Introduction to Design of Clinical Development Programs

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Disclaimer

The views expressed in this talk represent my opinions and do not necessarily represent the views of the FDA.
Objectives

• *What* is Clinical Development
• Components of the Clinical Development Program
  – Pre-IND
  – IND
  – Clinical Pharmacology
  – Efficacy
  – Safety
  – NDA and Exclusivity; Drug Labeling
  – Postmarketing Strategy
What is Clinical Development
Aim of Drug Development

• **CMC [21 CFR 312.23(a)(7)]:**
  To assure the proper identification, quality, purity, and strength of the investigational drug.

• **Preclinical [21 CFR 312.23(a)(8)]:**
  To assure that it is reasonably safe to conduct the proposed clinical investigations.

• **Clinical [FD&C Act Sec. 505]:**
  To establish efficacy and safety of a drug for use in humans, in a dose range and schedule that provides an acceptable risk benefit relationship.
Why Develop Drugs Clinically

• **Legal:** You have to!
    – (a) Necessity of effective approval of application. No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

• **Medical:** Physicians and patients need the information
• **Business:** You need to demonstrate some Benefit / Risk advantage for your product
STOP 1: The Investigational New Drug (IND) Application
Before the IND

• Many Sponsors opt to have a type B, "Pre-IND meeting" before filing the IND
  – Clarify questions
  – Showcase certain data; get buy in on next course of action
  – Agreement on development plan
    • first in man
    • primary variable in Ph3
    • sequence of studies
The Code of Federal Regulations
Title 21 Section 312…A Must Read

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfsearch.cfm?cfrpart=312
The Investigational New Drug Application

• The IND requests to start human testing of a new drug in the US
  – Other countries have their own version of this application
  – You can do some of your early studies in other countries but the key ones should be done under IND
    • Ensures the FDA has seen them before hand
  – If you want to study an approved drug in a population and indication substantially different from that in the marketing application, you need a new IND
    – Each unique formulation should have a new IND
• Must wait 30 days before dosing
Components of the IND

• Sec. 312.23 IND content and format.
  – The 1571 form
  – Cover letter
  – CV (check for qualifications; may submit a 1572 form)
  – Investigator’s brochure
  – General investigational plan
  – **Clinical protocol (s)**
  – Clinical pharmacology (dose, drug interactions, etc.)
  – Pharm / Tox (safety signals)
  – CMC (chemistry)
Grounds for Imposing a Clinical Hold: Phase 1

• 21 CFR 312.42 (b)(1)
  – Human subjects at unreasonable and significant risk
  – Unqualified investigator(s)
  – Investigator brochure misleading, erroneous or incomplete
  – Insufficient information to assess risk
  – Exclusion by gender if for life-threatening condition
STOP 3: Clinical Pharmacology - A Question Based Approach

How do the drug and body interact?
What would I want to know if…

- I have a drug, Dontsnuzenall with X# of unit doses (let's say 1, 2, and 4 mg) for the treatment of staying awake in NIH lectures.

What do I want to know about the PK of Dontsnuzenall and how can I study the drug to know these things?
How much Don'tsnuzenall gets in blood?

- **Objective**: First in Human (Single Ascending Dose (SAD))
  - Start dosing at level below the No Observable Adverse Event (or sometimes the No Observable Effect Level)
  - Intensive monitoring with Safety group allowing dosing to progress
  - Dose escalation in ½ log units (more or less)
  - Informs you of tolerability, safety, PK
  - Plan on 1-2 quarters from First Person / First Visit (FPFV) to topline data; some start their second study (Multiple AD; MAD) once they have passed a dose that will be in the MAD
How much Dontsnuzenall gets in blood?

