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NIH Clinical Pharmacology Series

"Design of clinical drug development programs"

April 17, 2008

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Principal, NDA Partners LLC &

Center for Drug Development Science

UCSF-DC

"Design of clinical drug development programs"?

Conflict of Interest Statement:

* ***NDA Partners LLC***
* ***Board member, Immunomic Therapuetics***
* ***PERI faculty***
* ***American Course in Drug Development and Regulatory Science***
* ***CDDS at UCSF-DC***
* ***SAB Cary Pharmaceuticals***
* ***SDAB Panacos***
* ***Pharmaceutical and biotech stockholder***

Decision points and criteria setting

* Unmet medical need	*(treatment, prevention…)*
* Identification	(*animal pharmacology, virology, immunology)*
* Optimization	*(potency, animal safety, manufacturing, IP)*
* POM	(*Proof of mechanism--IND/FIH)*
* POC	*(Proof of Concept)*
* EOP2*	*(Safe & Effective?)*
* Prepare NDA/BLA	*(Benefit to risk profile)*
* Launch	

*EOP2=End of Phase 2

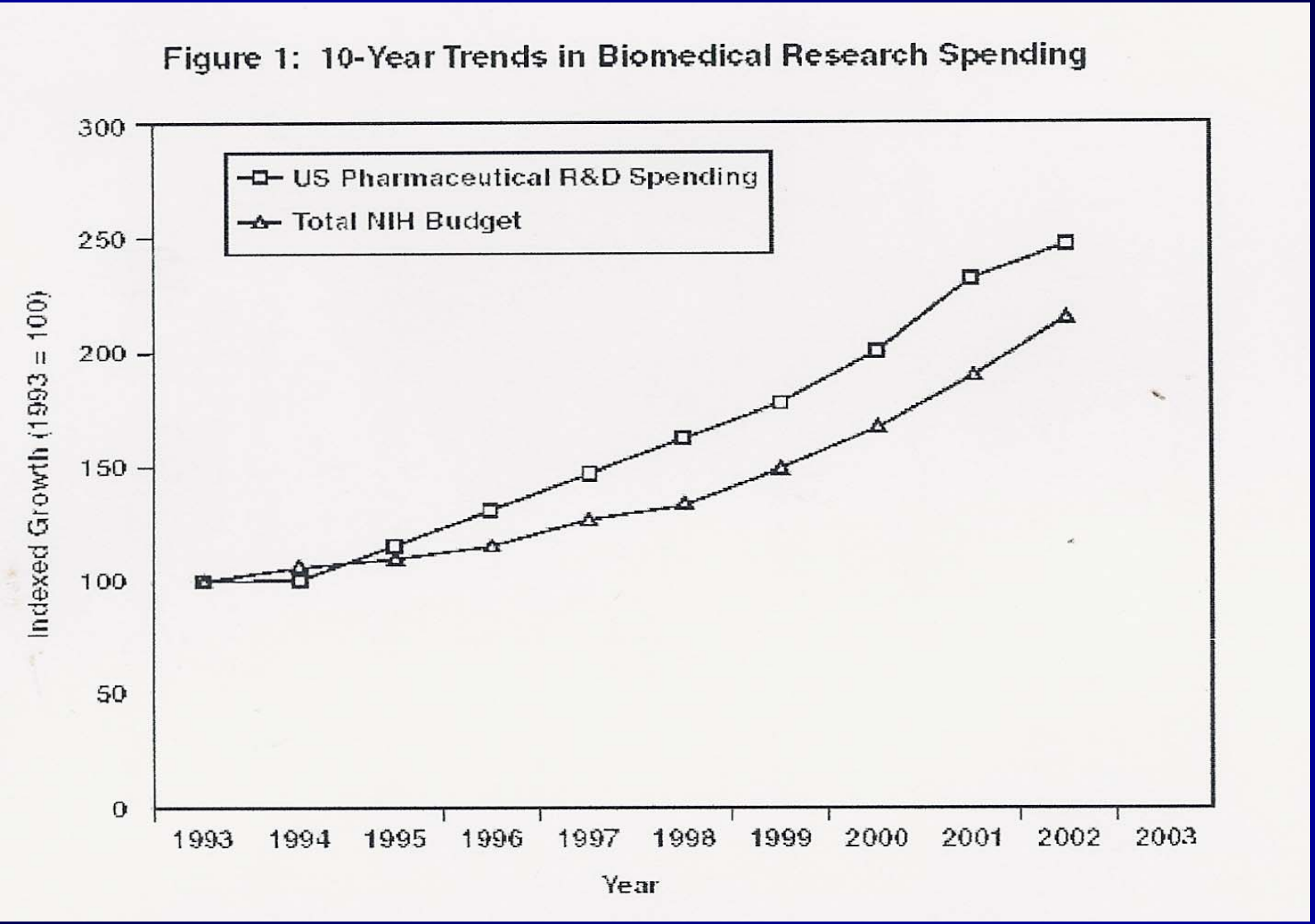
Milestones and criteria setting

Prespecified criteria for advancing or terminating!

* **Identify target** **(hypothesis?)**
* **Characterize target** **(antigen?)**
* **Validate target** **(predictive model?)**
* **Screens (*In vitro* and *in vivo*)** **(predictive?)**
* **Identify lead/analytical methodology**
* **Optimize lead** **(drug; vaccine/adjuvant?)**
* **Assess safety** **(predictive model?)**
* **Assess chemistry/manufacturing/clinical supplies**
* **Benefit-risk ratio (non-clinical)** **(activity vs. safety?)**
* **Define clinical Proof of Concept trial**
* **Prepare file IND** **(reasonably safe?)**
* **FIH (First in human)** **(proof of mechanism?)**
* **POC** **(activity/safety/titer/antibodies?)**

