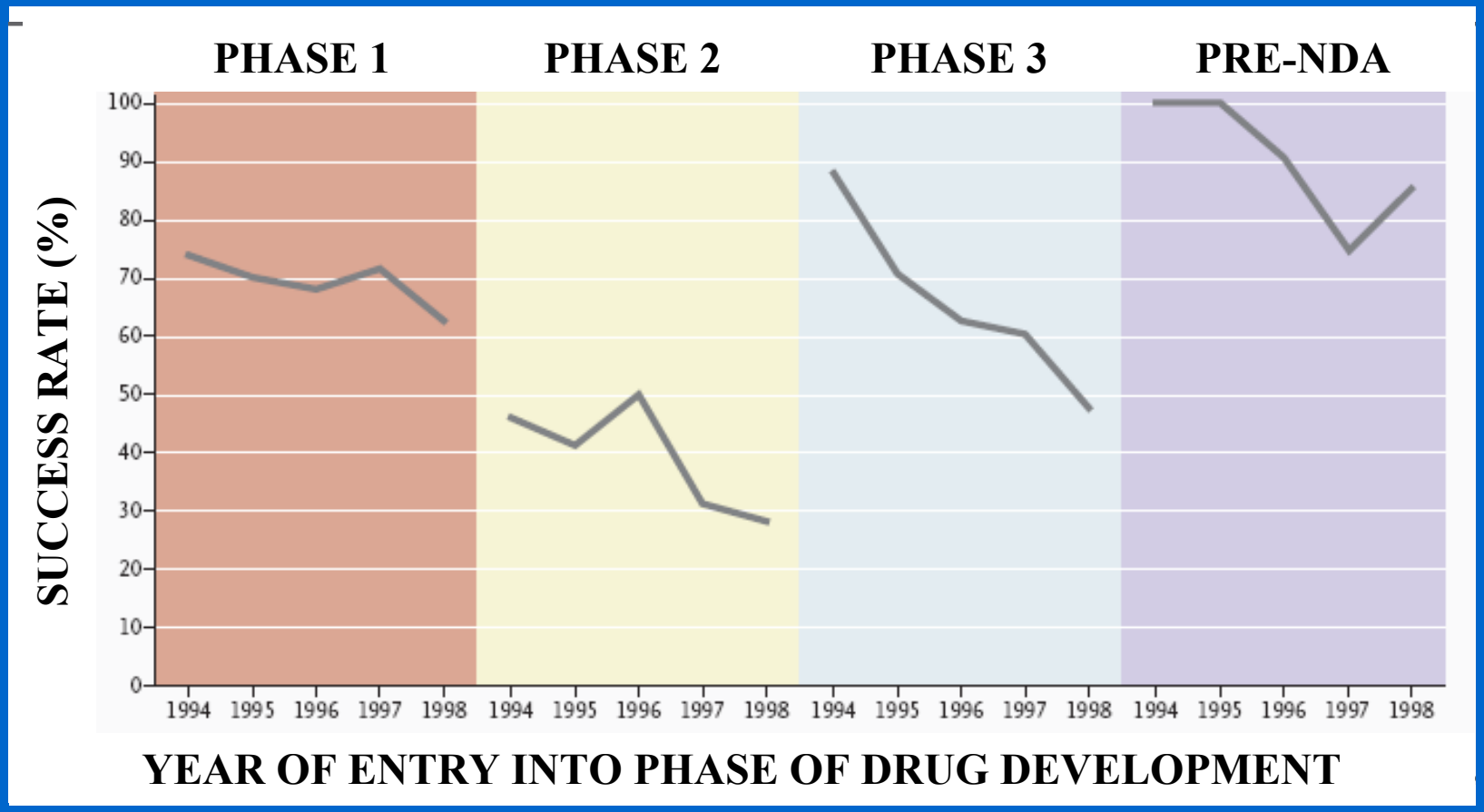


COMPOUND ATTRITION DURING DRUG DEVELOPMENT*



* Grudzinskas C. Portfolio & Project Planning & Management in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology

SUCCESS RATES BY DRUG DEVELOPMENT PHASE*



* Wood AJJ. A Proposal for Radical Changes in the Drug Approval Process. N Engl J Med 2006; 355: 618-623.

CLINICAL DEVELOPMENT COSTS*

CLINICAL PHASE	TIME (months)	EXPECTED COSTS ($ x 10^6)	
		OUT-OF-POCKET	CAPITALIZED†
PHASE I	12.3	15.2	30.5
PHASE II	26.0	16.7	29.5
PHASE III	33.8	27.1	37.4
TOTAL	72.1	59.0	97.4

† BASED ON 11.9% COST OF CAPITAL

* DiMasi JA, et al. J Health Econ 2003;22:151-85.

COSTS PER APPROVED DRUG*

	COST ($ x 10^6)†	
	OUT-OF-POCKET	CAPITALIZED
TOTAL COSTS	403	802
CLINICAL COSTS (% TOTAL)	274 (68%)	453 (56%)

† BASED ON 21.5% SUCCESS RATE

* DiMasi JA, et al. J Health Econ 2003;22:151-85.

CLINICAL DEVELOPMENT PROGRAMS OF SOME RECENTLY DEVELOPED DRUGS*

DRUG *INDICATION*	FIH-NDA FILE (YEARS)	PHASE I TRIALS/ SUBJECTS	PHASE II TRIALS/ SUBJECTS	PHASE III TRIALS/ SUBJECTS	TOTAL TRIALS/ SUBJECTS
HERCEPTIN® *BREAST CA*	6 – 10	3/48	8/532	1/469	12/1069
ENBREL® *RHEUM. ARTHRITIS*	6 - 7	8/163	23/503	23/1381	34/2048
RELENZA® *INFLUENZA*	4 - 5	18/446	3/3275	3/1588	28/5309
VIAGRA® *ERECT. DYSFUNCT.*	5	42/905	13/498	13/4679	68/6082
VIOXX® *OA & PAIN*	4 - 5	31/940	2/1855	13/5733	46/8528

* Grudzinskas C. Design of clinical development programs in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology

GOALS OF CLINICAL DRUG DEVELOPMENT LECTURE

- CURRENT STATE ANALYSIS
- TARGETED APPROACH TO DRUG DEVELOPMENT
- INFORMATION TO BE OBTAINED DURING EACH DEVELOPMENT PHASE
- DECISION MAKING IN DRUG DEVELOPMENT

WHAT DOES THIS EXPENDITURE PRODUCE?*

"We Sell Only the Package Insert,

We Give Away the Product !"

* Grudzinskas C. Design of clinical development programs in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology

CENTRAL ROLE OF DRUG LABEL

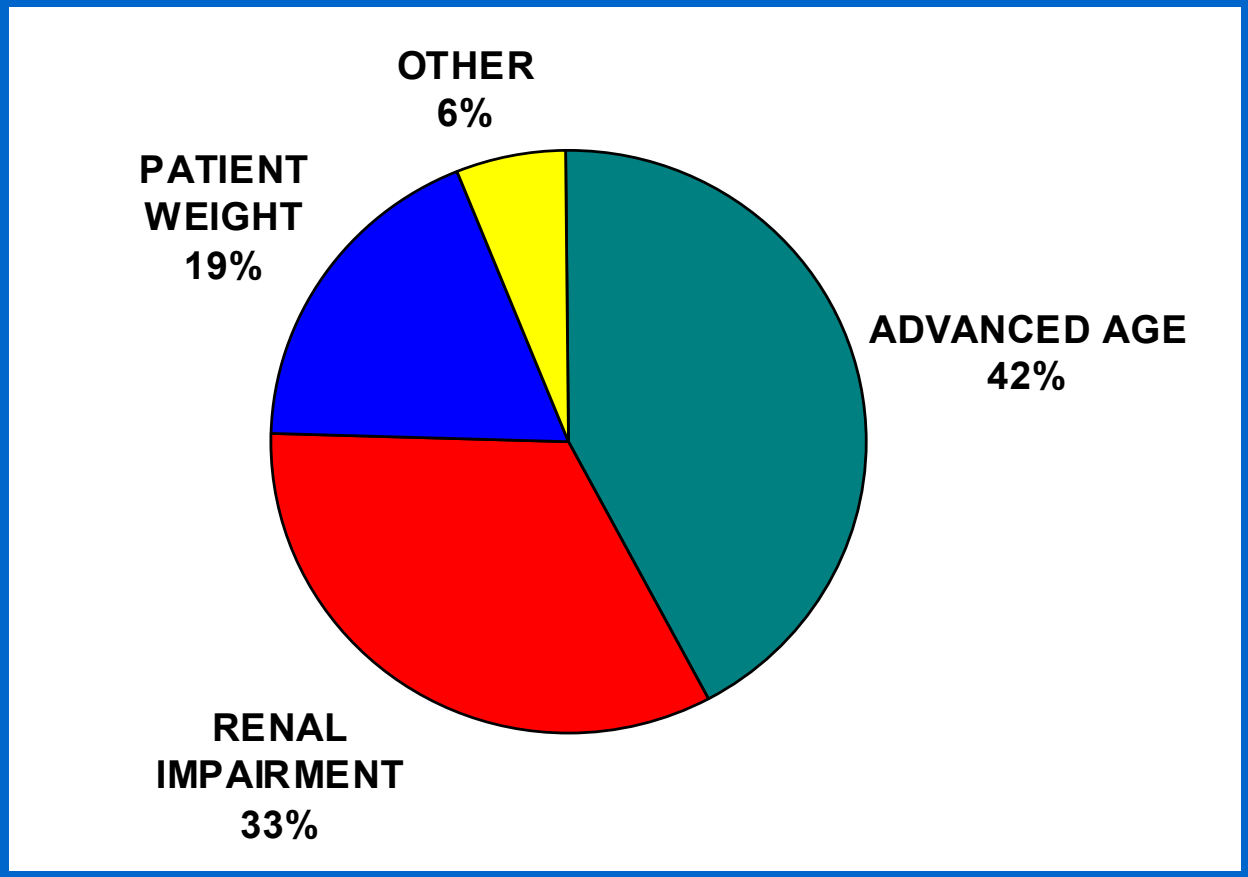
- THE DRUG LABEL IS THE PRIMARY SOURCE OF DRUG PRESCRIBING INFORMATION AND IS REVIEWED BY THE FDA AS PART OF THE DRUG APPROVAL PROCESS.
- AS SUCH, THE DRUG LABEL IS A DISTILLATE OF THE ENTIRE DRUG DEVELOPMENT PROCESS.
- DESPITE THIS, THE DRUG LABEL OFTEN IS CREATED AS AN AFTERTHOUGHT.

INFORMATION CONTENT OF CURRENT DRUG LABELS*

CORE INFORMATION CATEGORY	INCLUSION OF DESIRABLE DATA ELEMENTS MEAN (95% CI)	
MECHANISM OF ACTION	88%	(84% - 93%)
PHARMACODYNAMICS	43%	(37% - 49%)
DRUG METABOLISM	23%	(16% - 29%)
PHARMACOKINETICS	42%	(35% - 49%)
DOSE ADJUSTMENT	37%	(32% - 42%)

* Spyker DA, et al. Clin Pharmacol Ther 2000;67:196-200.