- **Objective:** What is PK and tolerability when drug is dosed repeatedly as planned once marketed (MAD)?
  - Start dosing below anticipated dose; go to maximal tolerated dose
  - Informs you of tolerability, safety and steady state PK
  - Plan on 2 quarters from FPFV to topline data
  - Precedes Phase 2

![Multiple Dose (MD)]
How is Don’tsnuzenall Distributed in the body and to its “target” organ

- Objective: How is the drug distributed after administration?
  - Nonclinical
    - Tissue levels
    - Whole body Autoradiography
  - Clinical
    - Positron Emission Tomography
    - Tissue fluid levels
The Uof I Drug Metabolism Table

http://medicine.iupui.edu/clinpharm/DDIs/table.asp

<table>
<thead>
<tr>
<th>INHIBITORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

**SUBSTRATES**

- MAOIs: 
- PDEs: 
- E-selectin: 
- Anti-epitopes: 
- Oral Hypoglycemic Agents: 
- Antidepressants: 

**INHIBITORS**

- A Strong Inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- A Weak Inhibitor is one that causes a > 2.5-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- All other inhibitors.

**FDA-preferred and acceptable inhibitors** for in vivo experiments:

- Fluoxetine
- Paroxetine
- Sertraline
- Citalopram
- Escitalopram
- Duloxetine
- Venlafaxine
- Bupropion
- Lithium
- Carbamazepine
- Olanzapine
- Haloperidol
- Clozapine
- Quetiapine
- Aripiprazole
- Risperidone
- Ziprasidone
- Quetiapine
- Paliperidone
- Ziprasidone
- Olanzapine
- Clozapine
- Aripiprazole
- Risperidone
- Ziprasidone
- Quetiapine
- Paliperidone
What’s the metabolic fate of Don'tsnuzenall?

• Objective – metabolism in vivo
  – track metabolites in PK studies

• Objective – characterize excretion
  – Same mass balance experiment as in animals
    …no cage
  – Usually precedes
What factors affect the absorption and metabolism of Dontsnuzenall?

- **Objective** – Determine effect of food on drug absorption
  - A crossover study of fed vs fasted state
  - Optimally precedes Ph2
    - Need to use highest clinical dose
  - Pilot study as a part of an early single dose study
    - Allows early modification of formulation
  - Usually 1 quarter FPFV to Topline data

- **Objective** – Evaluate interactions from Nonclinical CYP studies
  - Known as Drug Drug Interaction studies (“DDI”)
  - Give Dontsnuzenall and drug known to inhibit, induce, or be a substrate of a given CYP
  - Usually 1 quarter FPFV to Topline data
  - Optimally precedes Ph2
Does the Formulation Behave as the Doses Suggest?

- Objective – Linearity of dosing through the proposed clinical dose range
  - Ensure plasma levels increase linearly as dose increases

- Objective – Proportionality of Dosing Units
  - e.g., compare 4x1 mg, 2x2mg and 1x4 mg to see if they give same plasma level

- Both studies 1 quarter FPFV to topline data
  - Optimally precedes Ph2

Drugs Today 2000, 36(1): 55
Lornoxicam, a new potent NSAID with an improved tolerability profile
Radhofer-Welte, S., Rabasseda, X.
Are there any populations with Special ADME Considerations?

• Renally Impaired
• Hepatically Impaired
• Children
  – During Ph3; plan 12 mo FPFV to topline data
  – Pediatric studies required under PREA
• Gender – if effect noted
• Elderly
  – As needed per indication and metabolism; plan on 1 quarter FPFV to topline data
Extended Release (ER) versus Immediate Release (IR) Plasma Profiles
How does the **Clinical Pharmacology Program** For a Modified Release Differ from An Immediate Release

- **Generally**, if the excipients are *Generally Recognized as Safe* (GRAS) and the PK levels, are lower than the IR, you don't need more toxicology studies
  - Exceptions exist, e.g., reformulating drugs approved long ago

- The dose range of the MR should be very close to the IR – IR dosing levels are *usually* used for planning Phase 3 trials (hence Ph 2 not usual)

- The goal in the tolerability comparison is often to show comparison to the IR *more so* than Pbo.