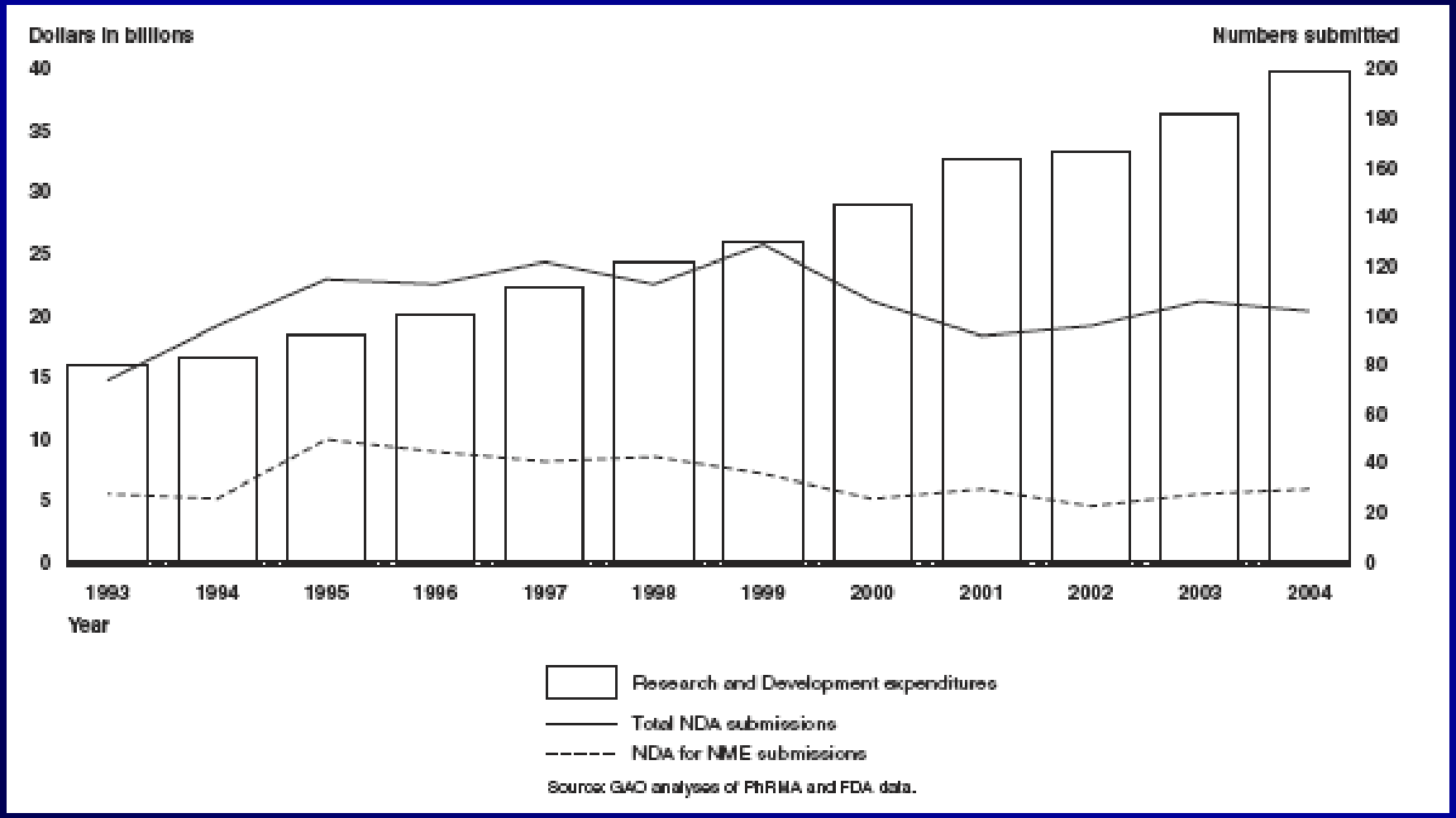
Drug Development Metrics

10 year Trend in Biomedical R&D Spending



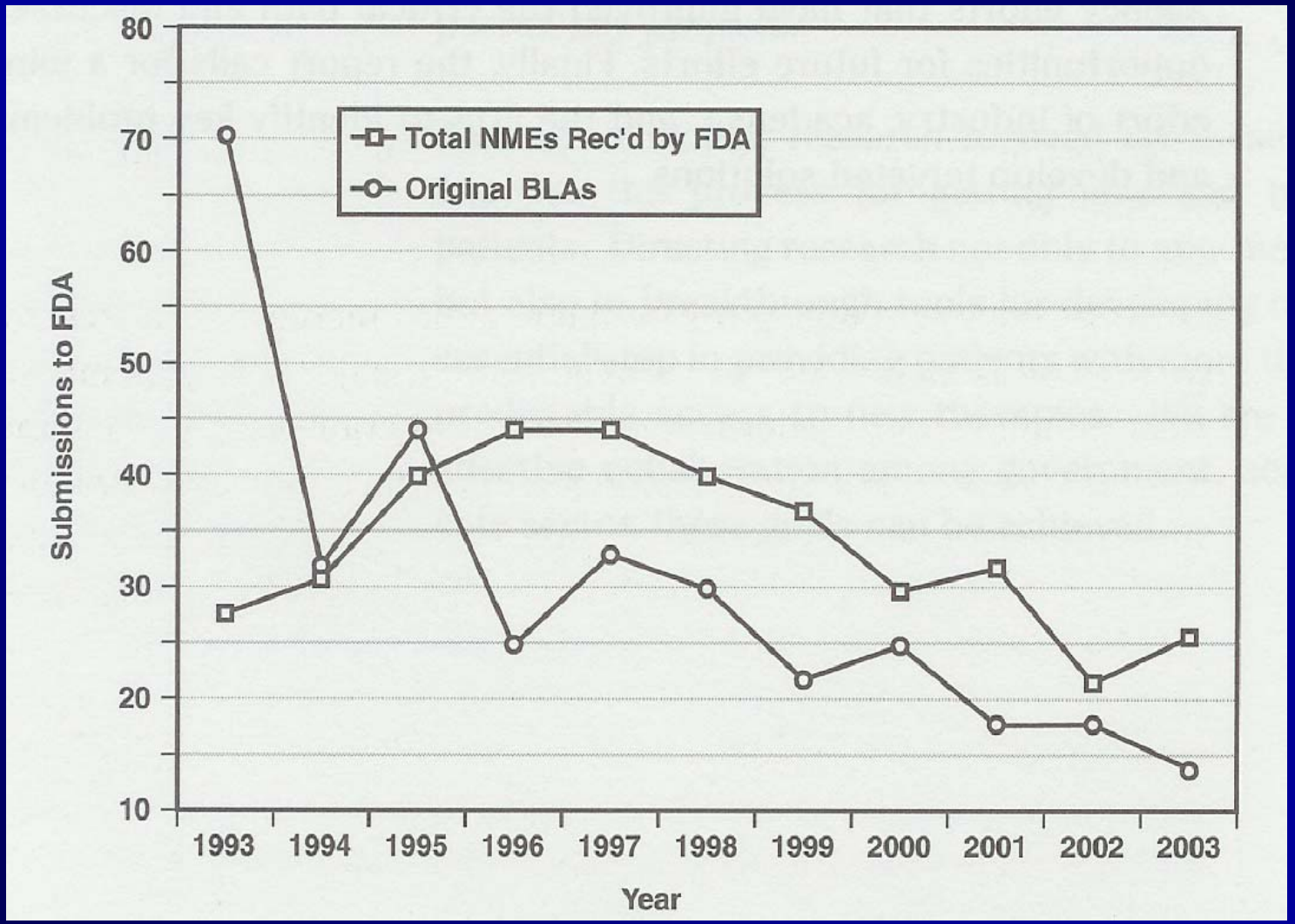
Adapted from J. Cossman: "The Critical Path Institute" 2007 & FDA Critical Path Initiative 2004

Trends in R&D Spending vs. New Drug & Biologic Applications



Source: GAO Analysis of PhRMA and FDA data

10 year Trend in New Applications to FDA



Adapted from J. Cossman: "The Critical Path Institute" 2007 & FDA Critical Path Initiative 2004

Goals of a Clinical **Development** Program

1. Effective, efficient and speedy path to an approved product with the optimal label
2. Core Data Sheet
   - A. CSS, CSE and Integrated Summary of Risks & Benefits and EU/Japan Equivalents
   - B. Clinical Expert Report
   - C. US Package Insert and the SmPC
3. Publications

Where Can We Learn
Label-Driven Clinical Development?

- *Courses-PERI, CDDS, CSDD, DIA, FDLI, NIH, ACDRS, ECPM*
- *FDA Advisory Committee Mtgs.*
- *FDC Reports "The Pink Sheets"*
- *FDC Reports "Pharmaceutical Approvals Monthly"*
- *Analyze Package Inserts*

Clinical Development Programs

* Label-Driven clinical development
* Clinical development program (CDP) metrics
* What is the size of CDP?
* Doing research right: TPP & DPIs
* Help in preparing a CDP
* Learning and Confirming
* Real-time examples

Clinical Development Programs

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There is Enormous Room for Dramatically Reducing the "Uncertainties"

The Uncertainty about Which NCE

- ➔Developability
- ➔Dose & Schedule
- ➔Safe & Effective?
  - ➔Vs. Placebo
  - ➔Vs. Competitor

The Uncertainty about Development Program

- ➔Yield of useful information
  - ➔Internal
  - ➔Regulatory
  - ➔Commercial

The Uncertainty about Market Success

- ➔Demand for various product attributes
- ➔New competitors

Only 1/12 NCEs in development make it to market

2/3 to 5/6 clinical trials produce no useful knowledge

Most drugs fail to meet commercial expectations

Definitions

* PI (Package Insert-the label)
* CSS
  - Combined Summary of Safety (FDA)
* CSE
  - Combined Summary of Effectiveness (FDA)
* EU
  - European Union
* SmPc
  - Summary of Product Characteristics (EU)

Definitions

* TPP
  - Target Product Profile
* TPI
  - Target Package Insert
* DPI
  - Draft Package Insert

Definitions

* Phase 1-4

Drug and Biologic Development Phases

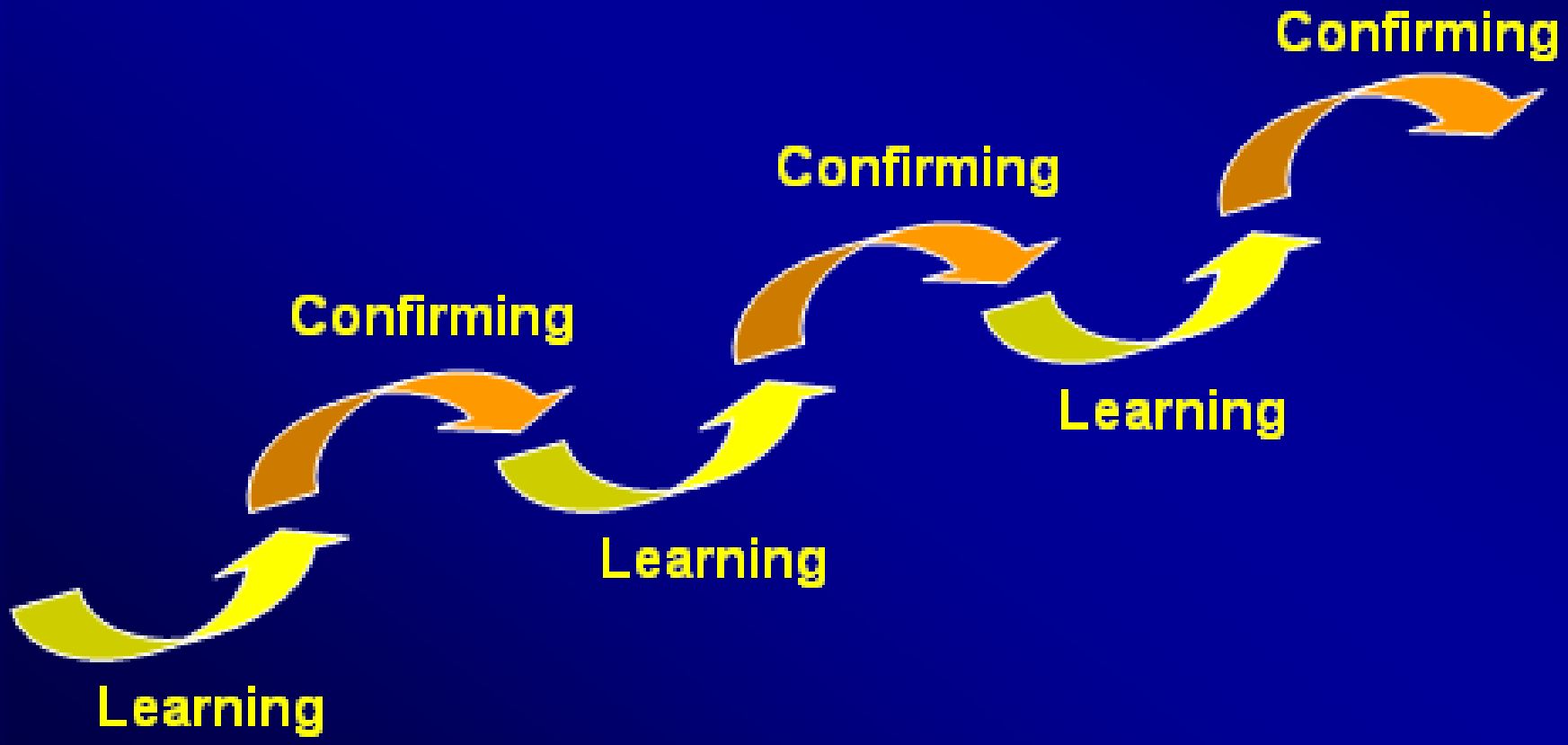
Phase 1	Healthy volunteers Exception: Cancer/AIDS etc.	12 to 24 subjects/ trial	Safety-tolerability; (PoM/Activity?)
Phase 2	Subjects with the illness (narrow pop'n)	24 to 300 subjects/ trial	PoM, PoC, PoP; ID population
Phase 3	Subjects with the illness (broad pop'n)	250 to 1000 subjects/ trial	Confirm efficacy; Assess safety; Extrapolation
Phase 4/5	Special pop'n; Subjects with the illness (broad pop'n)	12 to 1000 subjects/ trial	Add'l safety; DDI; Special pop'n; New indication; New formulation

Learning
&
Confirming

Sheiner, LB. *Learning versus confirming in clinical drug development.* Clinical Pharmacology and Therapeutics, 1997, No. 61, pages 275-291

Learning & Confirming-2

* A cascade of "learning" & "confirming" cycles



L & C Development Program

* Phase 1 *Learning*- Healthy Volunteers
* *Safety & tolerance, PK-ADME, drug-drug interactions*

* Phase 2 *Learning*- Patients
* *PK-ADME & PK-PD in patients*

* Phase 3 *Confirming*- Patients
* *Evidence of safety*
* *Evidence of effectiveness*

* Phase 4 *L & C*
* *Market expansion & life-cycle management*

Phase 1: Learning
In Healthy Volunteers

* Safety & tolerance, PK-ADME, drug-drug interactions
  - *Single dose: healthy ?*
  - *Multiple dose: healthy ?*
  - *PK-ADME with food, age, gender, disease state*
  - *PK in liver, renal, etc.*

Phase 2: Learning
In Patients

* PK-ADME & PK-PD in patients
  - *Dose-exposure-response in tumor A*
  - *Dose-exposure-response in tumor B*
  - *Use in combinations*

Purpose of "Phase 2"

* *Proof of Concept (activity)*
  - *Patient identification*
  - *Dose*
    + *Exposure-response-relationship*
  - *Dose frequency*
  - *Dose duration*

Phase 3: Confirming
In Patients

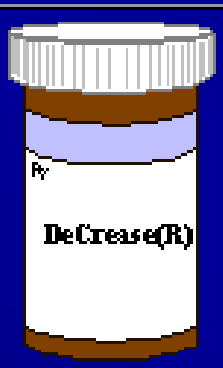
* Evidence of safety and effectiveness
  - *Pivotal trial(s)*
  - *Long-term safety*

Phase 4: Learning & Confirming

* Market expansion & life-cycle management
  - *New indications*
  - *Pharmacovigilance*
  - *New formulations*
  - *Combinations*
  - *New regimens*

Why Label-Driven Clinical Development?

* One way to remember the "label-driven question-based" concept is to think:
* "We Sell Only the Package Insert,



Why Label-Driven Clinical Development?

* One way to remember the "label-driven question-based" concept is to think:
* "We Sell Only the Package Insert,
* We Give Away the Product !"

What is Drug Discovery, Development & Review?

* ***Drug Discovery & Development*** *is the integration of the many disciplines, including:*
* *basic research*
* *non-clinical development*
* *clinical development*
* *pharmacometrics*
* *regulatory*
* *marketing*

What is Drug Development & Review?

