CHALLENGES AND OPPORTUNITIES IN CLINICAL DRUG DEVELOPMENT

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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

DO MERGERS AFFECT THE RATE OF NEW DRUG DEVELOPMENT?

POST-DISCOVERY PHASES OF DRUG DEVELOPMENT
**COMPOUND ATTRITION DURING DRUG DEVELOPMENT**

<table>
<thead>
<tr>
<th>INDs</th>
<th>I</th>
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<th>III</th>
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**SUCCESS RATES BY DRUG DEVELOPMENT PHASE**

<table>
<thead>
<tr>
<th>PHASE</th>
<th>SUCCESS RATE (%)</th>
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<tbody>
<tr>
<td>Phase 1</td>
<td>30.5</td>
</tr>
<tr>
<td>Phase 2</td>
<td>26.0</td>
</tr>
<tr>
<td>Phase 3</td>
<td>15.2</td>
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</table>


**CLINICAL DEVELOPMENT COSTS**

<table>
<thead>
<tr>
<th>CLINICAL PHASE</th>
<th>TIME (months)</th>
<th>EXPECTED COSTS ($ x 10^6)</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>12.3</td>
<td>15.2</td>
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<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>
</tr>
</tbody>
</table>

† BASED ON 11.9% COST OF CAPITAL


**CLINICAL DEVELOPMENT COSTS**

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### Costs per Approved Drug

<table>
<thead>
<tr>
<th></th>
<th>Cost ($ x 10^6)†</th>
<th>Out-of-Pocket</th>
<th>Capitalized</th>
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<tbody>
<tr>
<td><strong>TOTAL COSTS</strong></td>
<td>403</td>
<td></td>
<td>802</td>
</tr>
<tr>
<td><strong>CLINICAL COSTS</strong></td>
<td>274 (68%)</td>
<td>453 (56%)</td>
<td></td>
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</table>

† Based on 21.5% success rate

### Clinical Development Programs of Some Recently Developed Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>FDA-NDAs 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>
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</thead>
<tbody>
<tr>
<td>HERCEPTIN®</td>
<td>BREAST CANCER</td>
<td>6 – 10</td>
<td>3/48</td>
<td>8/532</td>
<td>1/469</td>
<td>12/1069</td>
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<tr>
<td>ENBREL®</td>
<td>RHUMATOID ARTHRITIS</td>
<td>6 – 7</td>
<td>8/163</td>
<td>23/503</td>
<td>23/1381</td>
<td>34/2048</td>
</tr>
<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>MEAN (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MECHANISM OF ACTION</td>
<td>88% (84% - 93%)</td>
</tr>
<tr>
<td>PHARMACODYNAMICS</td>
<td>43% (37% - 49%)</td>
</tr>
<tr>
<td>DRUG METABOLISM</td>
<td>23% (16% - 29%)</td>
</tr>
<tr>
<td>PHARMACOKINETICS</td>
<td>42% (35% - 49%)</td>
</tr>
<tr>
<td>DOSE ADJUSTMENT</td>
<td>37% (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.

ADVANCED AGE 42%
PATIENT WEIGHT 19%
RENAL IMPAIRMENT 33%
OTHER 6%

Whenver 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)


TARGETED APPROACH TO DRUG DEVELOPMENT*

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.”

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

- 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*

<table>
<thead>
<tr>
<th>PHENYTOIN</th>
<th>CARBAMAZEPINE</th>
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<tbody>
<tr>
<td>PREDNISONE</td>
<td>CODEINE</td>
</tr>
<tr>
<td>DIGOXIN</td>
<td>LITHIUM</td>
</tr>
<tr>
<td>AMIODARONE</td>
<td>THEOPHYLLINE</td>
</tr>
<tr>
<td>ASPIRIN</td>
<td>DESIPRAMINE</td>
</tr>
<tr>
<td>CO-TRIMOXAZOLE</td>
<td>DEXAMETHASONE</td>
</tr>
<tr>
<td>PENTAMIDINE</td>
<td>GENTAMICIN</td>
</tr>
</tbody>
</table>

* 1988 NMH Data (Clin Pharmacol Ther 1996;60:363-7)

LEVELS NOT PROPORTIONAL TO DOSE
STEADY STATE EQUATIONS

FIRST ORDER KINETICS
\[ \text{DOSE} / \tau = \frac{\text{CL}_e}{\tau} \cdot \overline{C}_{SS} \]

MICHAELIS-MENTEN KINETICS
\[ \text{DOSE} / \tau = \frac{V_{\text{max}}}{K_m + \overline{C}_{SS}} \cdot \overline{C}_{SS} \]

DOSE DEPENDENCY?

AUC = AREA UNDER PLASMA LEVEL VS. TIME CURVE

Increase: Dose = 4-Fold AUC = 13.6-Fold
- 100 mg Dose AUC = 17.91 \mu g.hr/ml
- 25 mg Dose AUC = 1.32 \mu g.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 ENTIRELY CONFINED TO THE PLASMA SPACE.”

• “A TOO SHORT BLOOD SAMPLING PROTOCOL GIVES FLAWED RESULTS NOT ONLY FOR TERMINAL T½ BUT ALSO FOR THE MODEL INDEPENDENT PARAMETERS.”


DISTRIBUTION VOLUME OF REPRESENTATIVE MACROMOLECULES

<table>
<thead>
<tr>
<th>MACROMOLECULE</th>
<th>MW (kDa)</th>
<th>V1 (mL/kg)</th>
<th>Vd(ss) (mL/kg)</th>
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</thead>
<tbody>
<tr>
<td>INULIN</td>
<td>5.2</td>
<td>55 IVS</td>
<td>164 ECF</td>
</tr>
<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>63</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  

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

**ESTIMATING DOSE RANGE FOR SUBSEQUENT PIVOTAL TRIAL**

![Graph showing cholesterol decrease vs simvastatin dose](Mol MJM, 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

DOSE DISCREPANCIES BETWEEN PDR & MEDICAL LITERATURE*

<table>
<thead>
<tr>
<th>DRUG †</th>
<th>PDR INITIAL DOSE (mg)</th>
<th>EFFECTIVE LOWER DOSE (mg)</th>
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</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>PROPANOLOL</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)*

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

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**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.

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, 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
Schematic of Pump Placement

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

INTRATEHICAL AMPHOTERICIN B PHARMACOKINETICS


CHOROID PLEXUS

BULK FLOW

ARACHNOID VILLI

MIC C. neoformans

CHOROID PLEXUS

BULK FLOW

ARACHNOID VILLI

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

CSF (139 mL)

$K_d$

BRAIN ECF (677 mL)

INTRATHECAL CYTARABINE PHARMACOKINETICS

CL_e = 0.42 mL/min


SIMULATED CYTARABINE INTRATHECAL DOSE REGIMENS


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

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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*

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<th>III</th>
<th>NDAs FILED</th>
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<td>1.6</td>
<td>1.3</td>
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</tr>
</tbody>
</table>


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

PHARMACEUTICAL PRODUCT LIFE CYCLE

Pre-clinical Development

Lead Optimization

Lead Identification

Clinical Development

Regulatory Review

Marketing

Post Marketing

Scale up & Launch

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>LINE MANAGEMENT</th>
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<tbody>
<tr>
<td>DISCIPLINE</td>
<td>ADME</td>
</tr>
<tr>
<td>PROJECT 1</td>
<td>X</td>
</tr>
<tr>
<td>PROJECT 2</td>
<td>X</td>
</tr>
<tr>
<td>PROJECT 3</td>
<td>X</td>
</tr>
<tr>
<td>PROJECT N</td>
<td>X</td>
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</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
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