- The number of Phase 3 trials *can be* less than 2 since you already have evidence the active ingredient works. The Phase 3 trial must show the formulation has not rendered the molecule ineffective.
Stop 4: Ph2/3 Clinical Trials… from Design to Report
Study Objective/Research Question

Population of Interest → Sample

Test Drug → Control Drug

Measurement of Outcome

Statistical Comparisons

Interpretation

Extrapolation
Design of Phase 2/3 Studies

• A study in the patient population testing a hypothesis regarding the efficacy of a drug

• When done as part of a regulatory package, the study should support (“map to”) the indication and dosing guidance in terms of the
  – Primary endpoint + Population ⚫ Indication
  – Doses and dosing regimen ⚫ Dosing guidance
Where does it all start? The Protocol

• **General Information**
  – Identifying information for study and Investigators

• **Background Information**
  – Background literature and data

• **Trial Objectives and Purpose**

• **Trial Design**
  – Design, endpoints, measures taken to minimize/avoid bias, treatments, schedule, etc

• **Selection and Withdrawal of Subjects**
  – Subject inclusion /exclusion , stopping, withdrawal criteria .

• **Treatment of Subjects**
  – The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
Where does it all start? The Protocol

• **Assessment of Efficacy**
  – Efficacy parameters, methods and timing for assessing, recording, and analysing of efficacy parameters.

• **Assessment of Safety**
  – Safety parameters, The methods and timing for assessing, recording, and analysing safety parameters.

• **Statistics**
  – Analysis of endpoints an assessments, sample size determination, missing data

• **“Boilerplate”**
  – Definitions, Standard procedures

• **Appendices**
DESIGN
Common Study Designs

• Case-Control Study
  – Retrospective (typically) Observational Study
    • Disease+ vs Disease- is exposure different

• Cohort Study
  – Prospective (typically) Observational Study
    • Exposure+ vs Exposure - is risk of disease different

• Controlled Clinical Trial
  – Prospective Experimental Study
  – Best design to study causality
  – Design of confirmatory trials
Parallel Study Design

Baseline

New Drug

Control Drug

Randomization
Cross-over Study Design

Baseline

Randomization

Control Drug

New Drug

Washout Period

Control Drug

New Drug
OBJECTIVE
What you want to show with this trial?

Efficacy

- New drug is more efficacious than sham treatment - *placebo controlled (superiority) trial*
- New drug is as efficacious as the current therapy - *active controlled equivalence trial*
- Combination of new drug and existing drug (or two existing drugs) is better than no treatment and better than each component drug - *combination trial*
What you want to show with this trial?

• Do better with this drug than prior to treatment - baseline controlled trial
  – Not typically accepted because of changes in disease over time

• New drug is more efficacious than you would with past medical practice - historically controlled trial

Safety Studies

• That new drug is as safe (regarding specific endpoint) as current therapy or placebo
  – Should assess efficacy and safety simultaneously
  – The playing field must be level, or you must have what is known as equipoise
POPULATION
Assignment - Randomization

• Randomization attempts to assign individuals to groups (or vise-versa) without bias.
  – Protects Against Selection Bias
  – Balances Treatment Groups
    • With respect to factors known or suspected to influence outcome.
    • With respect to factors which are not known to affect outcome.
  – Insures the Validity of Statistical Tests
Blinding or Masking

• Double Blind - Neither the patient nor the investigator know group assignment (test or control)
• Single Blind - The patient does not know group assignment
• Open Label – Group assignment known by patient, investigator, etc.
Study Sample

What is the population of interest?

- **Intent to Treat (ITT)** - All people randomized to a given treatment
- **Modified ITT** - ...and who took one dose of medication
- **Completers** - ...and who made it to the endpoint
- **Per Protocol** - ...and without major violations of the protocol
Inclusion Exclusion Criteria

• An inclusion criterion is an exclusion criterion with a smile :)
  – e.g., Ages 18-65 allowed = No one under age 18 or over 65 is allowed.