* *identify*
* *evaluate*
* *develop*
* *achieve regulatory approval*
* *successful launch*

for the successful marketing of new chemical entities (NCEs) and new biological entities (NBEs).

What is Drug Development & Review?

* ***Regulatory Review*** *is…* *the integration of many disciplines, including*
* *pharmacology*
* *non-clinical*
* *clinical*
* *pharmacometrics*
* *biostat*
* *regulatory & DDMAC*

What is Drug Development & Review?

* *...to determine whether there is:*
* *adequate knowledge about the new NME/NBE*
* *to make an informed evaluation about the benefit to risk profile...*

What is Drug Development & Review?

* *...to decide whether the product should be:*
* *approved for marketing, and*
* *for which segments of the population*

What are the Critical Clinical Development Decision Points?

* In order to put the drug development and review decisions in context, we need to recognize that the product we are producing...

Knowledge

* *…knowledge and the information about our product that will allow a health care professional to decide:*

End of Phase 2 Criteria

* For whom? - Is this drug appropriate for treating this patient, and...
* ...what dose is needed?
* ...how often (interval) will we need to take the drug?
* ...for how long will we need to take the drug?

Time & Dose

* *...what is the right time(s) of day for dosing?*
* *...do we use the same dose for different levels of disease progression?*

Age and Gender

* *...will we need to adjust the dose in children or the elderly?*
* *...is there any gender effect?*

Side Effect and "Avoid"

* *...what kinds of side-effects can be expected?*
* *...are the side-effects reversible?*
* *...are there any patients who should not take this drug?*

*Effect of **Other** Drugs on Our Drug?*

* *...are there any other drugs that are not compatible with this drug?*
* *...will some individuals metabolize the drug differently and have drug-drug interactions?*

*Effect of **Our** Drugs on Other Drug?*

* *...will our drug change the metabolism of drugs that patient is already taking?*
  - *Increase blood levels?*
  - *Reduce blood levels?*

Free vs. Bound Drug

* *...is the drug highly protein bound? Will other drugs compete and increase this drug's blood levels or will this drug compete and raise blood levels of another drug the patient is taking?*

Adherence & Persistence (Compliance)

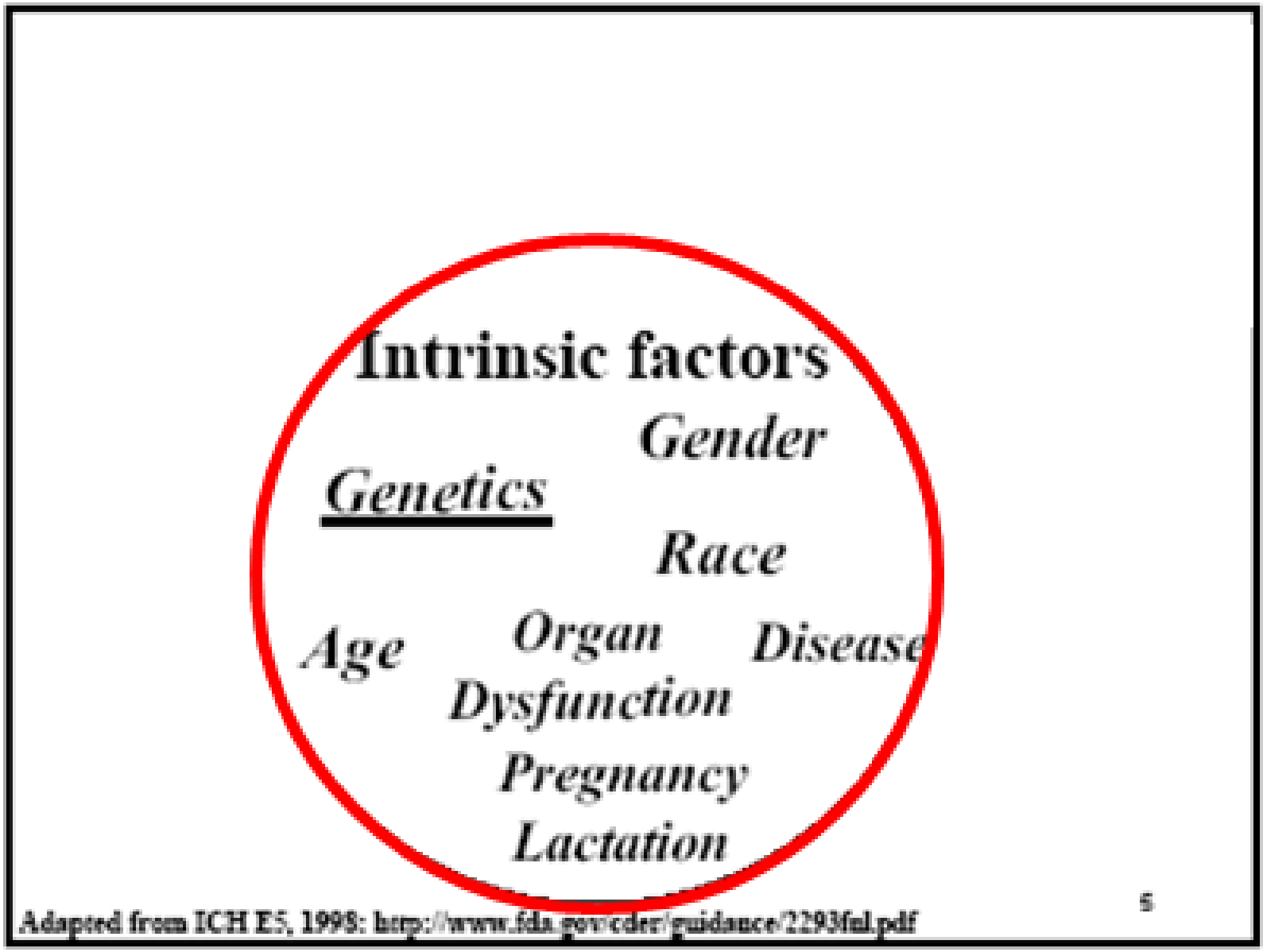
* *…what happens when the patient suddenly stops taking the drug (or misses a few doses)? Is there a rebound?*

Dependence?

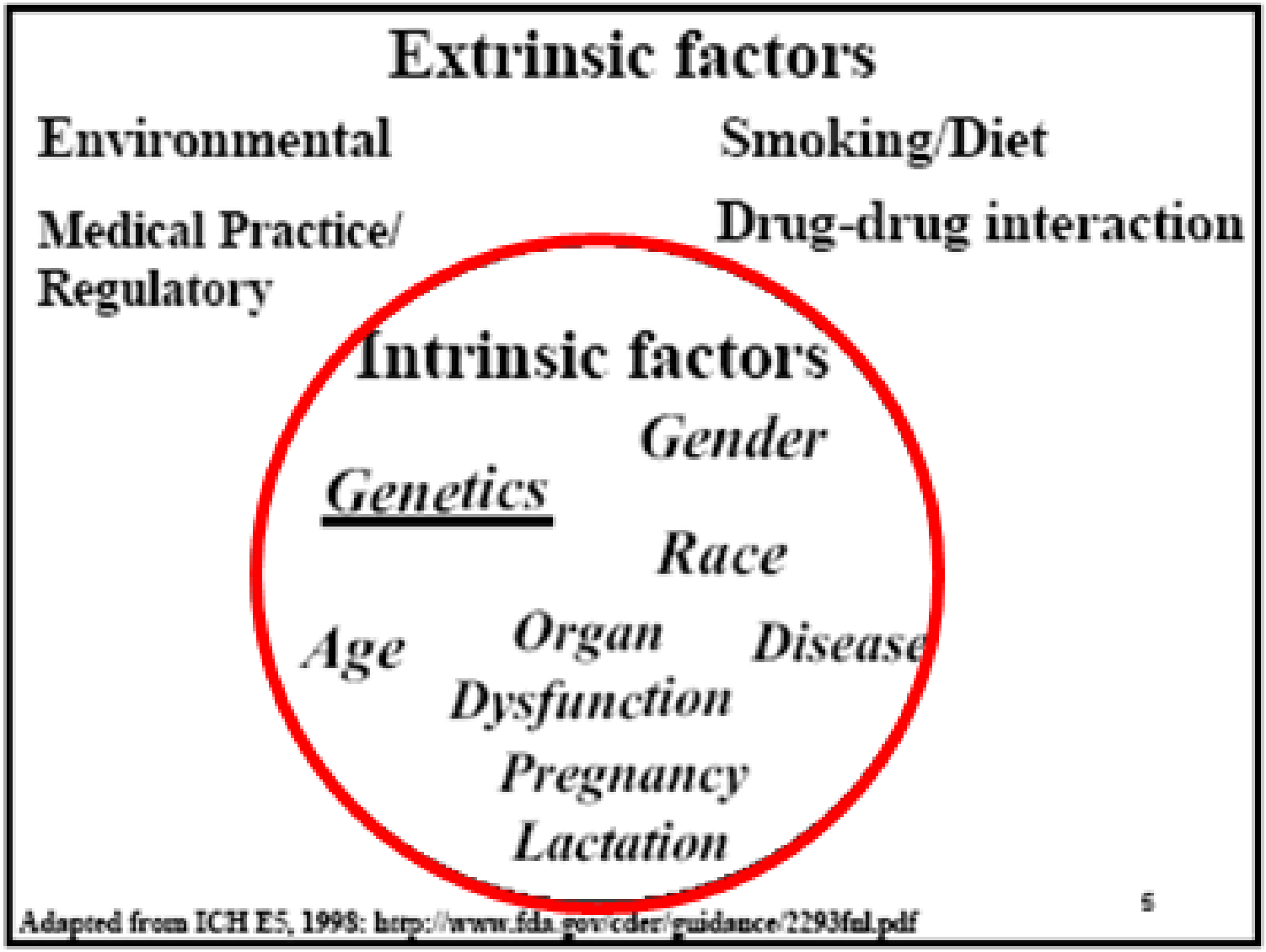
* *...is the drug associated with "liking" or dependence?*
  - *What level of dependence?*
  - *How well liked?*
    + *Do subject "lose" their clinical supplies?*

Individualized Dosing

* *...will we need to adjust the dose of our drug in renal and hepatic insufficiency?*
* *...will there be any food effect upon the blood levels of our drug?*



Shiew-Mei Huang, FDA/Johns Hopkins/PhRMA Workshop on "Drug Metabolizing Enzymes and Pharmacogenomics Testing, September 13, 2004, Rockville, MD



Shiew-Mei Huang, FDA/Johns Hopkins/PhRMA Workshop on "Drug Metabolizing Enzymes and Pharmacogenomics Testing, September 13, 2004, Rockville, MD

How to Save $1,700 Per Month or More on Lapatinib ...

“The Value Meal”

Tykerb® (lapatinib) + 

http://jco.ascopubs.org/cgi/content/full/25/23/3397

The Value Meal: How to Save $1,700 Per Month or More on Lapatinib ...

* ***"… the bioavailability of lapatinib is greatly increased by food, especially a high-fat meal.***
* **A randomized, cross-over, food-effect study demonstrated that both peak concentration and area under the concentration–time curve were increased markedly when a single 1,500-mg dose of lapatinib was taken with food as opposed to when fasting, and was increased further by a high-fat meal.**
* ***The (geometric) mean increase for the area under the concentration–time curve was 167% for low-fat meals and 325% for high-fat meals."***

http://jco.ascopubs.org/cgi/content/full/25/23/3397

The Value Meal: How to Save $1,700 Per Month or More on Lapatinib ...