PATHOPHYSIOLOGIC FACTORS NOT ACCOUNTED FOR IN DRUG DOSING*



* Lesar TS, Briceland L, Stein DS. JAMA 1997;277:312-7.

TARGETED APPROACH TO DRUG DEVELOPMENT*

Whenever a decision is made to develop a compound, two fundamental components of the development plan should be the Target Product Profile (TPP) and the Target Package Insert (TPI).

- TPP: Specific targets for compound, including toxicology, pharmaceutical development, manufacturing, clinical research, clinical safety, etc. (~ 40 - 80 pages)
- TPI: Draft label for compound that is amended as data accumulate (~ 3 – 10 pages)

* Tansey, M. Targeted treatment solutions. 11th EUFEPS Conference on Optimising Drug Development. Basel, December 8-10, 2003.

TARGET PRODUCT PROFILE (TPP) *

A document in which "the sponsor specifies the labeling concepts that are the goals of the drug development program, documents the specific studies intended to support the labeling concepts, and then uses the TPP to assist in a constructive dialogue with the FDA."

* CDER Draft Guidance:
http://wwwfda.gov/cder/guidance/6910dft.pdf

FDA GOALS OF TARGETED PRODUCT DEVELOPMENT *

- TO HELP SPONSORS DESIGN, CONDUCT, AND ANALYZE CLINICAL TRIALS TO OPTIMIZE PURSUIT OF THE DESIRED OUTCOME
- TO PROMOTE A SHARED UNDERSTANDING OF A SPONSOR'S DRUG DEVELOPMENT PROGRAM
- TO PROVIDE A FORMAT FOR DISCUSSIONS BETWEEN SPONSORS AND THE FDA

* CDER Draft Guidance:
http://wwwfda.gov/cder/guidance/6910dft.pdf

UTILITY OF TPI FOR SPONSOR

- PROVIDES FOCUS FOR PLANNING CLINICAL TRIALS
- SERVES AS A CONTRACT BETWEEN DEVELOPMENT AND MARKETING
- PROVIDES BASIS FOR CORPORATE DECISION MAKING
- THEREFORE, OF MAXIMAL BENEFIT IF DRAFTED EARLY IN THE DRUG DEVELOPMENT PROGRAM

GOALS OF CLINICAL DRUG DEVELOPMENT LECTURE

- CURRENT STATE ANALYSIS
- TARGETED APPROACH TO DRUG DEVELOPMENT
- INFORMATION TO BE OBTAINED DURING EACH DEVELOPMENT PHASE
- DECISION MAKING IN DRUG DEVELOPMENT

PHASE I GOALS

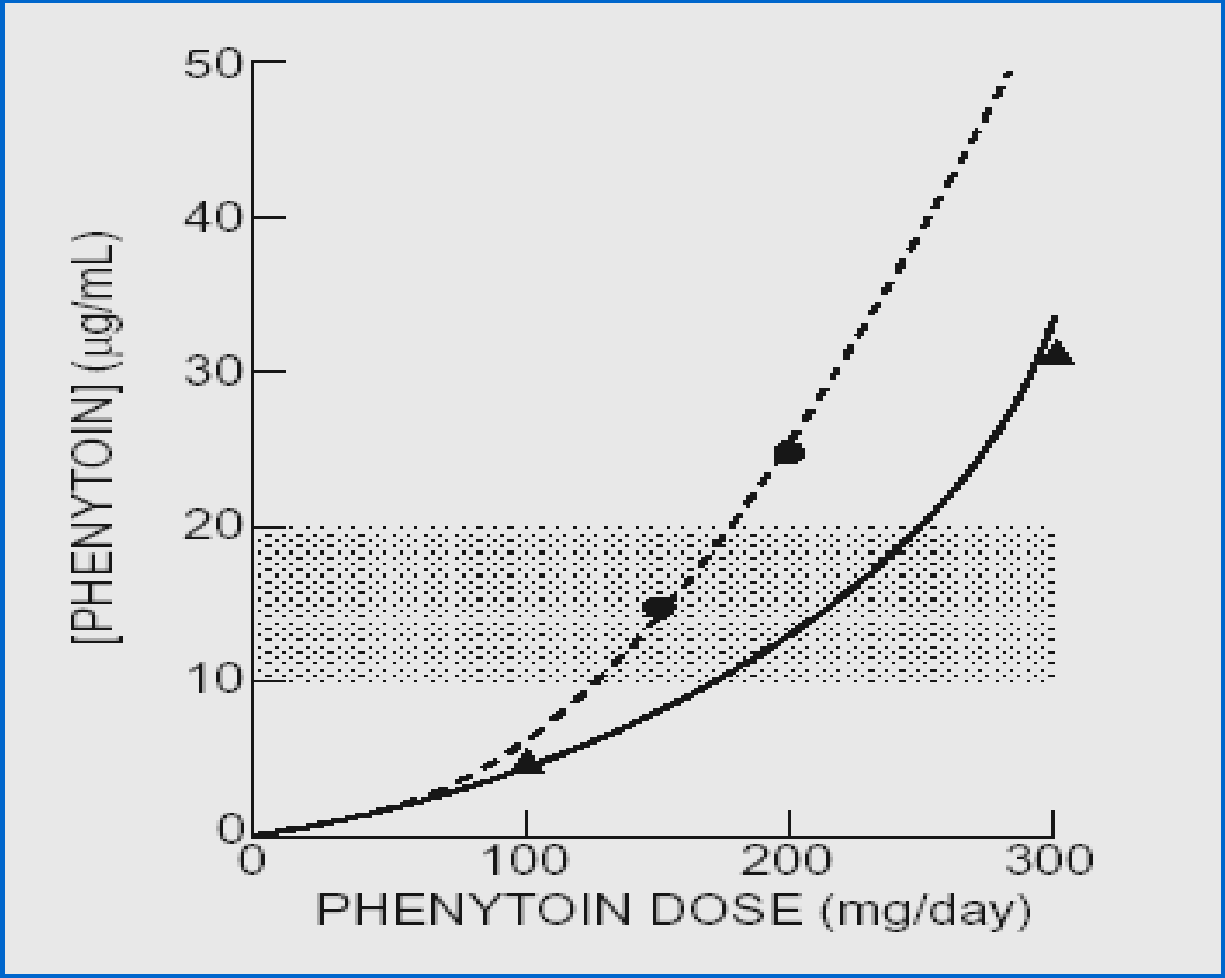
- DOSE PROPORTIONALITY
- ELIMINATION-PHASE T½
- ADEQUATE BA FOR ORAL ADMINISTRATION
- METABOLIC PATHWAYS
- EVIDENCE OF PHARMACOLOGIC ACTIVITY

NONCANCER DRUGS CAUSING ADR'S*

PHENYTOIN
PREDNISONE
DIGOXIN
AMIODARONE
ASPIRIN
CO-TRIMOXAZOLE
PENTAMIDINE
CARBAMAZEPINE
CODEINE
LITHIUM
THEOPHYLLINE
DESIPRAMINE
DEXAMETHASONE
GENTAMICIN

* 1988 NMH DATA (CLIN PHARMACOL THER 1996;60:363-7)

LEVELS NOT PROPORTIONAL TO DOSE



STEADY STATE EQUATIONS

FIRST ORDER KINETICS

$$\text{DOSE}/\tau = CL_E \bullet \overline{C}_{SS}$$

MICHAELIS - MENTEN KINETICS

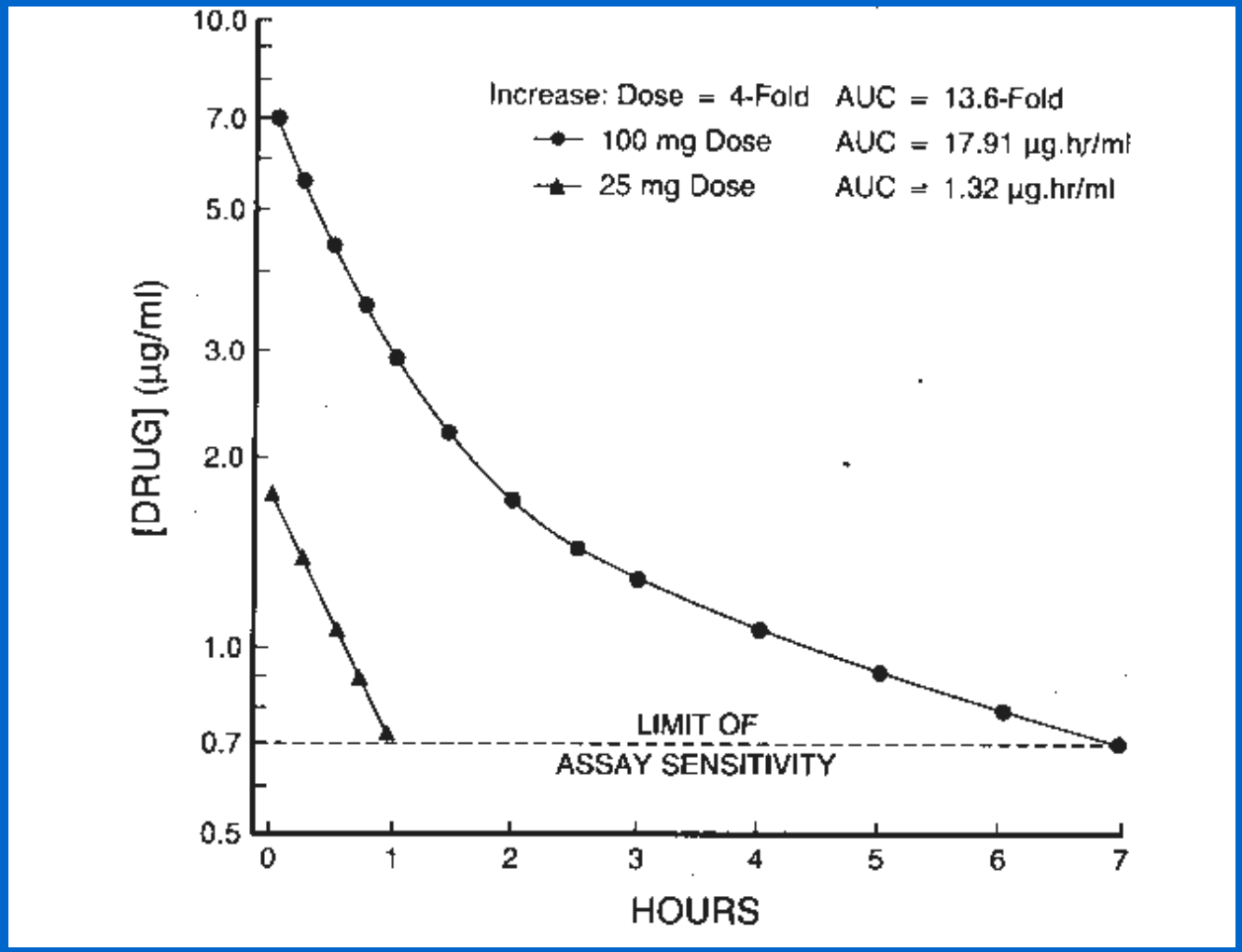
$$\text{DOSE}/\tau = \left[\frac{V_{max}}{K_m + \overline{C}_{SS}}\right]\overline{C}_{SS}$$

DOSE DEPENDENCY ?