• Frequently used to exclude DDIs
  – e.g., No one taking medications metabolized by CYP3A4 allowed

• Frequently used to exclude subject for whom there is insufficient safety information
  – e.g., No one with unstable cardiac disease

• "Common wisdom"
  – Every criterion cuts your population down by 5%
Study Size?

- Adequate to demonstrate desired outcome
- Factors which determine sample size:
  - the size of the Type I error (alpha)
  - the size of the Type II error (Beta or 1-power)
  - the difference between the expected improvement in the treated group and the control group responses
  - the variability of the responses (variance)

\[
n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\delta^2} = \frac{(1.960 + 1.282)^2 2^2}{1^2} = 42.04 \approx 43
\]

Two-sided test, \( \alpha = 0.05 \), power = 90% Difference = 1 unit (e.g. hr)
Standard deviation = 2 hr

www.nihtraining.com/cc/ippcr/current/.../Johnson111505bw.ppt
TREATMENT
Control Group

• The drug, device, or test procedure administered in a clinical trial that serves as a standard against which experimental group are evaluated.

• For non-life-threatening diseases, the control group can be a placebo.

• For life-threatening diseases, the control group is often the standard care for the disease.
  – May be historical; placebo rate of similar trials
The Dose Response

• The most typically accepted study design is the parallel fixed-dose study
• What you should know about your dose range
  – The “maximum tolerated dose”
  – The minimum dose (MED) that gives a significant effect
  – The shape of the curve leading up to the MED
  – The effect of titration on the drug's tolerability
# Dose Response Rationale

**TABLE 1**

**DATA OF MATERSON**

Fall in blood pressure (systolic/diastolic) from baseline in erect and supine position with each of four dose levels of chlorthalidone and placebo.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Fall in Blood Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
</tr>
<tr>
<td>Placebo</td>
<td>0/2</td>
</tr>
<tr>
<td>12.5 mg</td>
<td>5/4</td>
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<tr>
<td>25 mg</td>
<td>11/5</td>
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<tr>
<td>50 mg</td>
<td>10/6</td>
</tr>
<tr>
<td>75 mg</td>
<td>11/6</td>
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</tbody>
</table>
ENDPOINTS
Endpoints

• The primary goal in choosing endpoint(s) is to select definitive and appropriate measures of the condition being studied
  – Should be clinically relevant
  – Should coincide with current medical practice
  – Should be measurable/interpretable

• NEED A CENTRAL or PRIMARY ENDPOINT…this drives design, analysis, etc
  – ☹…to study X and Y and Z and AA…
  – ☹…to study the efficacy and safety of Drug X
Choice of Endpoints

• Numeric, Categorical, Ordinal
  – Change in weight
  – Yes vs. No
  – None, Mild, Moderate, Severe…

• Single vs. composite
  – Composite endpoints – Is one component driving outcome?

• Objective or subjective
  – Time until asleep
  – I slept good/bad
After the Study Visit…

<table>
<thead>
<tr>
<th>Source Document</th>
<th>Case Report From</th>
<th>Database</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written</td>
<td>Paper</td>
<td>Electronic</td>
<td>Statistical</td>
</tr>
<tr>
<td>Electronic</td>
<td></td>
<td>Electronic</td>
<td>PK</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical</td>
</tr>
</tbody>
</table>
Study Reports... The Icing on Cake

Read ICH E3
Stop 5: Clinical Assessment of Efficacy

...Transfer to the Safety Line
What is Efficacy…Why do We Care

• Efficacy ¹ – The power to produce an effect

• Efficacy vs Effectiveness ²
  – Efficacy is a narrower definition that means how well something works in an ideal or controlled setting, such as a clinical trial. Effectiveness describes how well it works under “real-world” conditions. Effectiveness, for example, takes into consideration how easy a drug is to use, and potential side effects, whereas efficacy measures only how well it produces the desired result.