* ***"At the current price of $2,900 per month, a cost savings of 60% or $1,740 per month would be realized if the drug were taken with food.***
* If one were so inclined, there are also opportunities for additional cost savings through dietary modification. The package insert notes that strong CYP3A inhibitors, including grapefruit juice, "may also increase plasma concentrations." Thus, it is possible that one 250-mg lapatinib pill, accompanied by food and washed down ***with a glass of grapefruit juice***, may yield plasma concentrations comparable to five 250-mg pills on an empty stomach, which would result in a total cost savings of 80% (minus the cost of the food and juice). As a separate issue, the lapatinib label also notes that dividing the daily dose results in a doubling of drug exposure, which would be another approach that may allow a reduction in the number of daily pills (and costs)."

http://jco.ascopubs.org/cgi/content/full/25/23/3397

Is the Drug from Heaven or from Hell?

* *...if the dose of the drug is doubled, will the blood levels also double? (what if they triple?, or what if they only increase by 50%--or less?)*

Short list for CRITICAL clinical development goals

EOP2

* Population?
  - Mild, moderate, severe?
  - Px, Tx or Cure?
* Dose? (How much drug?)
* Frequency? (qd/bid, 1x wk)?
* How long?
  - A single dose, for 10-days, or forever?

What are the Critical Clinical Development Decision Points?

* *Congratulations*
* *You have just completed an introduction to a "Question-Based Label Driven" Clinical Development Plan.*

Drug Development & Review Stages

* *The key decisions in drug development & review include:*
* *Candidate selection*
* *FIH dose*
* *Dose*
* *Dose interval (regimen)*
* *Patient populations*

Clinical Development Programs

* Label-Driven clinical development
* Clinical development program (CDP) metrics
* What is the size of CDP?
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Differentiation

* "Differentiation" could be a better effectiveness profile, a better safety profile (the COX-2 inhibitors are a good example of this), better patient compliance,...

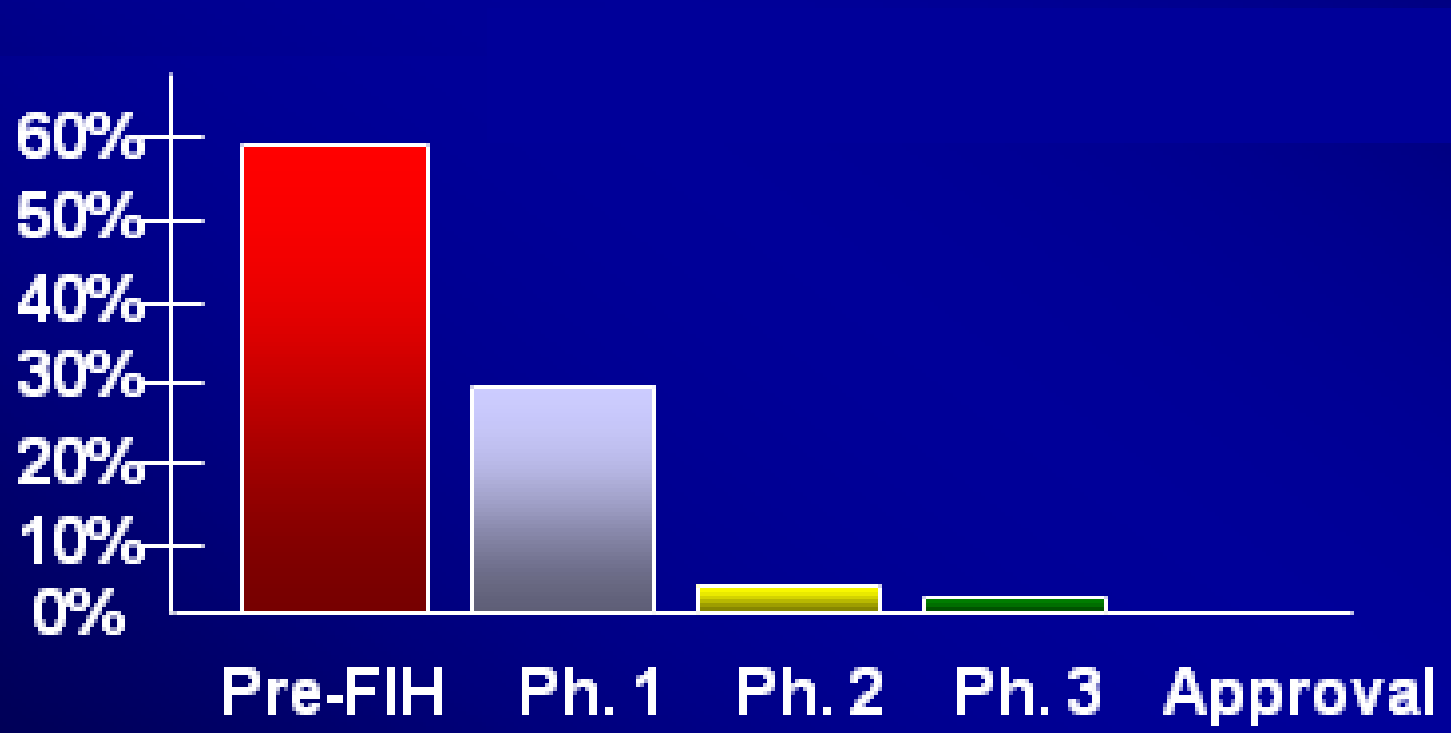
Differentiation

* *... or an easier to use formulation (e.g., oral or inhaled insulin vs. injected insulin).*

Decisions--Fail Early

* The intend here is to conduct the "killer experiments" early in order to identify as soon as possible projects that normally would be failing later in the clinical development process.

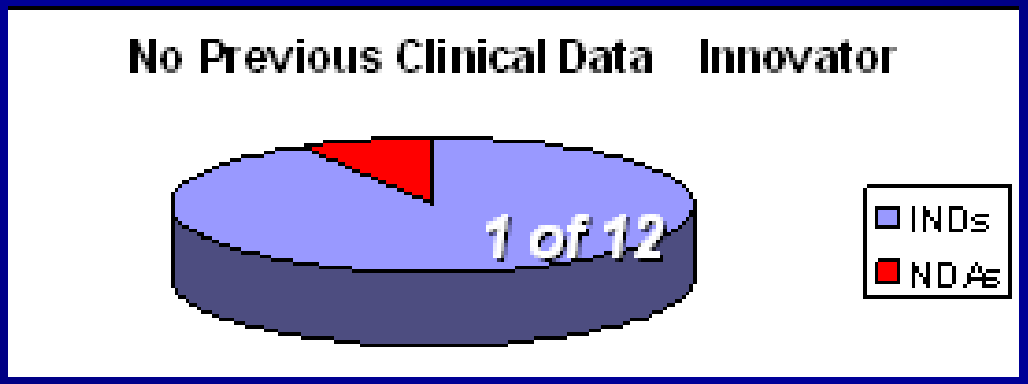
Impact of Established ***Decision Criteria*** *(Management of the failures)*



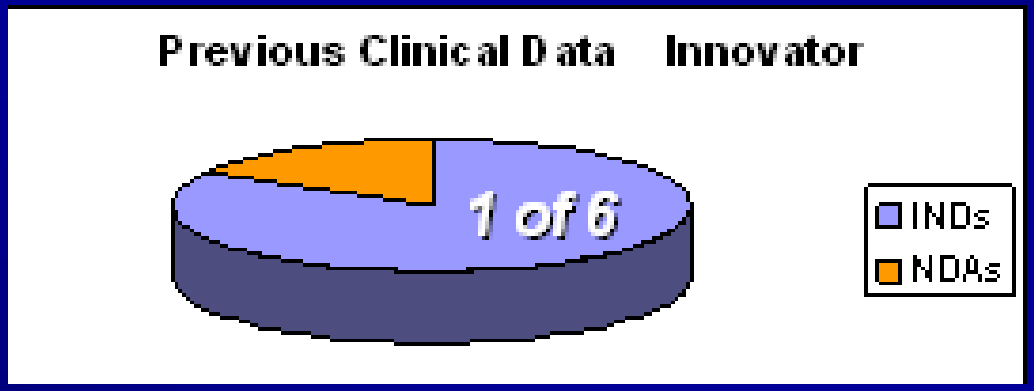
What are the Critical Drug Development & Review Decision Points?

* One way to remember the "label driven" concept is to think:
* "We Sell Only the Package Insert,
* We ...

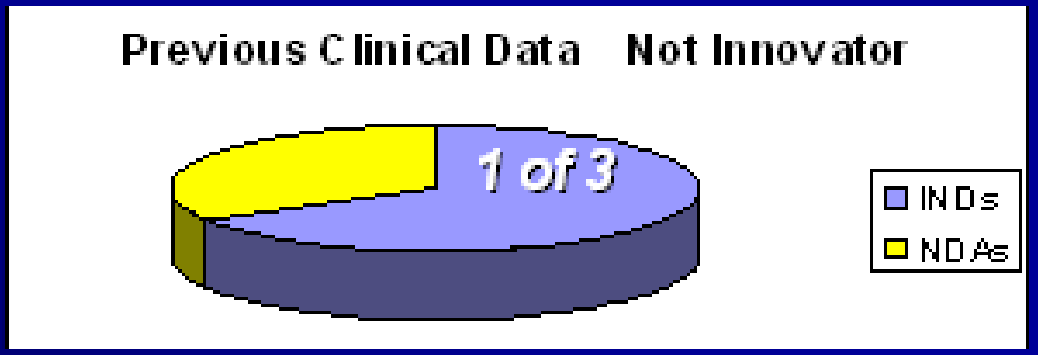
The Current Success Rates for US IND to NDA: There is Enormous Room for Improvement