AUC = AREA UNDER PLASMA LEVEL VS. TIME CURVE

Increase: Dose = 4-Fold	AUC =	13.6-Fold
100 mg Dose	AUC =	17.91 µg.hr/ml
25 mg Dose	AUC =	1.32 µg.hr/ml

PSEUDO DOSE DEPENDENCY



CLOTTING FACTOR PHARMACOKINETICS*

- "THE $V_{(dss)}$..... ALWAYS EXCEEDS THE ACTUAL PLASMA VOLUME, IMPLYING THAT NO DRUG, NOT EVEN LARGE MOLECULAR COMPLEXES AS FVIII, IS ENTRIELY CONFINED TO THE PLASMA SPACE."

- "A TOO SHORT BLOOD SAMPLING PROTOCOL GIVES FLAWED RESULTS NOT ONLY FOR TERMINAL T ½ BUT ALSO FOR THE MODEL INDEPENDENT PARAMETERS."

* Berntorp E, Björkman S. Haemophilia 2003;9:353-9.

DISTRIBUTION VOLUME OF REPRESENTATIVE MACROMOLECULES

MACROMOLECULE	MW (kDa)	V_1 (mL/kg)	$V_{d(ss)}$ (mL/kg)
INULIN	5.2	55 IVS	164 ECF
FACTOR IX (FIX)	57	136	271
INTERLEUKIN-2 (IL-2)	15.5	60	112
INTERLEUKIN-12 (IL-12)	53	52	59
GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)	20	44	60
RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (RT-PA)	65	59	106

PHASE II GOALS

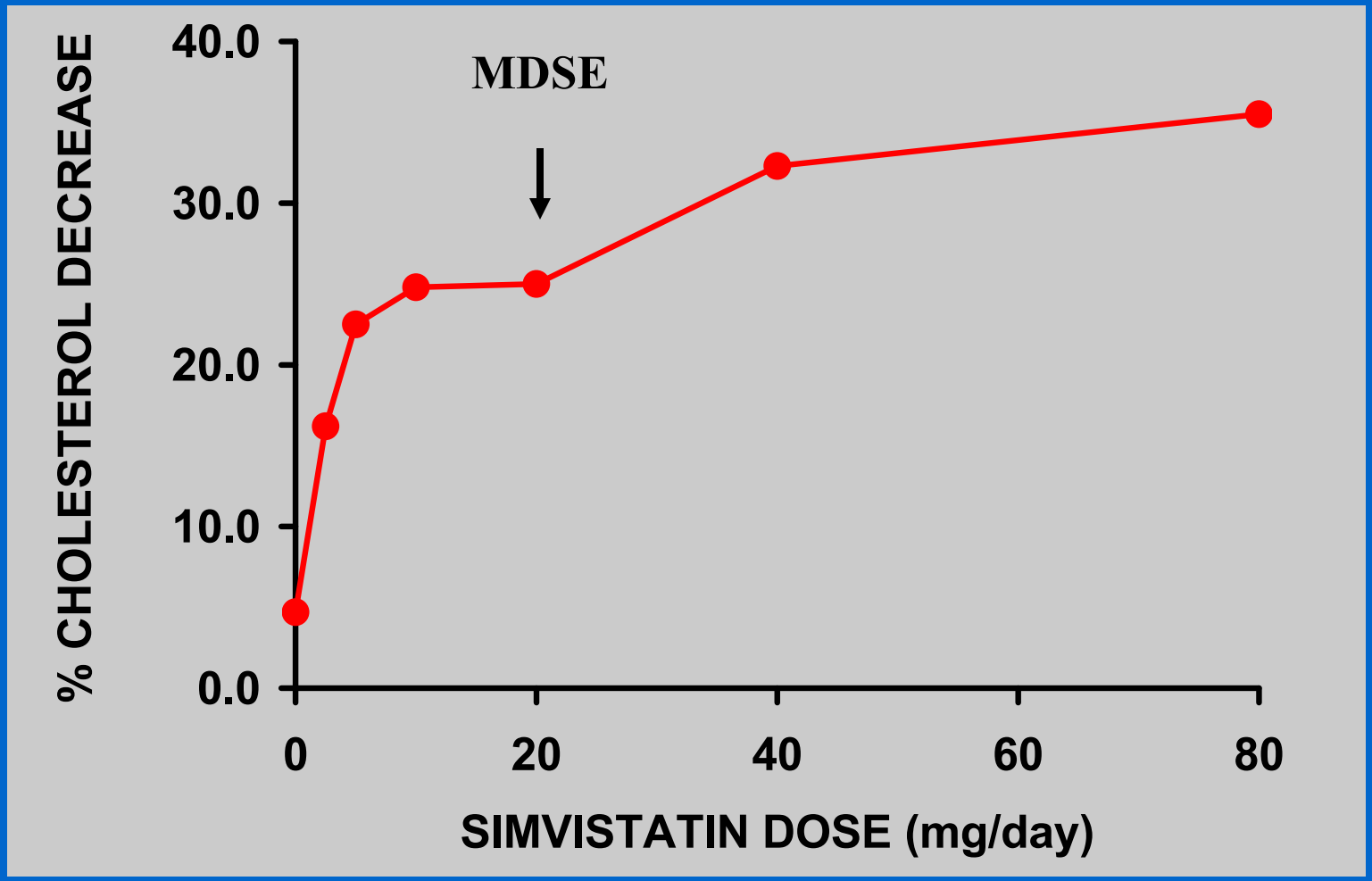
- PROOF OF CONCEPT
  - THERAPEUTIC EFFICACY
  - SATISFACTORY EARLY SAFETY DATA
- DOSE RESPONSE
  - BIOMARKER
  - CLINICAL ENDPOINT
- FREQUENCY OF DOSE ADMINISTRATION

SIMVASTATIN DOSE-RESPONSE STUDY *

NUMBER OF 1° ↑ CHOL PATIENTS:	43
NUMBER OF STUDY CENTERS	4
STUDY DURATION:	6 weeks
SIMVASTATIN DOSE RANGE:	
ONCE DAILY:	2.5 - 40 mg/day
TWICE DAILY:	1.25 - 40 mg bid

* Mol MJTM et al. Lancet 1986;ii:936-9

ESTIMATING DOSE RANGE FOR SUBSEQUENT PIVOTAL TRIAL



Mol MJTM, et al. Lancet 1986;ii:936-9.

POST-MARKETING DRUG DOSE CHANGES BASED ON PDR REVIEW*

- DRUGS EVALUATED (354)
- DOSE CHANGES (73 = 21% EVALUATED DRUGS)
  - DOSE INCREASES (15 = 21% OF CHANGES)
  - DOSE DECREASES (58 = 79% OF CHANGES)
    - ↓ DOSE STRENGTH
    - ↓ TREATMENT DURATION
    - ↑ DOSE INTERVAL
    - POPULATION RESTRICTION
    - REMOVAL OF INDICATION

* Cross J, et al. Pharmacoepidemiol Drug Safe 2002;11:439-46.

DOSE DISCREPANCIES BETWEEN PDR & MEDICAL LITERATURE*

DRUG †	PDR INITIAL DOSE (mg)	EFFECTIVE LOWER DOSE (mg)
ACEBUTOLOL	400	200
CELECOXIB	100 BID	50 BID
LISINOPRIL	10	5
OMEPRAZOLE	20	10
PROPRANOLOL	80	40

† SELECTED FROM A TABLE OF 48 COMMONLY PRESCRIBED DRUGS

* Cohen JS. Arch Intern Med 2001;161:957-64.

PHASE III GOALS

- PIVOTAL TRIALS
  - CONFIRM EFFICACY
  - EVALUATE SAFETY
- POPULATION PK OR SPECIAL STUDIES
  - EFFECTS OF ORGAN DYSFUNCTION
  - DRUG INTERACTIONS
- COMPARE WITH STANDARD THERAPY
- EVALUATE BIOMARKER VS. CLINICAL ENDPOINT

SIMVASTATIN SURVIVAL STUDY*

NUMBER OF CHD PATIENTS: 4444

NUMBER OF STUDY CENTERS: 94

MEDIAN FOLLOW-UP DURATION: 5.4 years

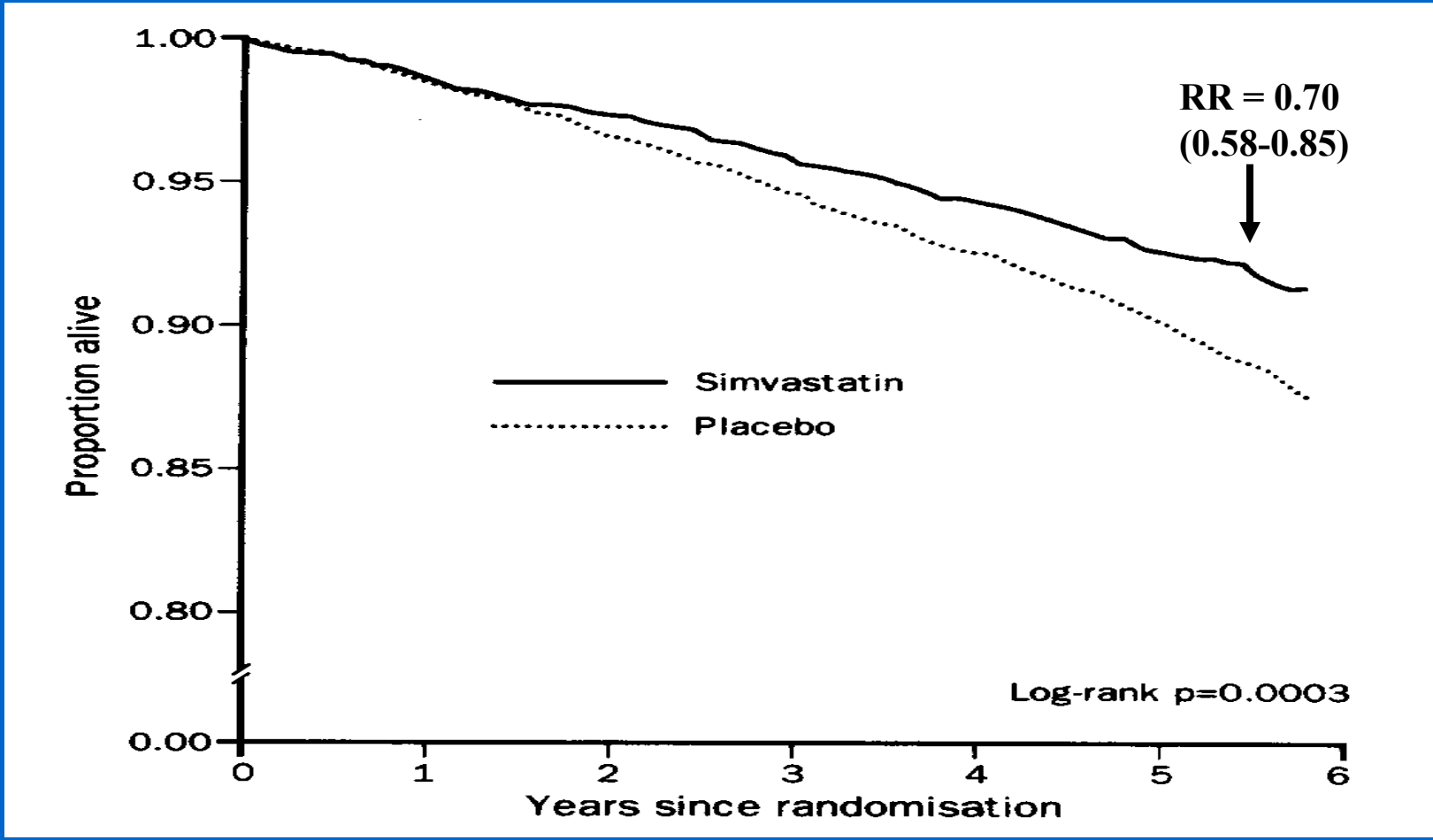
SIMVASTATIN DOSING:

INITIAL: 20 mg/day

SUBSEQUENT TITRATION: ↓ [Chol] to 117-200 mg/DL

* 4S Study Group. Lancet 1994;344:1383-9

KAPLAN-MEIER CURVES FOR ALL-CAUSE MORTALITY*



* Scandinavian Simvastatin Survival Study Group. Lancet 1994:344;1383-9.

PHASE IV GOALS

- NEW INDICATIONS
- ACTIVE COMPARATOR TRIALS
- NEW PATIENT GROUPS
  - PEDIATRICS (See FDA Guidance*)
  - PREGNANT WOMEN (See FDA Guidance*)
- PHARMACOVIGILANCE

* http://www.fda.gov/cder/guidance/index.htm

PHASE IV STUDY: ARA-C "USELESS" *

- SPONSOR: AIDS CLINICAL TRIALS GROUP
- GOAL: EVALUATE EFFICACY OF INTRATHECAL (IT) CYTARABINE (ARA-C) IN PATIENTS WITH PROGRESSIVE MFL

* Hall CD, et al. N Engl J Med 1998;338:1345-51.

MULTIFOCAL LEUKOENCEPHALOPATHY (MFL)

- OCCURS IN 4% OF PATIENTS WITH AIDS
- THERE IS NO ESTABLISHED EFFECTIVE THERAPY
- SURVIVIAL AVERAGES 2.5 TO 4 MONTHS
- OCCURRED IN PATIENTS RX'D WITH TYSABRI
- OCCURRED IN PATIENTS RX'D WITH RITUXAN

LABELLED INDICATIONS FOR CYTARABINE (ARA-C)

- IV for remission induction of acute non-lymphocytic leukemia (in combination with other approved cancer drugs).
- IV for treatment of acute lymphocytic leukemia
- IV for treatment of blast phase of chronic myelocytic leukemia.
- IT for prophylaxis and treatment of meningeal leukemia.

RATIONALE FOR PHASE IV STUDY

- The JC virus (etiologic agent of progressive multifocal leukoencephalopathy) is sensitive to ARA-C *in vitro*.
- ARA-C crosses the blood-brain barrier (BBB) only slowly.
- Intrathecal/intraventricular administration might improve the therapeutic efficacy of ARA-C by circumventing the BBB.

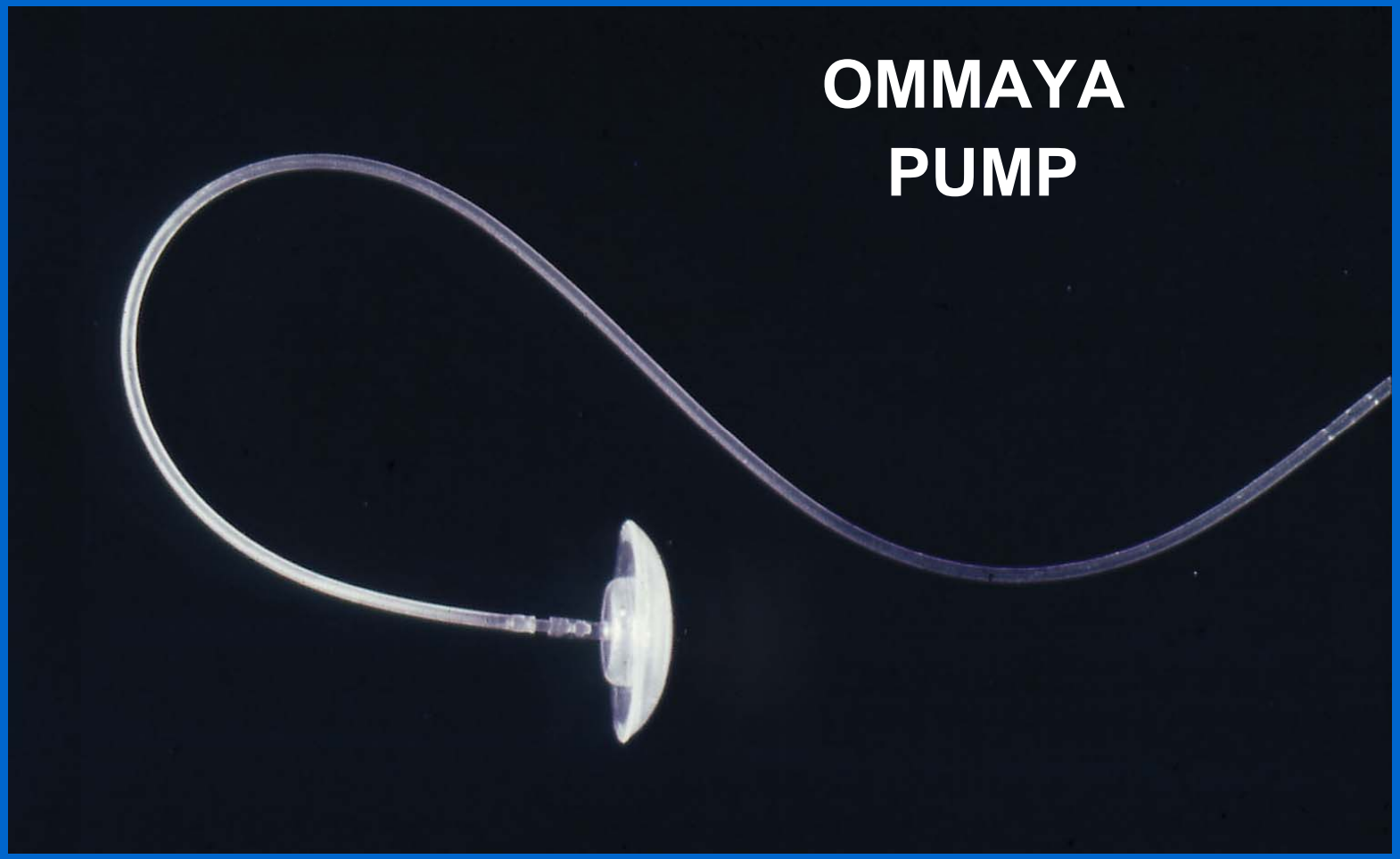
PATIENT ENROLLMENT

- 57 PATIENTS WITH PML RANDOMIZED IN MULTICENTER ACTG TRIAL
- THREE TREATMENT GROUPS
  - ONLY CONTINUE ANTIRETROVIRAL DRUGS
  - ADD 4 MG/KG ARA-C DAILY IV FOR 5 d q 21 d
  - ADD INTRATHECAL ARA-C

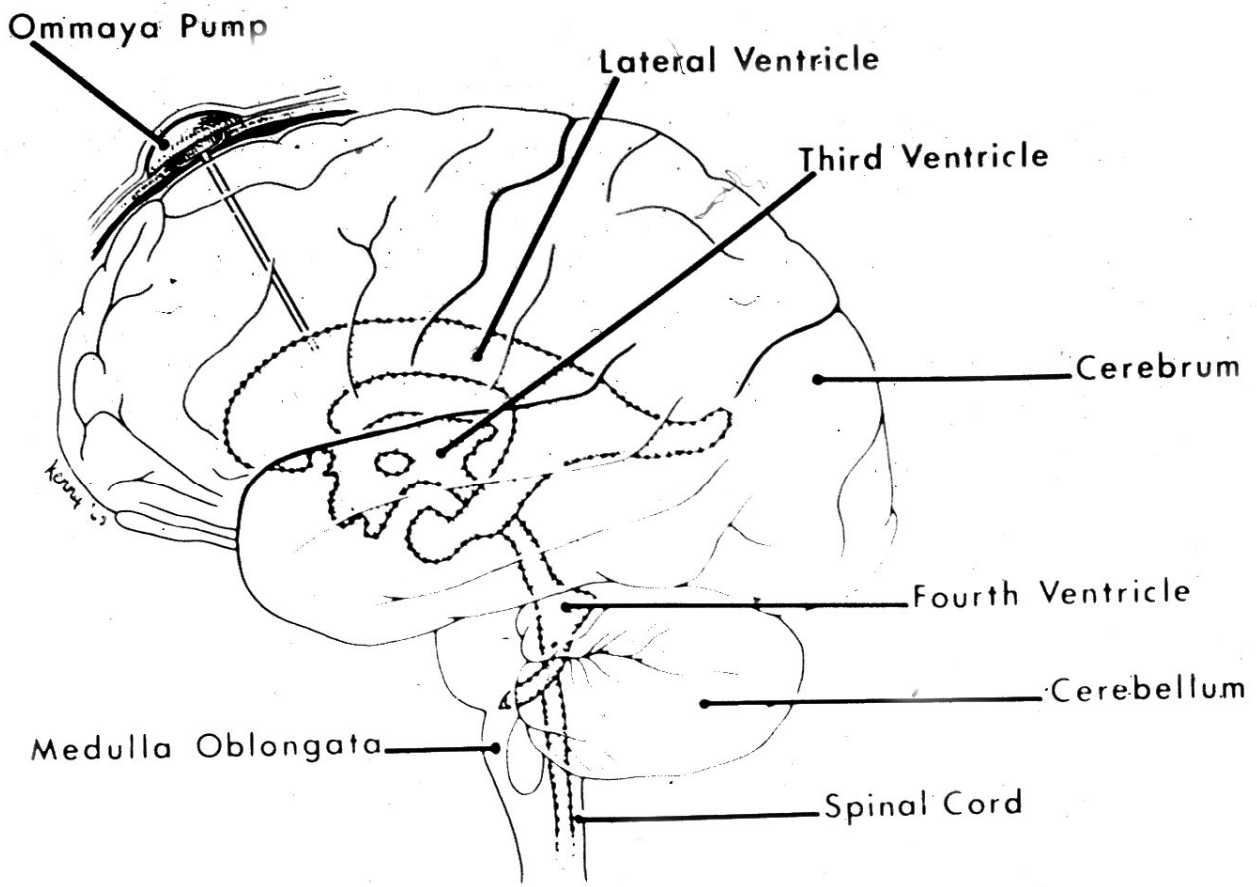
IT DOSE REGIMEN: 19 SUBJECTS

"GROUP 3 RECEIVED ANTIRETROVIAL THERAPY PLUS 50 MG OF CYTARABINE, ADMINISTRED INTRATHECALLY WITH AN OMMAYA RESERVOIR, ONCE A WEEK FOR FOUR WEEKS, THEN ONCE EVERY 2 WEEKS FOR 8 WEEKS, THEN ONCE EVERY 4 WEEKS FOR THE REMAINDER OF THE STUDY."

