CHALLENGES AND OPPORTUNITIES IN CLINICAL DRUG DEVELOPMENT

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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
DO MERGERS AFFECT THE RATE OF NEW DRUG DEVELOPMENT?

**PHARMA SYNERGY: N = 9 → N = 1**

- KABI
- PHARMACIA
- FARMITALIA
- UPJOHN
- PARKE DAVIS
- WARNER LAMBERT
- GD SEARLE
- CELECOXIB
- WYETH
- PFIZER

- ATORVASTATIN

**Do mergers affect the rate of new drug development?**
POST-DISCOVERY
PHASES OF DRUG DEVELOPMENT

IND

Chemical Synthesis and Formulation Development

Animal Models for Efficacy

Assay Development

Animal PK and PD

Animal Toxicology

Pre-Clinical Development

PHASE I

Dose Escalation and Initial PK

Proof of Concept and Dose Finding

PK and PD Studies in Special Populations

Clinical Development

PHASE II

PHASE III

Large Efficacy Trials with PK Screen

PHASE IV

NDA
COMPOUND ATTRITION DURING DRUG DEVELOPMENT*

INDs FILED

I

II

III

NDAs FILED NDA APR

SUCCESS RATES BY DRUG DEVELOPMENT PHASE*

### CLINICAL DEVELOPMENT COSTS*

<table>
<thead>
<tr>
<th>CLINICAL PHASE</th>
<th>TIME (months)</th>
<th>EXPECTED COSTS ($ x 10^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OUT-OF-POCKET</td>
</tr>
<tr>
<td>PHASE I</td>
<td>12.3</td>
<td>15.2</td>
</tr>
<tr>
<td>PHASE II</td>
<td>26.0</td>
<td>16.7</td>
</tr>
<tr>
<td>PHASE III</td>
<td>33.8</td>
<td>27.1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>72.1</td>
<td>59.0</td>
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</table>

† BASED ON 11.9% COST OF CAPITAL

## COSTS PER APPROVED DRUG*

<table>
<thead>
<tr>
<th></th>
<th>OUT-OF-POCKET</th>
<th>CAPITALIZED</th>
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<tbody>
<tr>
<td>TOTAL COSTS</td>
<td>403</td>
<td>802</td>
</tr>
<tr>
<td>CLINICAL COSTS (%) TOTAL</td>
<td>274 (68%)</td>
<td>453 (56%)</td>
</tr>
</tbody>
</table>

† BASED ON 21.5% SUCCESS RATE

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

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!”

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*

<table>
<thead>
<tr>
<th>Core Information Category</th>
<th>Inclusion of Desirable Data Elements</th>
<th>Mean (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>88%</td>
<td>(84% - 93%)</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>43%</td>
<td>(37% - 49%)</td>
</tr>
<tr>
<td>Drug Metabolism</td>
<td>23%</td>
<td>(16% - 29%)</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>42%</td>
<td>(35% - 49%)</td>
</tr>
<tr>
<td>Dose Adjustment</td>
<td>37%</td>
<td>(32% - 42%)</td>
</tr>
</tbody>
</table>

PATHOPHYSIOLOGIC FACTORS NOT ACCOUNTED FOR IN DRUG DOSING*

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

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:
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

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

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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
**FIRST ORDER KINETICS**

\[
\text{DOSE} / \tau = \text{CL}_E \cdot \bar{C}_{ss}
\]

**MICHAELIS - MENTEN KINETICS**

\[
\text{DOSE} / \tau = \left[ \frac{V_{\text{max}}}{K_m + \bar{C}_{ss}} \right] \bar{C}_{ss}
\]
DOSE DEPENDENCY?

AUC = AREA UNDER PLASMA LEVEL VS. TIME CURVE

Increase: Dose = 4-Fold  
- 100 mg Dose  
- 25 mg Dose

AUC = 13.6-Fold
AUC = 17.91 μg.hr/ml
AUC = 1.32 μg.hr/ml
PSEUDO DOSE DEPENDENCY

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

[DRUG] (μg/ml)

LIMIT OF ASSAY SENSITIVITY

HOURS
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 $T^{1/2}$ BUT ALSO FOR THE MODEL INDEPENDENT PARAMETERS.”