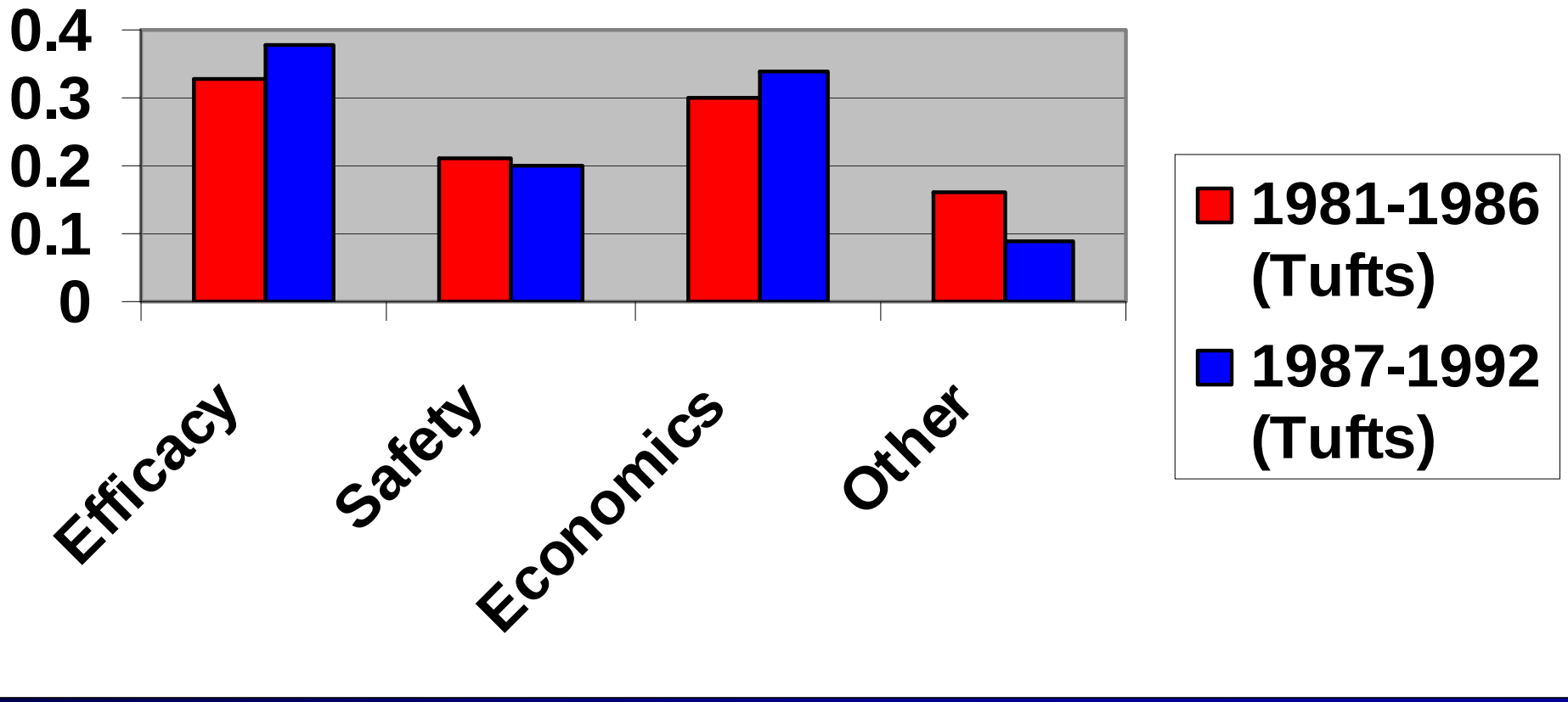
J. DiMasi (Tufts)
Clinical Pharmacology & Therapeutics
May 2001



Will your probability of success be 1 of 12, or 1 of 3?



Reasons for IND Terminations



J. DiMasi, *Clinical Pharmacology & Therapeutics*, page 297, May 2001

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Size of Clinical Programs

Drug FIH-NDA		Ph 1	Ph1 subj	Ph 2	Ph2 subj	Ph 3	Ph3 subj	Total trial	Total subj
Herceptin 6-10 yrs.	Breast Cancer	3	48	6	532	1	489	10	1069
Enbrel 6-7 yrs.	RA	8	163	3	503	23	1381	34	2048
Relenza 4-5 yrs.	Flu	18	446	7	3275	3	1588	28	5309
Viagra 5 yrs.	ED	42	905	13	498	13	4679	68	6082
Vioxx 4-5 yrs	OA Pain	31	940	2	1855	13	5733	46	8528

Prepared with data from CDDS fellows using FDA web site

Herceptin Clinical Trials

Study#	Phase	Regimen	#pts	Indication	Accrual Status
H0407g	1	Single dose 10,50,100,250,500mg	16	met. cancer Her2(1-3+)	closed
H0452g	1	Weekly dosing 10,50,100,250,500mg plus MTP	17	met.cancer Her2(1-3+)	closed
H0453g	1	Weekly dosing 10,50,100,250,500mg plus Cisplatin 100mg/m^2 plus MTP	15	met. cancer Her2(1-3+)	closed
H0551g	2	Weekly dosing 250mg LD, 100mg MD plus MTP	46	met. breast ca Her2(2-3+)	closed
H0552g	2	Weekly dosing 250mg LD, 100mg MD plus Cisplatin 75mg/m^2 plus MTP	39	met. breast ca Her2(2-3+)	closed

MTP = Maintenance Treatment program. Allows the patient to continue to receive Herceptin until progressive disease (PD)

Herceptin Clinical Trials (continued)

Study#	Phase	Regimen	#pts	Indication	Accrual Status
H0648g Pivotal	3	Weekly dosing 4 mg/kg LD, 2 mg/kg MD Plus AC or Paclitaxel vs chemo alone, May go to H0659g at PD	469	met. breast ca Her2(2-3+)	closed (FDA Rev)
H0649g	2	Weekly dosing 4 mg/kg LD, 2 mg/kg MD plus at PD 2 or 4 mg/kg ± chemo	222	met. breast ca Her2(2-3+)	closed (FDA Rev)
H0650g	2	Weekly dosing 4 mg/kg LD, 2 mg/kg MD or 8 mg/kg LD, 4 mg/kg MD	62	met. breast ca Her2(2-3+)	ongoing
H0659g ext. to H0648g	2	Weekly dosing 4 mg/kg LD, 2 mg/kg MD ± antitumor therapy	157	met. breast ca Her2(2-3+)	ongoing (FDA Rev)
H0693g	2	Weekly dosing 4 mg/kg LD, 2 mg/kg MD ± antitumor therapy	163	met. breast ca Her2(any test)	ongoing

What are the Critical Drug Development & Review Decision Points?

* *"Question-Based Label Driven" Drug Development Plans are now being used to guide the drug development and review process.*
* *A well designed drug development plan starts with the questions to be answered.*

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What are the Critical Drug Development & Review Decision Points?

* *Remember that part about "drug development **&** review?"*
* *Recently Dr. Lesko at the FDA published an article in the "Journal of Applied Clinical Trials" in June 1999 on "Question Based Reviews."*

Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

DRAFT GUIDANCE

March 2007
Procedural

TPP, TPI & DPI

* *TPP = Target Product Profile*
* *TPI = Target Package Insert*
* *DPI = Draft Package Insert*

Target Product Profile

"A Target Product Profile (TPP) is a document, prepared by the sponsor, to facilitate clinical drug development and enhance constructive dialogue between the sponsor and reviewing Division at the Food and Drug Administration (FDA). A TPP is written and updated during the investigational phases of development in order to capture the goals of clinical drug development as statements of proposed claims for a prescription drug or biologic product. In the TPP, each proposed claim should be annotated to the specific study or other source of data that is intended to support the key sections and statements in the TPP.

FDA-PhRMA Whitepaper (Published June 24, 2004) www.fda.gov/cder/tpi/default.htm

TPI-Target Package Insert

* **Target Package Insert (TPI)**
  + The ultimate product
    - Drug, biologic, device, diagnostic, etc.)
  + Evidence:
    - Safe
    - Effective
* **“We give away the product,**
* **We sell the package insert”**

TPP

* **Indications**
* **Differentiation for *effectiveness***
  - ***Optimal***
  - ***Threshold***
  - **Differentiation in the labeling (PI)**
  - **Differentiation targets?**

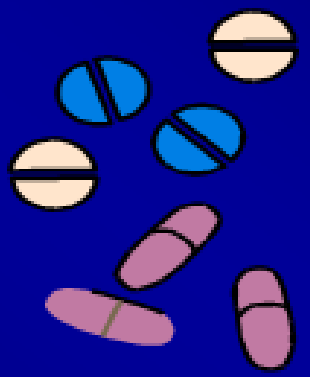
+ Animal studies

+ Human clinical trials

(PI = Package Insert)

TPP-Nerve Gas Prophylactic

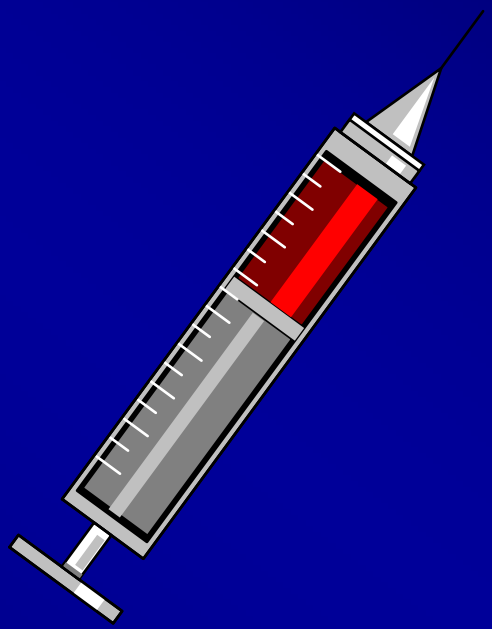
* A prophylactic treatment that is effectiveness against a nerve gas attack
  - Effective in reducing the incidence of death associated with nerve gas
    + By how much?
    + For how long?
  - Orally active? Transdermal patch?



TPP-Nerve Gas Treatment

+ A post-exposure treatment that is effectiveness against a nerve gas attack

- **Effective in arresting seizures associated with nerve gas**
  * **By how much?**
  * **How rapidly?**
  * **For how long?**



TPP

* Effectiveness in clinical trials
  - Versus leading competitor?
  - Threshold
  - Superiority or Non-inferiority?
* Subpopulations
  - Optimal
  - Threshold
* Time to onset of activity
  - Prevention, Treatment, Cure…
* Durability

Decision points and criteria setting

* **Unmet medical need**	***(treatment, prevention…)***
* **Identification**	**(*animal pharmacology, virology, immunology)***
* **Optimization**	***(potency, animal safety, manufacturing, IP)***
* **POM**	**(*Proof of mechanism--IND/FIH)***
* **POC**	***(Proof of Concept)***
* **EOP2***	***(Safe & Effective?)***
* **Prepare NDA/BLA**	***(Benefit to risk)***
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***EOP2=End of Phase 2**

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Prespecified criteria for advancing or terminating!