REPETITIVE IT ADMINISTRATION IS NON-TRIVIAL



SCHEMATIC OF PUMP PLACEMENT



Lateral view of brain.

RESERVOIR PLACEMENT

ELEMENTS OF STUDY DESIGN

- STATISTICAL SAFEGUARDS
  - RANDOMIZATION OF PATIENTS
  - BALANCED TREATMENT GROUPS
  - INTENTION TO TREAT ANALYSIS
  - DATA ANALYZERS BLINDED
- JUSTIFICATION FOR IT DOSE REGIMEN
  - NONE PROVIDED

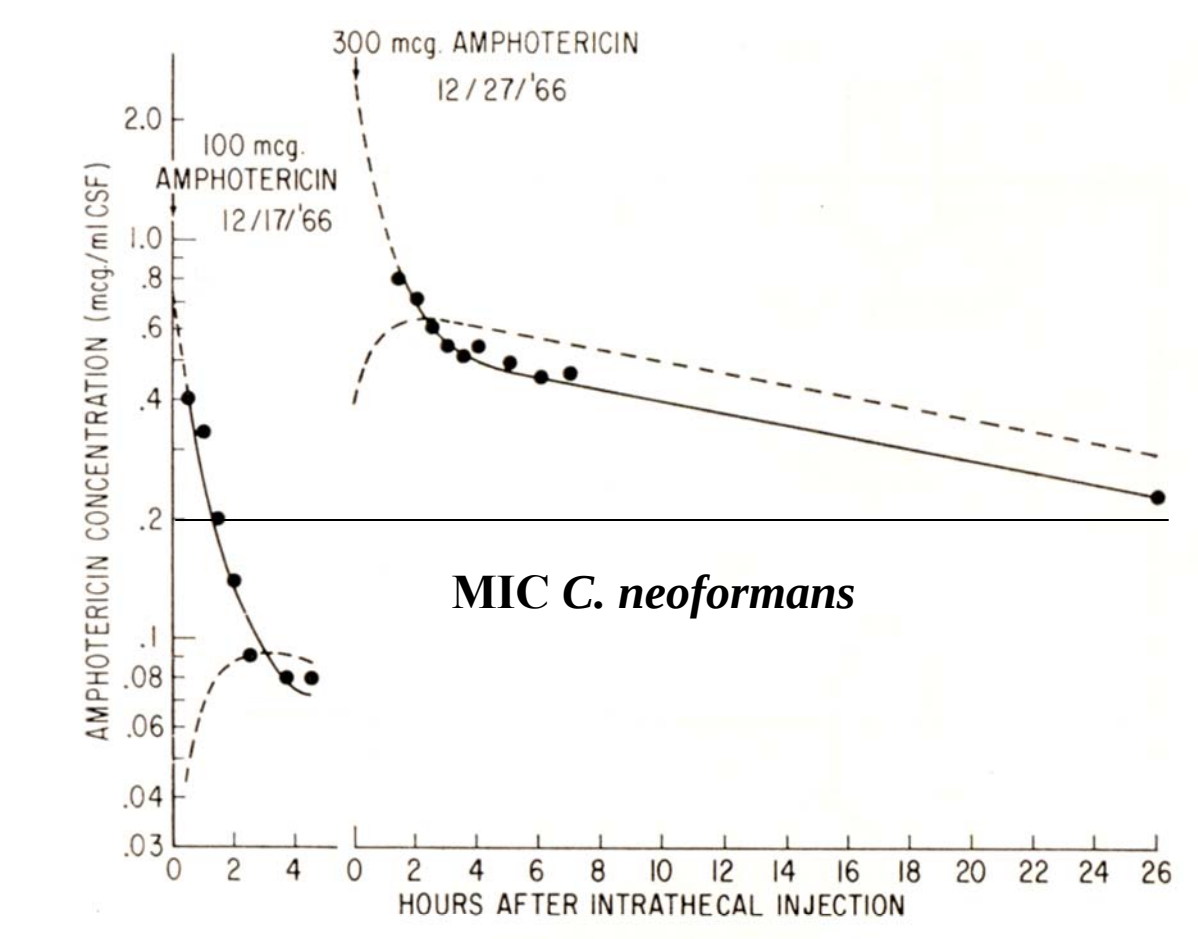
THE MOST WIDELY USED BIOMARKER/SURROGATE ENDPOINT

DRUG LEVELS USED AS A SURROGATE FOR CLINICAL EFFICACY AND TOXICITY IN THE EVALUATION OF GENERIC DRUGS *

IN VITRO ESTIMATES OF EFFECTIVE DRUG LEVELS WIDELY USED AS A BIOMARKER IN DEVELOPING ANTI-INFECTIVE DRUGS

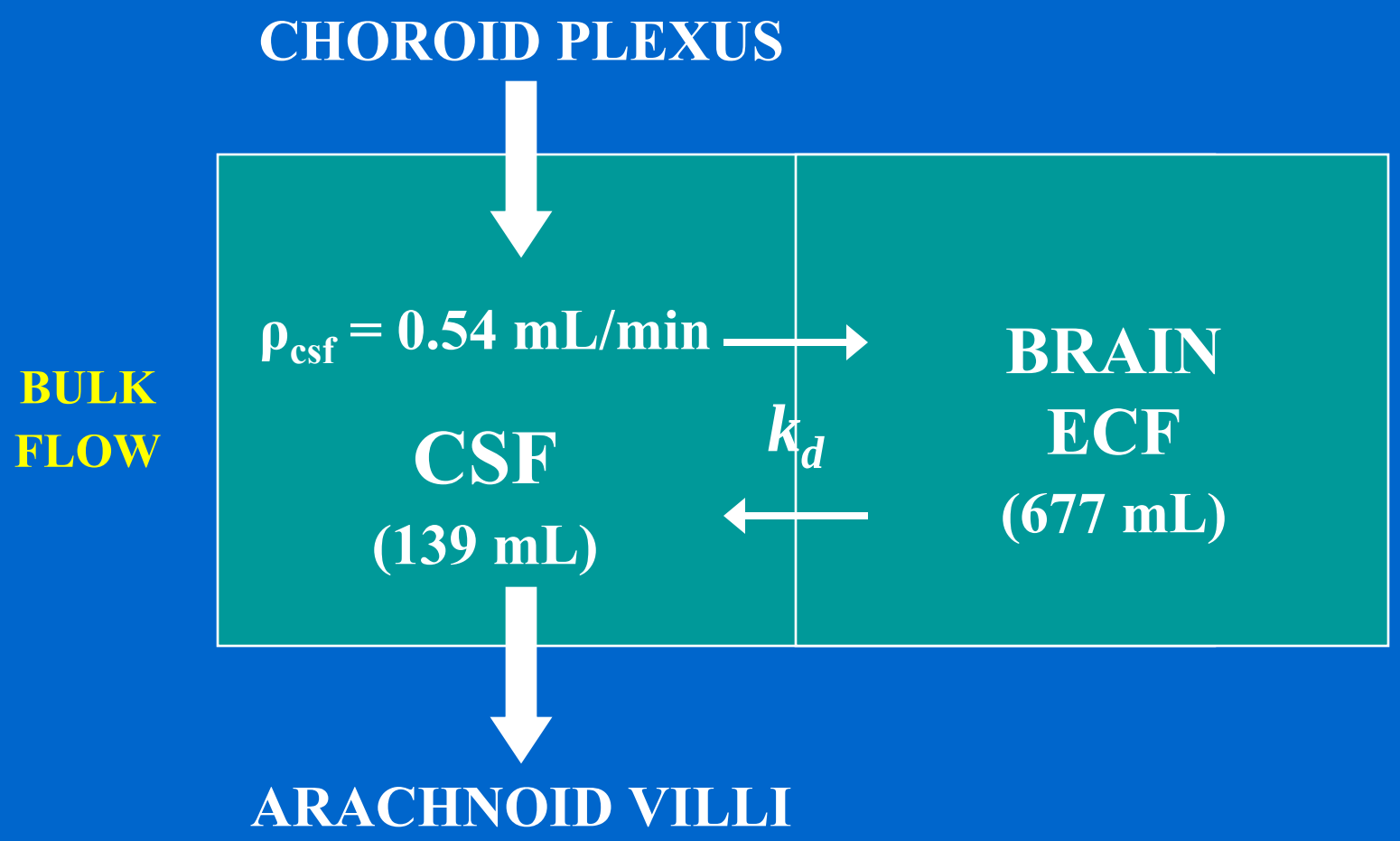
*** Comment by Carl Peck: CDDS WORKSHOP, McLean, VA, May 13, 1998**