## DISTRIBUTION VOLUME OF REPRESENTATIVE MACROMOLECULES

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

ESTIMATING DOSE RANGE FOR SUBSEQUENT PIVOTAL TRIAL

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

## DOSE DISCREPANCIES BETWEEN PDR & MEDICAL LITERATURE

<table>
<thead>
<tr>
<th>DRUG †</th>
<th>PDR INITIAL DOSE (mg)</th>
<th>EFFECTIVE LOWER DOSE (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEBUTOLOL</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td>CELECOXIB</td>
<td>100 BID</td>
<td>50 BID</td>
</tr>
<tr>
<td>LISINOPRIL</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>OMEPRAZOLE</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>PROPRANOLOL</td>
<td>80</td>
<td>40</td>
</tr>
</tbody>
</table>

† 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

KAPLAN-MEIER CURVES FOR ALL-CAUSE MORTALITY*

RR = 0.70
(0.58-0.85)

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

MULTIFOCAL LEUKOENCEPHALOPATHY (MFL)

• OCCURS IN 4% OF PATIENTS WITH AIDS

• THERE IS NO ESTABLISHED EFFECTIVE THERAPY

• SURVIVAL 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.
• 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
“GROUP 3 RECEIVED ANTIRETROVIAL THERAPY PLUS 50 MG OF CYTARABINE, ADMINISTERED 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

OMMAYA PUMP
SCHEMATIC OF PUMP PLACEMENT

Lateral view of brain.

- Ommaya Pump
- Lateral Ventricle
- Third Ventricle
- Cerebrum
- Fourth Ventricle
- Cerebellum
- Medulla Oblongata
- Spinal Cord
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

MIC *C. neoformans*

MODEL FOR ANALYZING INTRATHECAL AMPHOTERICIN B PHARMACOKINETICS

CHOROID PLEXUS

$\rho_{\text{csf}} = 0.54 \text{ mL/min}$

CSF (139 mL) $k_d$

BRAIN ECF (677 mL)

ARACHNOID VILLI

INTRATHECAL CYTARABINE PHARMACOKINETICS


CL_E = 0.42 mL/min

30 mg ARA-C, IT
SIMULATED CYTARABINE INTRATHECAL DOSE REGIMENS

30 mg qd x 3
70 mg

IN VITRO EFFECTIVE LEVEL FOR JC VIRUS

“FAILURE” OF IT CYTARABINE IN PML ASSOCIATED WITH HIV INFECTION*

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

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DECISION MAKING IN DRUG DEVELOPMENT

• GO – NO GO DECISIONS
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 CLINICAL DEVELOPMENT COSTS
COMPOUND ATTRITION DURING DRUG DEVELOPMENT*

INDs FILED: 5
I: 4.5-5
II: 3.5
III: 1.6
NDAs FILED: 1.3
NDA APR: 1

IDEAL DISTRIBUTION OF COMPOUND ATTRITION

DECISION MAKING IN DRUG DEVELOPMENT

- GO – NO GO DECISIONS
- 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

<table>
<thead>
<tr>
<th></th>
<th>NPV</th>
<th>$0.3B</th>
<th>$1B</th>
<th>$3B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NDA Filing</strong></td>
<td>18 mos.</td>
<td></td>
<td>12 mos.</td>
<td>6 mos.</td>
</tr>
<tr>
<td><strong>Doses per day</strong></td>
<td>TID</td>
<td>BID</td>
<td>QD</td>
<td></td>
</tr>
<tr>
<td><strong>Concomitant use</strong></td>
<td>None</td>
<td></td>
<td>All</td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity test available</strong></td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>COGs</strong></td>
<td>$70k/kg</td>
<td></td>
<td>$10k/kg</td>
<td></td>
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<tr>
<td><strong>Availability of IV at launch</strong></td>
<td>No</td>
<td></td>
<td>Yes</td>
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PHARMACEUTICAL PRODUCT LIFE CYCLE

- Pre-clinical Development
- Clinical Development
- Regulatory Review
- Scale up & Launch
- Post Marketing
- Patent Expiration

* 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

MANAGEMENT CONSIDERATIONS

DISCOVERY  
PRE-CLINICAL  
CLINICAL  
MARKETING
### MATRIX MANAGEMENT STRUCTURE

<table>
<thead>
<tr>
<th>PROJECT TEAMS</th>
<th>DISCIPLINE</th>
<th>LINE MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DISCOVERY</td>
<td>TOXICOL. PK</td>
</tr>
<tr>
<td>PROJECT 1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PROJECT 2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PROJECT 3</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>PROJECT N</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
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

SERVANT LEADERSHIP

LEADERSHIP IS AN ART

MAX DEPREE

"This book is thoughtful, personal, human, persuasive. Give it to a daughter, son, or Fortune 500 chairman. They should bless you for years to come."

—Tom Peters

ASTONISHING

—Bill Clinton
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](http://www.fda.gov/cder/guidance/index.htm)