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The Most Valuable Resource

* *FDA Guidances*
* *FDA Guidance page:*
* *http://www.fda.gov/cder/guidance*

* Acceptance of Foreign Clinical **Studies** [HTML] or [PDF] (Posted 3/12/2001)
* Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of **Rheumatoid Arthritis (RA)** (Issued 1/1999, Posted 2/16/1999) [HTML] or [PDF]

* *Clinical Evaluation of Hypnotic Drugs (Issued 9/77, Posted 3/2/1998)*
* *Clinical Evaluation of Psychoactive Drugs in Infants and Children (Posted 3/2/1998)*

* *DRAFT--Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the **Treatment of Osteoarthritis** [Word] or [PDF] (Issued 7/07/1999, Posted 7/14/1999)*
* *DRAFT--Systemic Lupus **Erythematosus** --Developing Drugs for Treatment [HTML] or [Word] or [PDF] (Issued 3/28/2005, Posted 3/28/2005)*

FDA Cancer Endpoints Guidance

Guidance for Industry

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2007
Clinical/Medical

http://www.fda.gov/cder/Guidance/7478fnl.pdf

FDA Cancer Endpoints Guidance

http://www.fda.gov/cder/Guidance/7478fnl.pdf

FDA Cancer Endpoints Guidance

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Clinical Development Programs

* Label-Driven clinical development
* Clinical development program (CDP) metrics
* What is the size of CDP?
* Doing research right: TPP & DPIs
* Help in preparing a CDP
* Learning and Confirming
* Real-time examples

Appendix

Learn & Confirm

Real-time Examples

Learn & Confirm Paradigm

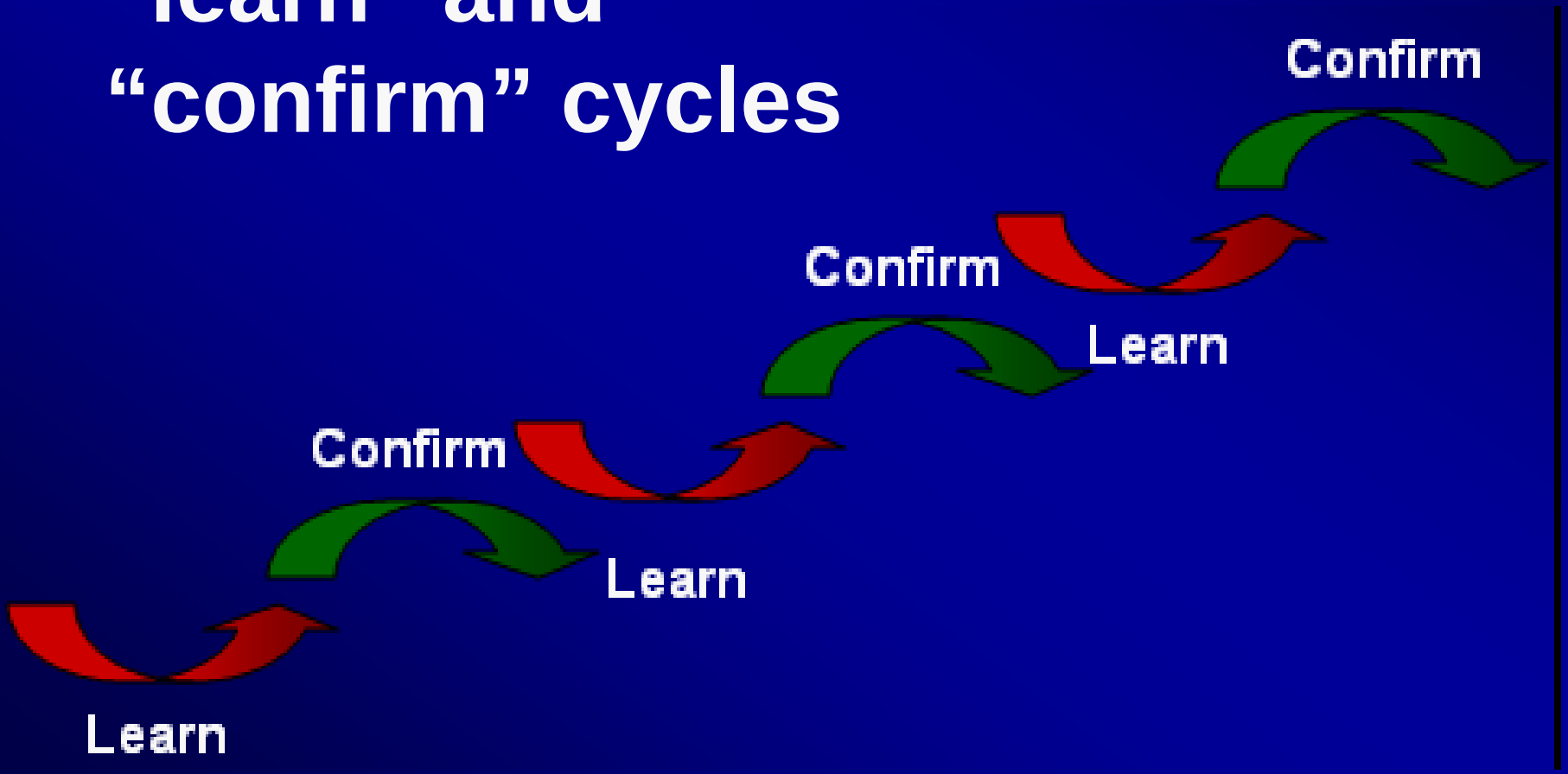
Learn & Confirm-1

* 1997--Lew Sheiner advocated the formal use of the Learning vs. Confirming paradigm for clinical drug development
* Drug development consists of three design choices
  1) “Assignment”
  2) “Observation”
  3) “Analysis”

Sheiner, LB. *Learning versus confirming in clinical drug development.* Clinical Pharmacology and Therapeutics, 1997, No. 61, pages 275-291

Learn & Confirm-2

* A cascade of "learn" and "confirm" cycles



Decision (Question)-Based Program Development

* **Identification of need ***
  - ***What question(s) do you need to answer?***
  - ***How well do you need to know the answer(s)?***
  - ***What do you want to do with the answer(s)?***
* **Prioritization of needs**
* **Implementation**

*** Lewis Sheiner, UCSF***

Learning Trial--Adaptive Design

* Addresses Rx imperative
* Allocate preferentially to currently most promising dose/regimen
* Adapt regimens as data accumulates.
* “Seamless” transition phase 2- 3
* Protocol Rx is more like real-world Rx
  - [up] patient acceptance & enrollment
  - More ethical
  - More predictive of real-world effects

CDDS Oncology Workshop, April 2003

Learn & Confirm-3

* **For learning trials the *knowledge regarding protocol compliance is imperative* to be able to make valid assumption**
  - **Learning must address an essentially infinite set of quantitative questions concerning the functional relationship between prognostic variables, dosage and outcomes**
* **Confirmation must thus answer only a single yes/no question: is the null hypothesis falsified or not**

Sheiner, LB. *Learning versus confirming in clinical drug development.* Clinical Pharmacology and Therapeutics, 1997, No. 61, pages 275-291

Oncologic Drug Discovery, Development & Review Stages

+ Learning

* Identification (Drug discovery)
* **Optimization** (Lead selection)
* Evaluation(s) (Proof of mechanism)
  (Proof of principle/concept)

+ Confirming

* Development (Evidence) Safety-Effectiveness
* Review (Regulatory review)
* **Launch** (Product introduction)
* Post-**Marketing** (Market expansion)
  + Formulations, indications, combinations, regimen

Clinical Development Program

* Phase I (Learning-PK, DDI,...)
  - *Single dose: normals ?*
  - *Multiple dose: normals ?*
  - *PK with food, age, gender, disease state*
  - *PK in liver, renal, etc.*

* Phase II (Learning)
  - *Dose-response in tumor A*
  - *Dose-response in tumor B*
  - *Use in combinations*

* Phase III (Confirming)
  - *Pivotal trial(s)*
  - *Long-term safety*

* Phase IV (L & C)
  - *New indications*
  - *Pharmacovigilance*
  - *Formulations*
  - *Combinations*
  - *Regimen*

Phase 3--Confirming

* **The goal of Phase 2 is to “Learn”**

* **The goal of Phase 3 Is to “Confirm”**
  Replicate positive Phase 2 learnings

* **How likely is it for Phase 3 to be successful if *“design mischief”* occurs between Phase 2 and Phase 3?**

* **Other reasons for Phase 3 failures?**

"Clinical Trial Phase II"

* "Learning & Confirming"
* *What do we want to learn in Phase II?*
* Why have oncology Phase II trials not been predictive of Phase III success?
* Proof of Concept trials
* Phase II Biologics
* RECIST: early stopping rules
* Clinical Endpoints (Already covered)
* Q&A

Evidence Based Relationships

+ ***Dose***
  + ***Exposure***
    + ***Pharmacodynamic*** **response relationships**
  * **Desired - - Effectiveness**
  * **Undesired - - Adverse events**

Classic Drug Development Phases

	Non-Oncology	*Oncology*
Phase 1	Safety & PK	MTD & PK?
Phase 2		
Phase 3		
Phase 4		

Classic Drug Development Phases

	Non-Oncology	*Oncology*
Phase 1	Safety & PK	MTD & PK?
Phase 2	*Learn*: Dose strategy	Tumor survey
Phase 3		
Phase 4		

Classic Drug Development Phases

	Non-Oncology	*Oncology*
Phase 1	Safety & PK	MTD & PK?
Phase 2	***Learn***: Dose strategy	Tumor survey
Phase 3	***Confirm***: Dose strategy & safety	***Learn***: Dose strategy & safety
Phase 4		

Classic Drug Development Phases

	Non-Oncology	*Oncology*
Phase 1	Safety & PK	MTD & PK?
Phase 2	***Learn***: Dose strategy	Tumor survey
Phase 3	***Confirm***: Dose strategy & safety	***Learn***: Dose strategy & safety
Phase 4	Expand indications	***Identify*** optimal dose and combos

Why Do We Conduct Oncology Clinical Trials?

To Make Smart Decisions

* **Identify**
* **Optimize**
* **Evaluate**
* **FIH**
* **Proof of Mechanism**
* **Proof of Concept**
  - **Who, dose, interval, duration**
* **EOP2**
* **Safe & effective**
* **FDA/EMEA/MHW Reviews *(Approvals?)***

Identify New Oncology Therapeutics

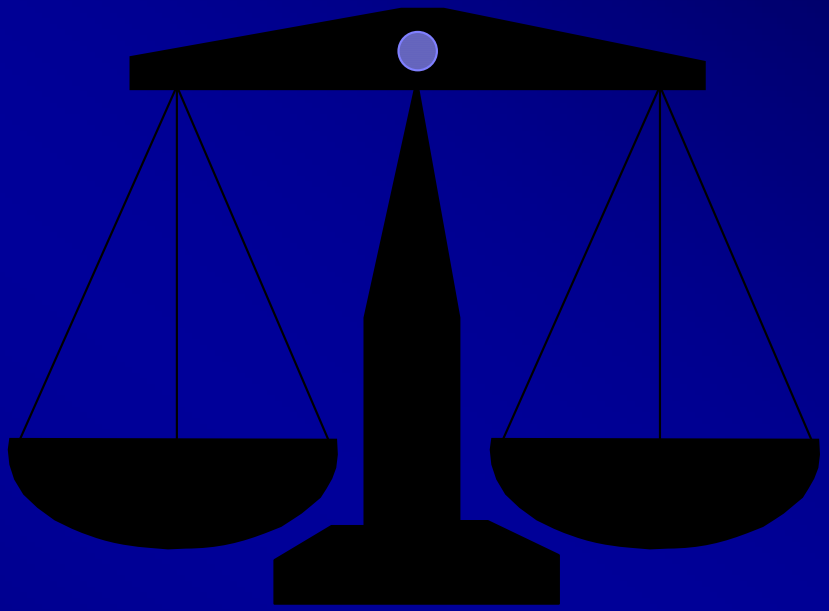
* **Small molecule**
  - **Cytotoxic**
    + **MTD**
  - **Cytostatic**
    + **Thalidomide**
    + **Right dose and exposure**
* **MAbs (Rituxan™)**
* **Proteins (Antiangiogenesis)**
* **Vaccines**

Why Do Oncology Clinical Trials?

* **To provide evidence that the test oncology drug is associated with:**
  - ***Living longer***
  - ***Living better***
  - ***Acceptable Benefit-Risk***

What Kind of Evidence?