INTRATHECAL AMPHOTERICIN B PHARMACOKINETICS



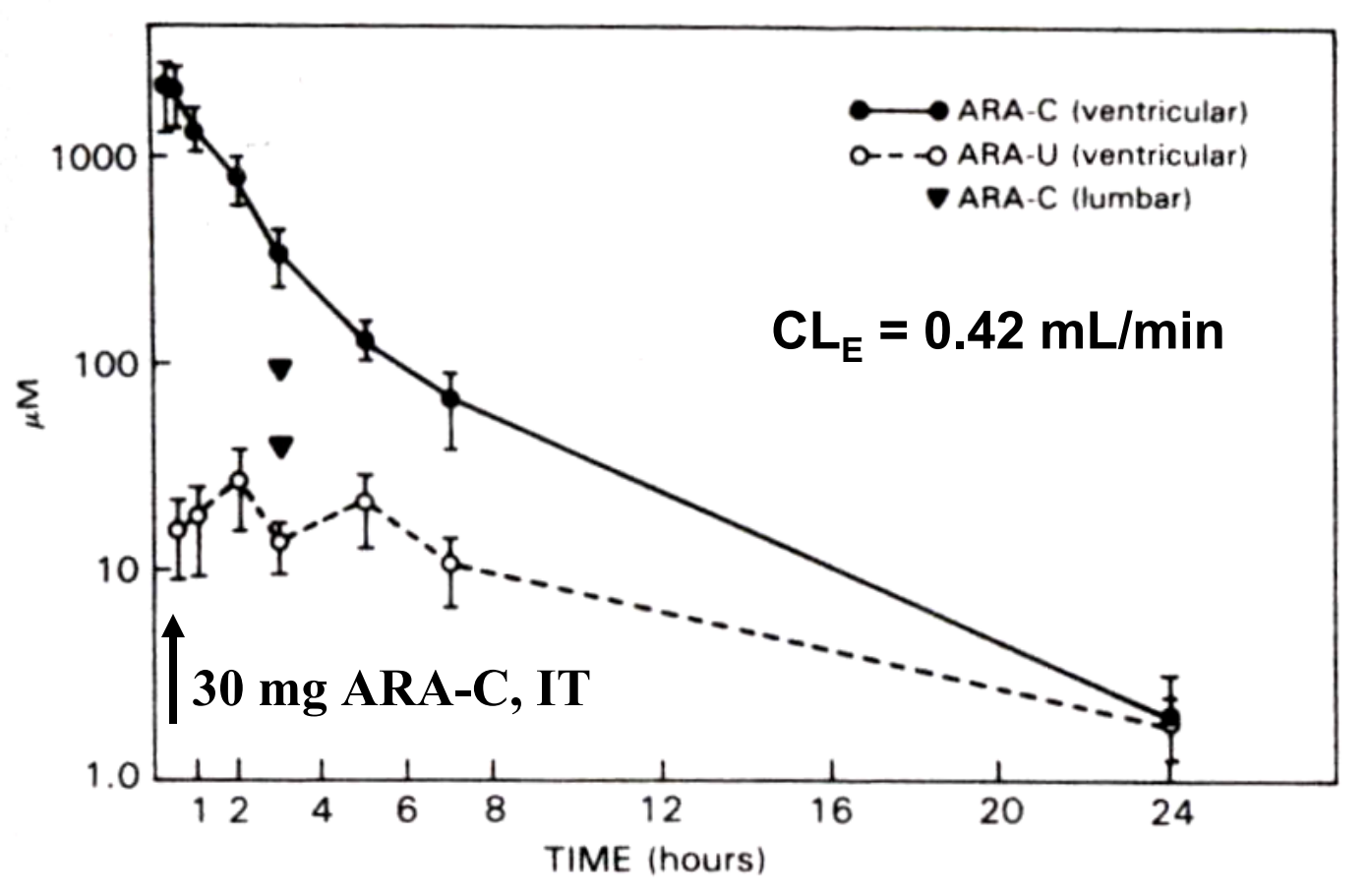
From: Atkinson AJ Jr, Bindschadler DD: Am Rev Resp Dis 1969;99:917-24.

MODEL FOR ANALYZING INTRATHECAL AMPHOTERICIN B PHARMACOKINETICS



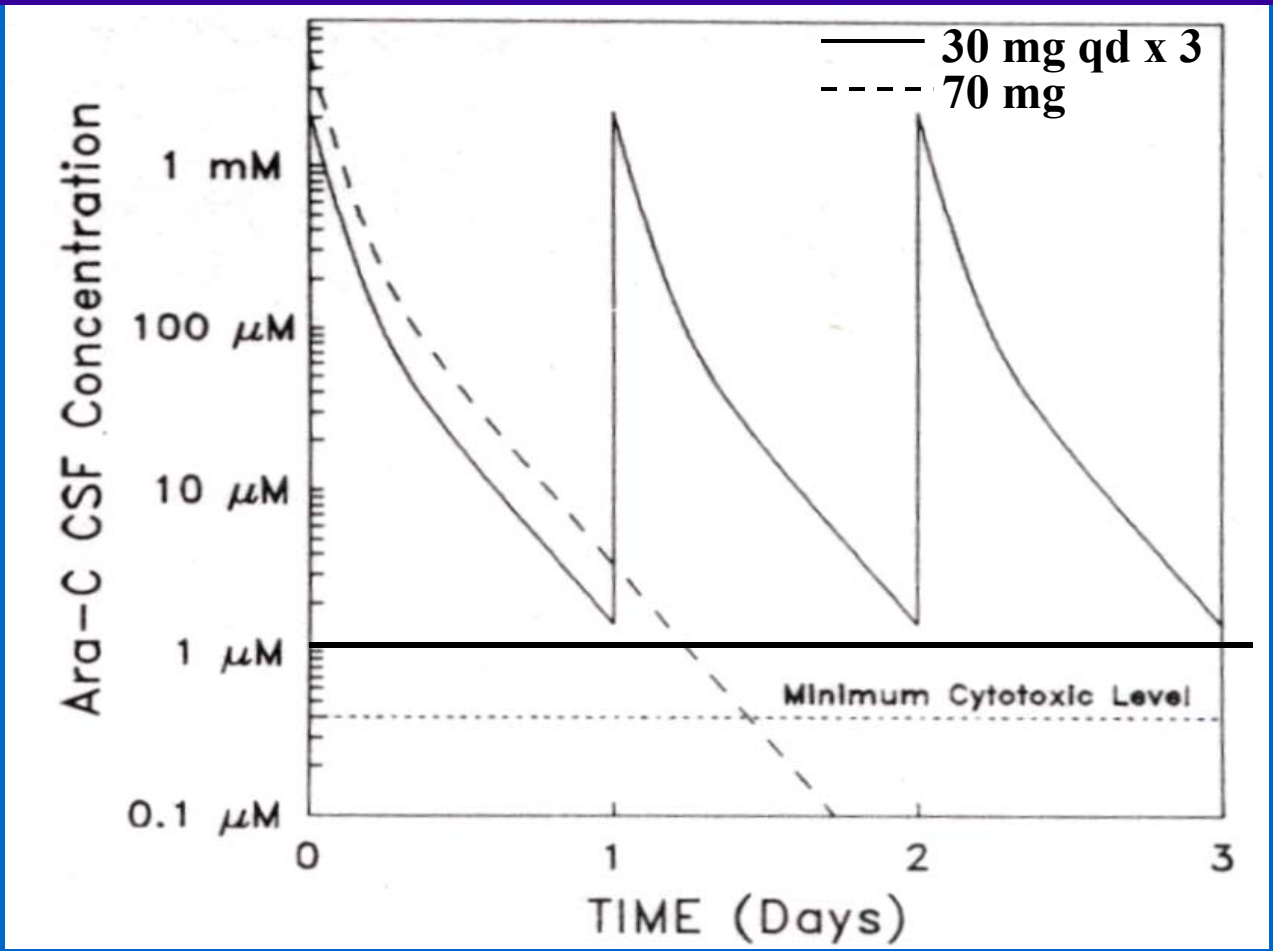
From: Atkinson AJ Jr, Bindschadler DD: Am Rev Resp Dis 1969;99:917-24.

INTRATHECAL CYTARABINE PHARMACOKINETICS



From: Zimm S, Collins JM, Miser J, Chatterji D, Poplack DG: Clin Pharmacol Ther 1984;35:826-30.

SIMULATED CYTARABINE INTRATHECAL DOSE REGIMENS



IN VITRO **EFFECTIVE LEVEL FOR JC VIRUS**

From: Zimm S, Collins JM, Miser J, Chatterji D, Poplack DG: Clin Pharmacol Ther 1984;35:826-30.

"FAILURE" OF IT CYTARABINE IN PML ASSOCIATED WITH HIV INFECTION*

FAILURE OF CYTARABINE IN PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY ASSOCIATED WITH HIV INFECTION

FAILURE OF CYTARABINE IN PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

COLIN D. HALL, M.B., CH.B., URANIA DAFNI, SC.D., DAVID SIMPSON, M.D., DAVID CLIFFORD, M.D., PATRICIA E. WETHERILL, M.D., BRUCE COHEN, M.D., JUSTIN MCARTHUR, M.B., B.S., M.P.H., HARRY HOLLANDER, M.D., CONSTANTIN YAINNOUTSOS, PH.D., EUGENE MAJOR, PH.D., LINDA MILLAR, B.S., JOSEPH TIMPONE, M.D., AND THE AIDS CLINICAL TRIALS GROUP 243 TEAM*

SINCE THE CHOSEN IT DOSE HAD NO POSSIBILITY OF BEING EFFECTIVE, IT IS ERRONEOUS TO CONCLUDE THAT THE DRUG IS INEFFECTIVE.

*** Hall CD, et al. N Engl J Med 1998;338:1345-51.**

GOALS OF CLINICAL DRUG DEVELOPMENT LECTURE

- CURRENT STATE ANALYSIS
- TARGETED APPROACH TO DRUG DEVELOPMENT
- INFORMATION TO BE OBTAINED DURING EACH DEVELOPMENT PHASE
- DECISION MAKING IN DRUG DEVELOPMENT

DECISION MAKING IN DRUG DEVELOPMENT

- GO – NO GO DECSIONS

WHY DRUG DEVELOPMENT FAILS*

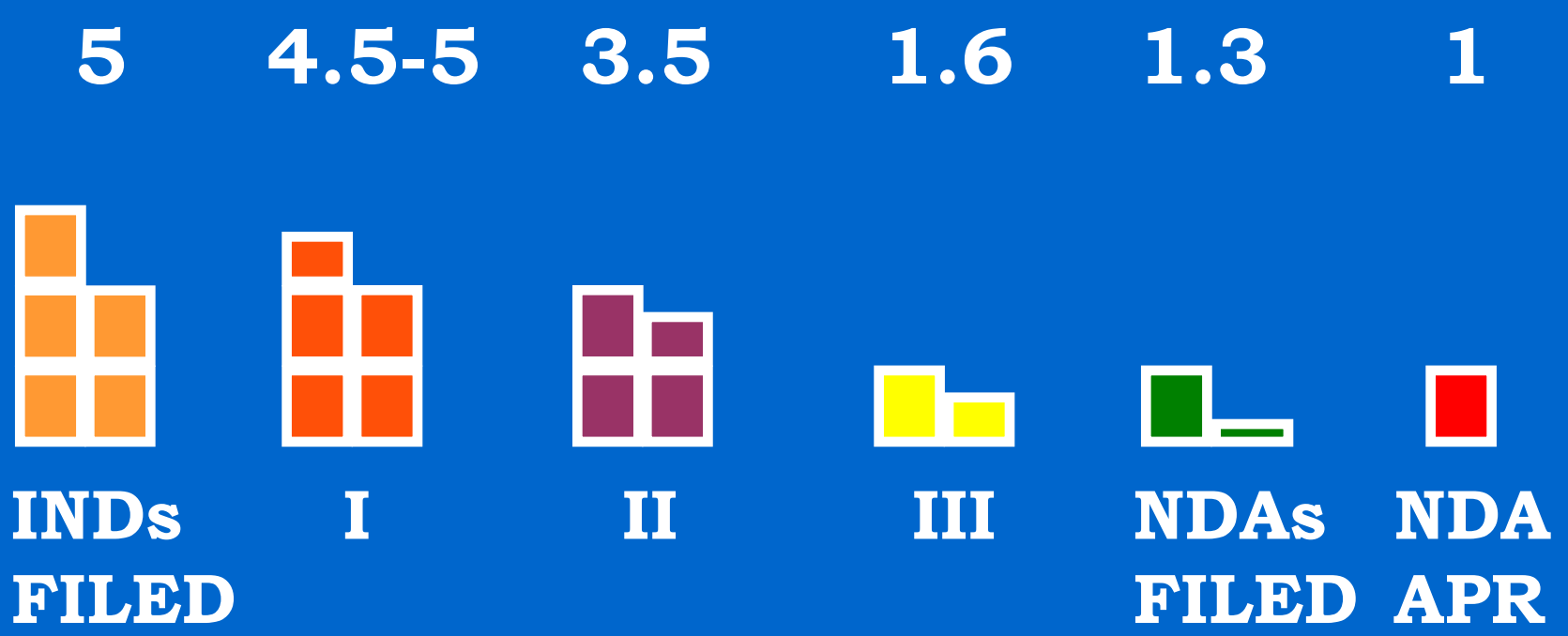
- UNSUITABLE BIOPHARMACEUTICAL PROPERTIES
- UNSUITABLE CLINICAL PK
- PHARMACOLOGY DOESN'T WORK IN HUMANS
- UNEXPECTED TOXICITY IS ENCOUNTERED