* Reliable
* Convincing
  - Minimize bias
  - Minimize uncertainty

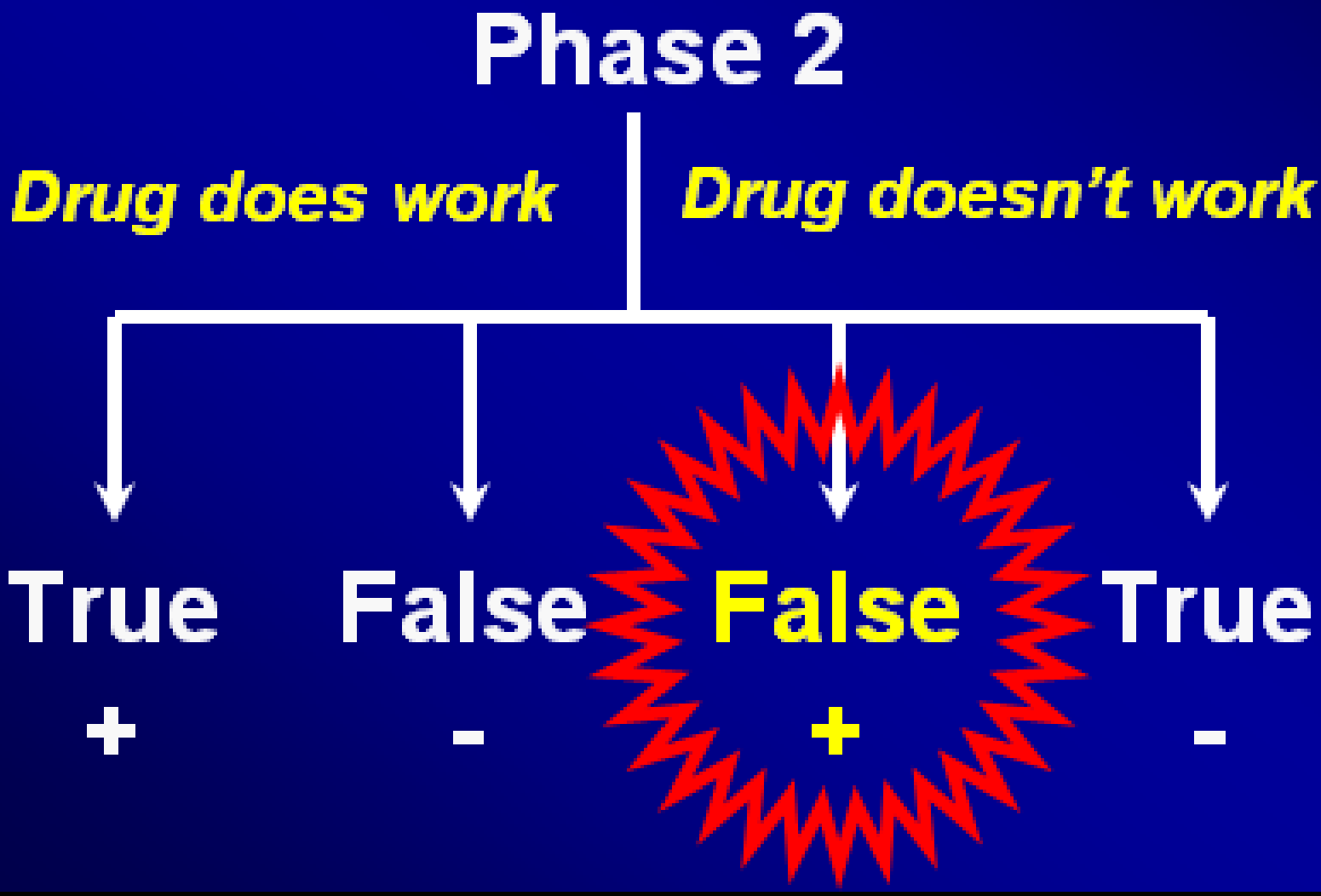


What Is Convincing Evidence?

* Large therapeutic effect
* Large study population

* But not:
  - Small therapeutic effect
  - Small study population

What is Convincing Evidence?



Phase 2 Goals: What Do We Want to Learn?

EOP2

* **Who is likely to respond?**
  - **Tumor type?**
  - **Performance status?**
  - **Previous treatment?**
  - **Additional—e.g., receptor status**
* **What type of response?**
* **Dose *What will be the "response-rate dose?"***
* **Dose regimen & interval (US vs. Europe…)**
* **Dose duration**
* **Dose combinations—*proper sequencing?***

Drug Development & Review Stages --Time & Cost

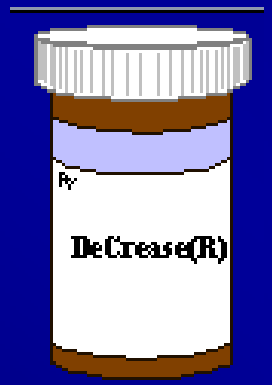
* The speed record may be held by Agouron for Viracept with the following metrics:

+ The first in human dose (FIH) was 18-weeks after the start of the non-clinical safety program.
+ Phase 2 started 9.5-months after the start of the non-clinical safety program.
+ The Viracept NDA was submitted 3.5-years after the discovery of the drug.

DIJ, 1999

Drug Development & Review Stages--Time & Cost

* In an annual report from Monsanto, they indicated that the development and NDA submission of celecoxib, the Searle COX-2 inhibitor was completed in 39-months from the FIH.
* This is even more remarkable when one takes into account that the NDA contained data from over 9000 OA, RA and surgical pain subjects.



What are the Critical Drug Development & Review Decision Points?

* Overview of the drug development decision points
* Focus on Disease State
* Real-life examples

Prove & Convince

Prove & Convince

- Ourselves
- Regulatory Agencies
- Purchasers
- Prescribers
- Patients

Clinical Development Programs

* Label-Driven clinical development
* Clinical development program (CDP) metrics
* What is the size of CDP?
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* Learning and Confirming
* Real-time examples

Eloxantin (oxaliplatin)

* *1993 IND filed by Axiom*
* *1995 Transferred - - **Debiopharm SA** - - Sanofi*
* *1997 Clinical hold due to CMC issues*
* *1999 NDA submitted*
  - *Advanced colorectal w/ 5-FU previously untreated subjects*
  - *2 Trials*

Eloxantin (oxaliplatin)

* 1999 NDA--2 Trials
* Neither trial designed with overall survival as primary
* EFC 2961 powered to show diff. in tumor response
* EFC 2962 powered to show diff. disease free survival (DFS)
* FDA reviewer
  - 2961 no trend towards survival advantage
  - 2962 did not show a survival advantage

Eloxantin (oxaliplatin)

* *March 2000 ODAC meeting*
  - ***Irinotecan** metastatic colorectal 1st line data presented*
  - *ODAC did not recommend approval of oxaliplatin*
  - ***Sanofi** withdraws NDA*
* *Lilly returns license for oxaliplatin to Sanofi*

Eloxantin (oxaliplatin)

* *2000 Several EOP2 meetings*
* *Survival as 1º endpoint, RR and TTP as supportive*
* *Treatment allocation*
* *Randomized Phase 3 trial*
* *FDA: Analysis to be based on prespecified total number of deaths*
* *Delete TTF*

Eloxantin (oxaliplatin)

* 12/2001 PreNDA clarification meeting
* 4/02 Fast Track status
* 7/02 Oxaliplatin NDA resubmitted
* 9/02 Oxaliplatin (with 5-FU/LV) approved for 2nd line colorectal
  - CMA with prelim data from combo vs. single
  - Reviewed in 46-days

Eloxantin (oxaliplatin)

* *Requirement for survival data in 2004 per 2002 NDA Phase 4*

* *1/04 NDA submitted for advanced colorectal 1st line*

Differentiation

Just which heart attack ARE we preventing?

Differentiation:

"Pravachol has just been proven to reduce the risk of stroke or mini-stroke by 26% and heart attack by 24%"

"Importantly, 84% of the patients in the study were already taking aspirin, a common medicine for reducing the risk of recurrent heart attacks."

Reader's Digest Ad, June 1998

Differentiation:

"**Pravachol has just been proven to** reduce the risk of stroke or mini-**stroke** by 26% and heart attack by 24%"

* *"A new clinical study in men and women with a history of heart attack and normal cholesterol proves Pravachol from Bristol-Myers Squibb Company, actually reduces the risk of heart attack and stroke or mini-stroke ."*
* *"Pravachol reduces the risk of first heart attack up to one-third."*

Reader's Digest Ad, June 1998

Dosage & Administration

Adults & children

&

the respective formulations

Dosage and Administration

*"**Adults and Children 12 years and older:** The recommended initial dose of ZYRTEC is 5 or 10 mg per day for adults and children 12 years and older, depending upon symptom severity. Most patients in clinical trials started at 10 mg.*

ZYRTEC is given as a single daily dose, with or without food. The time of administration may be varied to suit individual needs."

PI 9/96

Dosage and Administration

"In patients with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min) and in hepatically impaired patients, a dose of 5 mg once daily is recommended."

"Children 6 to 11 years: The recommended initial dose of ZYRTEC in children 6 to 11 years is 5 or 10 mg (1 to 2 teaspoons) once daily depending upon symptom severity."

PI 9/96

Differentiation

No drug-drug interaction

No Drug Interactions

"In two separate studies fexofenadine hydrochloride 120 mg twice daily (twice the recommended dose) was co-administered with erythromycin 500 mg every 6 hours or ketoconazole 400 mg once daily under steady-state conditions to normal healthy volunteers (n=24, each study).

PI 10/96

No Drug Interactions

No difference in adverse events or or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with erythromycin or ketoconazole.

The findings of these studies are summarized in the following table: ..."

PI 10/96

Differentiation

More Desirable Route of Administration

Inhale Announces Preliminary Phase IIb Results of Trial Combining Inhaled Insulin with Oral Agents

* *Inhale Therapeutic Systems, Inc. today announced preliminary results from a Phase IIb trial showing that individuals with type 2 diabetes can markedly improve their glycemic control without insulin injections by combining Inhale's pulmonary insulin with oral diabetes agents.*

BW HealthWire *9/8/98*

Inhale Announces Preliminary Phase IIb Results of Trial Combining Inhaled Insulin with Oral Agents

* *The complete results from the 56 patients showed that Hemoglobin A1c levels -- used to measure levels of glycemic control -- were lowered by an average of 2.3% percentage points from 9.8% to 7.5% in the group using pulmonary delivery, while patients using oral agents alone showed little change (9.9% to 9.8%).*

BW HealthWire *9/8/98*

Inhale Announces Preliminary Phase IIb Results of Trial Combining Inhaled Insulin with Oral Agents

* *Of the patients using pulmonary delivery in combination with oral agents, 97% opted to continue on pulmonary insulin following the completion of the trials.*

BW HealthWire *9/8/98*

Patient Populations

PATIENT POPULATION
Broad range of Subpopulations

* *"Pfizer's Viagra Efficacy Shown in Broad Range of Subpopulations - Labeling"*
* *"A review of population subgroups demonstrated efficacy regardless of baseline severity, etiology, race and age." Viagra labeling states.*
* *"In a study of 268 diabetes patients 57% of Viagra patients reported improved erections compared to 10% on placebo."*

"The Pink Sheet" 3/30/98 page 4

PATIENT POPULATION
Broad range of Subpopulations

* "Pfizer conducted two studies involving 179 patients with psychogenic etiology of dysfunction and found that "84% of Viagra patients reported improvement in erections compared with 26% of placebo…"
* "In a study involving 178 spinal cord patients, 83% reported improved erections on Viagra vs. 12% on placebo…"

"The Pink Sheet" 3/30/98 page 4

PATIENT POPULATION
Broad range of Subpopulations

* "The broad market segmentation included in labeling will help Pfizer preempt claims from other potential competitors in the erectile dysfunction market."
* "Sildenafil is contraindicated in patients who are taking nitrates. "Viagra was shown to potentiate the hypotensive effect of nitrates and its administration to patients who are currently using organic nitrates in any form is therefore contraindicated."

"The Pink Sheet" 3/30/98 page 4

NDA Withdrawal

Safety

SAFETY NDA Withdrawal
Hopes of Resubmitting the NDA

* *Wyeth is reanalyzing the safety data for its angiotensin II inhibitor Verdia in hopes of resubmitting the NDA.*
* *The Verdia (tasosartan) application was withdrawn from FDA consideration by the company March 3. Wyeth stated that the "action was the result of an unresolved question [with FDA] regarding the safety profile." The product was associated with liver enzyme elevations during clinical trials.*

"The Pink Sheet" 3/9/98 page 22

SAFETY NDA Withdrawal

Hopes of Resubmitting the NDA

* *With the cost of product launches soaring, companies are less willing to go to market without the acceptable promotional package.*

"The Pink Sheet" 3/9/98 page 22

DOUBLE BLIND STUDY

Revised Labeling
& Now NDA Withdrawal

Drug-drug interactions!

*REVISED LABELING--**Withdrawal***

Drug-**Drug Interactions**

"Propulsid Revised Labeling Reserves drug For Second-Line Use in GERD"

* *"Janssen's Propulsid (cisapride) should be reserved for second-line use, revised labeling recommends following additional reports of cardiac events and deaths associated with the drug for nocturnal heartburn caused by gastroesophageal reflux disease."*
* *"Revised labeling carries a boxed warning cautioning that "serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking Propulsid" with other drugs that inhibit cytochrome P450 3A4."*

"The Pink Sheet" 7/6/98 page 5

*REVISED LABELING--**Withdrawal***
Drug-**Drug Interactions**
"Propulsid Revised Labeling Reserves drug For Second-Line Use in GERD"

* *"The new labeling contraindicates the use of Propulsid with at least 20 different drugs. ...antibiotics erythromycin, clarithromycin, and troleandomyacin; the antidepressant nefazodone; antifungals fluconazole, itraconazole, ketoconazole and the protease inhibitors indinavir and ritonavir."*
* *"Propulsid is additionally contraindicated for use with certain medications known to prolong QT interval: anti-arrhythmics Class IA (such as quinidine and procainamide... sotalol... amitryptiline... maprotiline..."*

"The Pink Sheet" 7/6/98 page 5

PK Labeling

Sub-populations

Phase 2/3 Transition
10. Clinical Development

* Special Populations ?
* Gender ?
* Age (Elderly / Neonates) ?
* Ethnicity ?
* Impairments ?

Clinical Pharmacology

Pharmacokinetics and Metabolism: Omeprazole

*"In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-**fold** was noted in Asian subjects compared to Caucasians. Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.*

PI 2/97

“That is a breakthrough--

“That is a breakthrough--
a placebo with side effects!”

Indications

In which population was the drug tested?

PATIENT POPULATIONS

"Naprelan Onset of Action Data From Oral Surgery Do Not Apply to Arthritis"

* *"Wyeth-Ayerst cannot claim that Naprelan (naproxen) provides 30-minute relief in arthritis patients because the onset of relief **data is derived from oral surgery studies,** FDA's ad division said in a June 8 letter."*
* *FDA objected to statements the Naprelan "gets arthritis patients off to a fast start" with "30-minute onset of acute pain relief…"*

"The Pink Sheet" 7/6/98 page 28

PATIENT POPULATIONS

"Naprelan Onset of Action Data From Oral Surgery Do Not Apply to Arthritis"

* *"The approved product labeling for Naprelan states that in clinical trials designed to determine the efficacy of Naprelan in osteoarthritis and rheumatoid arthritis, clinical effectiveness was noted at one week."*

"The Pink Sheet" 7/6/98 page 28

NDA Withdrawal

Can’t be used with any other drug?

NDA Withdrawal
*Drug-**Drug Interactions***
*"**Posicor** Withdrawal Reflects "Complexity" of Interaction Profile"*

* *"Products identified as potentially dangerous in combination with mibefradil included cardiac drugs such as* **Cordarone, Vesture, Tambocor,** *and* Rythmol; *oncologic products such as tamoxifen,* Cytoxan, VePesid, Ifex,*and* Velban, *and the anti-rejection medications* Neoral *and* Prograf."
* *"Roche's **decision to withdraw the calcium channel blocker** **Posicor** (mibefradil) is based on the "complexity" of the drug interaction information that would have to be communicated to ensure safe usage, the company said June 8."*

"The Pink Sheet" 6/15/98 page 5

NDA Withdrawal

*Drug-**Drug Interactions***

*"**Posicor** Withdrawal Reflects "Complexity" of Interaction Profile"*

* *"With the calcium channel blocker category crowded with competitors and Posicor hampered with numerous drug interactions, the failure of the product to find a new therapeutic niche would have relegated the product to a limited use even if it had remained on the market."*

"The Pink Sheet" 6/15/98 page 5

NDA Withdrawal

Can't be used with any other drug?

When did they know?

When should they have known?

Differentiation

Doing it right!

Differentiation:

"Merck Singulair Clears FDA for Chronic Asthma in Patients Six and Up"

* *"Merck Singulair tablets were approved Feb. 20 for the prophylaxis and chronic treatment of asthma in patients 15 and older."*
* *"Singulair chewable tablets were also approved for the same indication in pediatric patients aged six to 14 under a separate NDA."*
* *"Singulair (montelukast) is indicated for a broader age range than the two other oral chronic asthma treatments that act on the leukotriene pathway. Both Abbott's Zyflo (zileuton) and Zeneca's Accolate (zafirlukast) are indicated for patients 12 and older."*

"The Pink Sheet" 3/2/98 page 23

Differentiation:

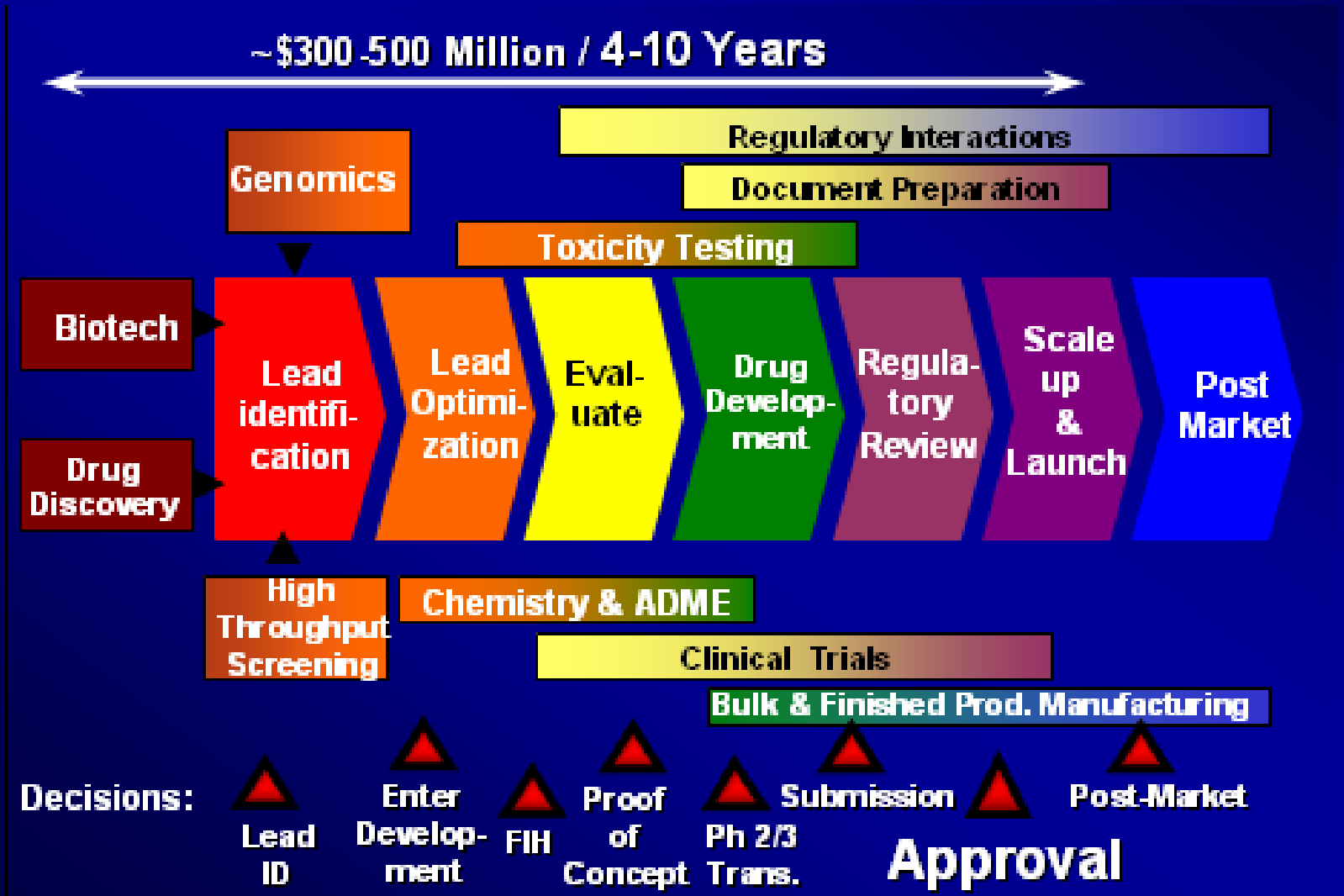
"Merck Singulair Clears FDA for Chronic Asthma in Patients Six and Up"

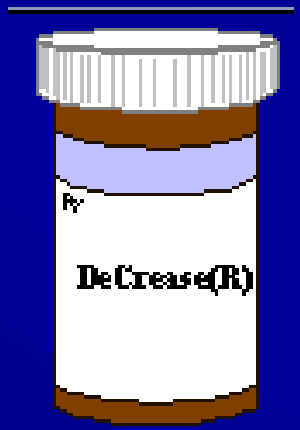
* *"Merck's Singulair labeling includes data demonstrating efficacy in exercise-challenged asthma patients." "Exercise challenge was conducted at the end of the dosing interval..."*
* *"Labeling for Singulair appears to allow Merck several possibilities to differentiate the leukotriene receptor antagonist from Zeneca's LTRA Accolate (zafirlukast) and Abbott's leukotriene inhibitor Zyflo (zileuton)."*
* *"Neither Zyflo nor Accolate labeling mention exercise-induced asthma. FDA had objected to any insinuation of efficacy in that population without clinical evidence..."*

"The Pink Sheet" 3/2/98 page 23

Drug Discovery, Development & Review

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

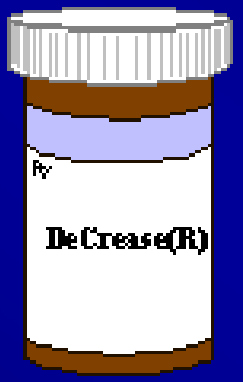




What are the Critical Drug Development & Review Decision Points?

* Overview of the drug development decision points

* Focus on Disease State
* Real-life examples



What are the Critical Drug Development & Review Decision Points?

* One way to remember the "label-driven question-based" concept is to think:
  + "We Sell Only the Package Insert,
  + We ...