* Ronald E. White, Bristol-Myers Squibb (From Good Ligands to Good Drugs, AAPS-NIGMS Symposium, February 19-21, 1998)

GO – NO GO DECISIONS

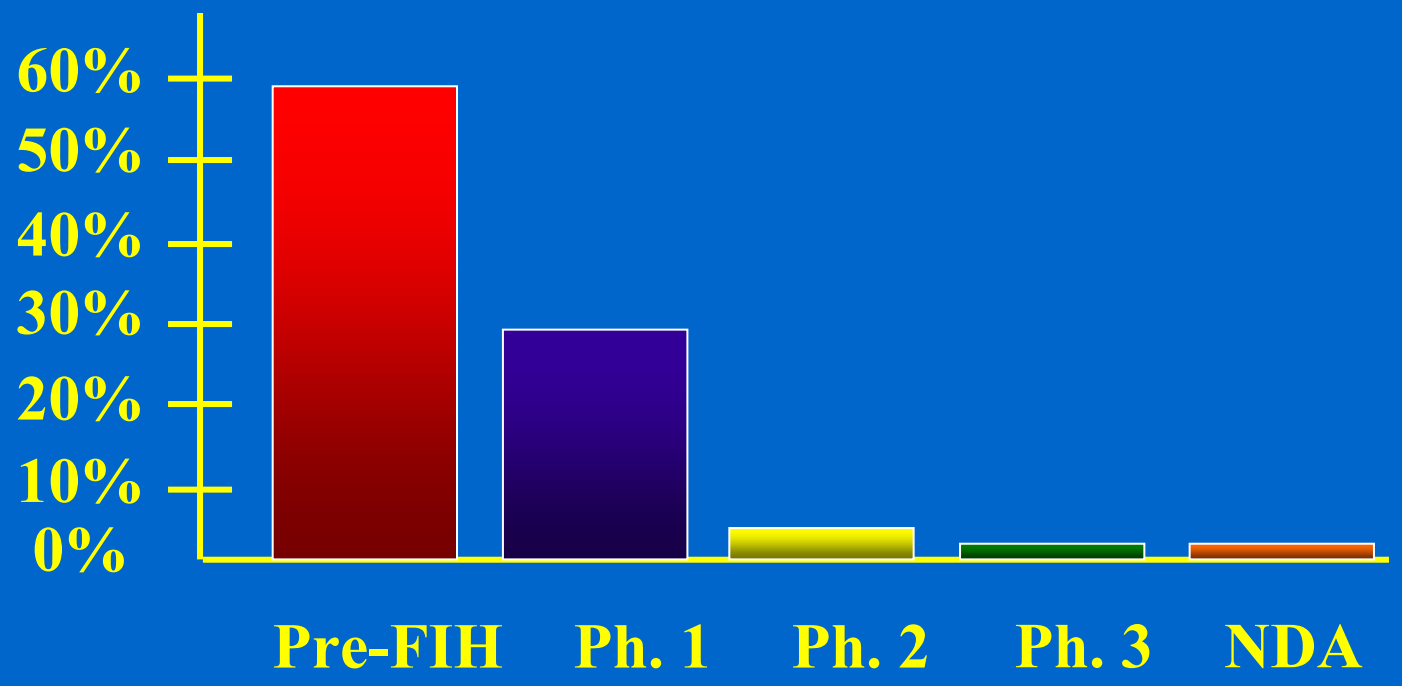
- COMPOUND RICH ENVIRONMENT
  - COMBINATORIAL CHEMISTRY
  - HIGH THROUGHPUT SCREENING
- FAIL EARLY PARADIGM DRIVEN BY CLINCAL DEVELOPMENT COSTS

COMPOUND ATTRITION DURING DRUG DEVELOPMENT*



* Grudzinskas C. Portfolio & Project Planning & Management in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology

IDEAL DISTRIBUTION OF COMPOUND ATTRITION*



* Grudzinskas C. Principles of Clinical Pharmacology Course 2002.

DECISION MAKING IN DRUG DEVELOPMENT

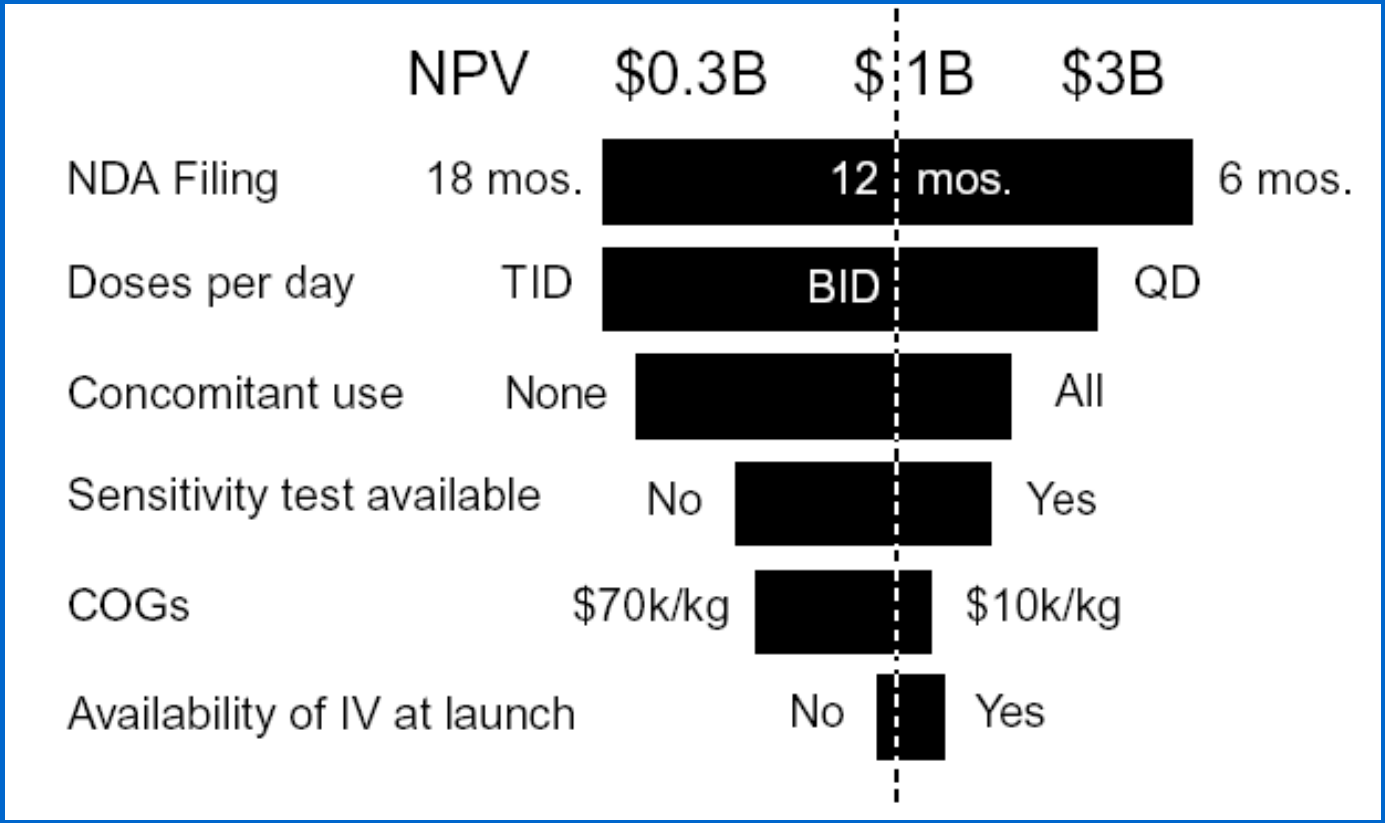
- GO – NO GO DECSIONS
- LESSER IMPACT DECISIONS

THREE MOST IMPORTANT CONSIDERATIONS IN MARKETING*

- DIFFERENTIATION
- DIFFERENTIATION
- DIFFERENTIATION

* Roberto C. Goizueta – 1931 – 1997 (former CEO CocaCola)

SENSITIVITY ANALYSIS FOR A HYPOTHETICAL ANTIBIOTIC



* Grudzinskas C. Portfolio & Project Planning & Management in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology

PHARMACEUTICAL PRODUCT LIFE CYCLE

* Adapted from *Pharmaceutical Executive*, January 2000, page 80

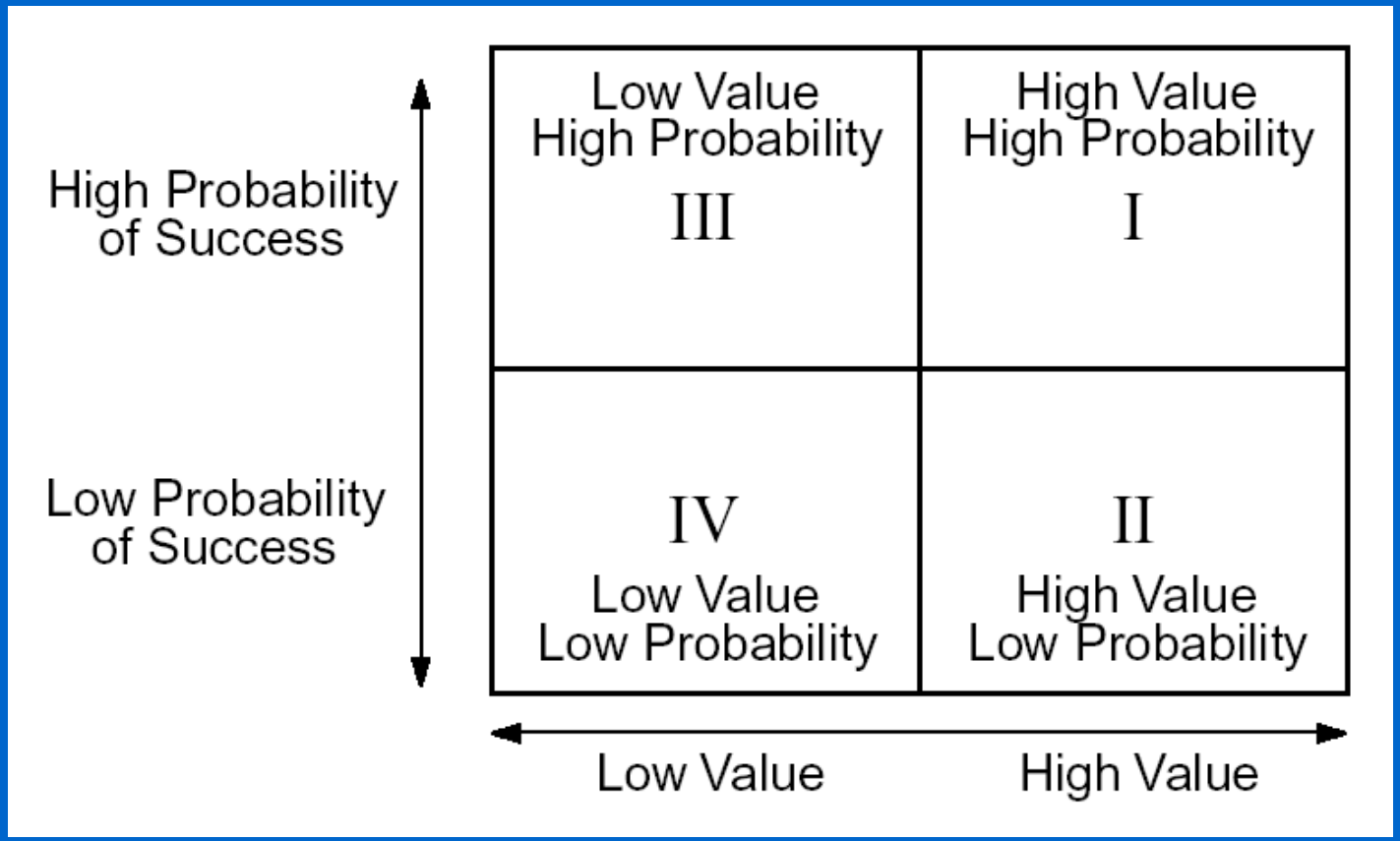
PROLONGING PRODUCT LIFE CYCLE

- POST-MARKETING STRATEGIES
  - DEVELOP NEW INDICATIONS
  - OBTAIN PEDIATRIC LABEL
- PATENT EXPIRATION STRATEGY
  - Rx TO OTC SWITCH
  - FRANCHISE GENERIC

MANAGEMENT CONSIDERATIONS

- PORTFOLIO DESIGN
- MATRIX STRUCTURE
- TIME-RESOURCE TRADE OFFS
- STRATEGIES AND CHALLENGES

PORTFOLIO ANALYSIS



* Grudzinskas C. Portfolio & Project Planning & Management in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology

MANAGEMENT CONSIDERATIONS

MATRIX MANAGEMENT STRUCTURE

PROJECT TEAMS

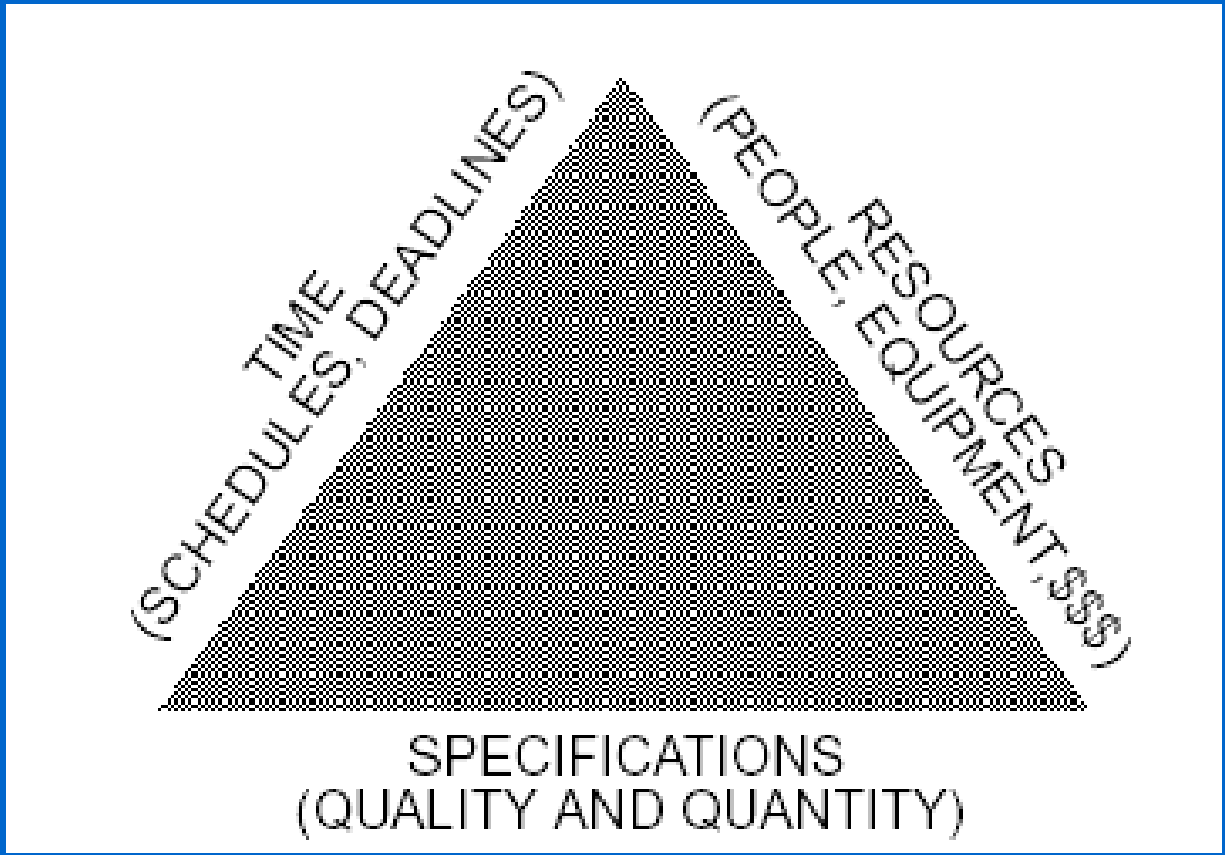
LINE MANAGEMENT

DISCIPLINE	DISCOVERY	TOXICOL.	PK	BIOSTAT.	DATA MGMT.	MEDICAL	REGULATORY	PROJECT MGMT.	MARKETING
PROJECT 1	X	X	X			X	X	X	X
PROJECT 2	X	X	X	X	X	X	X	X	X
PROJECT 3	X	X	X	X	X	X	X	X	X
⋮									
PROJECT N			X	X	X	X	X	X	X

PROJECT TEAM CONSIDERATIONS

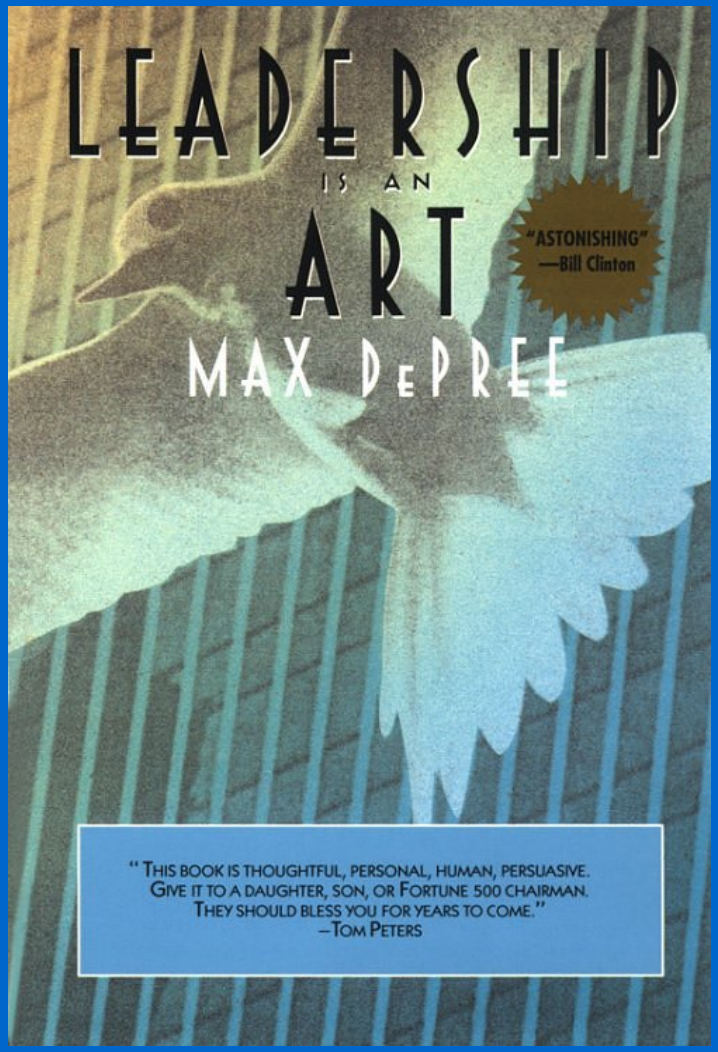
- STAFF QUALITY & CONTINUING EDUCATION
- LEVEL OF PROJECT TEAM AUTONOMY
- INCENTIVIZE EARLY NO-GO DECISIONS
- CO-LOCALIZATION OF TEAMS
- RESOURCE ALLOCATION
  - HEAVYWEIGHT PROJECT TEAMS
  - BUDGET
  - EQUIPMENT

THE PROJECT MANAGEMENT TRIANGLE



*** Grudzinskas C. Portfolio & Project Planning & Management in Atkinson AJ Jr, et al. Principles of Clinical Pharmacology**

SERVANT LEADERSHIP



LEARNING RESOURCES FOR DRUG DEVELOPMENT

- FDA Guidances*
- Courses- NORTHWESTERN, NIH, PERI, CDDS, CSDD, FDLI
- Workshops – DIA, EUFEPS, Commercial
- FDA Advisory Committee Meetings
- FDC Reports "The Pink Sheets"
- Package Inserts

* http://www.fda.gov/cder/guidance/index.htm