• Why do we care
  – Need to ensure the drug works (efficacy)
    • Obtain a claim in label ☞ able to promote
  – Need to assess safety in the context of an efficacious dose (Remember Paracelsus!)
  – Some authorities (e.g., payers) are also particularly interested in effectiveness.

¹ http://www.merriam-webster.com/dictionary/efficacy
² http://getedited.wordpress.com/2009/10/26/efficacy-vs-effectiveness/
“Substantial Evidence”

SEC. 505. [21 USC 355] New Drugs

• (d) Grounds for refusing application; approval of application; "substantial evidence" defined. If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that …. (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof…. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness…
“Confirmatory Evidence”

- If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.
Statistics is never having to say you’re certain

There are lies, damn lies and statistics

-Mark Twain
Significant Results

Clinical Significance
The amount of difference or relationship between treatments that assures that the results are clinically meaningful.

Sometimes a scale of the Global Clinical Impression (severity or improvement) is performed to assess this; the details around investigator or patient instructions are critical.
New Indications

The After-Life: Postmarketing Development

Pediatrics

Formulations / Follow On

Partner?

Generic

OTC
Shrinking time to second in class requires that you get out of the gates fast & hard

Years Between Drug Launch and First Competitor

<table>
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<tr>
<th>Years</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
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</thead>
<tbody>
<tr>
<td>Inderal 1968 (hypertension)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Longest</strong></td>
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<tr>
<td>Tagamet 1977 (ulcer)</td>
<td></td>
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<td></td>
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<tr>
<td>Capoten 1980 (hypertension)</td>
<td></td>
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<tr>
<td>Seldane 1985 (hayfever)</td>
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<tr>
<td>AZT 1987 (AIDS)</td>
<td></td>
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<tr>
<td>Mevacor 1987 (cholesterol)</td>
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<tr>
<td>Prozac 1988 (depression)</td>
<td></td>
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<tr>
<td>Diflucan 1990 (fungal infections)</td>
<td></td>
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</tr>
<tr>
<td>Recombinant 1992 (hemophilia)</td>
<td></td>
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</tr>
</tbody>
</table>

- Increased competitiveness
- Must maximize opportunity from day one

Source: A.T. Kearney, The Economist 09/20/97
How Companies Plan to Counter Generics

Life Cycle Management ROI

Dollars Earned Per $1 Spent

Want To Milk A Cash Cow? Try Pediatric Exclusivity Pharmalot By Ed Silverman // October 7th, 2010 //
Pediatric Development

- Best Pharmaceuticals for Children Act
- Pediatric Research Equity Act

The Carrot and Stick of Pediatric Drug Development
PREA vs. BPCA

- Studies mandatory
- Studies required only on product & indication being reviewed
- Studies not required for orphan indications
- Standard review – *unless it qualifies for priority*
- Drugs and biologics
  - Both - Pediatric studies must be labeled

- Studies voluntary
- Studies on entire active moiety
- WR may be issued for orphan indications
- Priority review
- Drugs only
Over-The-Counter Drugs

<table>
<thead>
<tr>
<th>OTC Category</th>
<th>2006 (in millions)</th>
<th>2007 (in millions)</th>
<th>2008 (in millions)</th>
<th>2009 (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne Remedies</td>
<td>$318</td>
<td>$328</td>
<td>$333</td>
<td>$333</td>
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<tr>
<td>Analgesics, External</td>
<td>$314</td>
<td>$318</td>
<td>$321</td>
<td>$307</td>
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<tr>
<td>Analgesics, Internal (includes other pain products)</td>
<td>$2,340</td>
<td>$2,419</td>
<td>$2,449</td>
<td>$2,486</td>
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<tr>
<td>Antidiarrheals</td>
<td>$170</td>
<td>$174</td>
<td>$169</td>
<td>$104</td>
</tr>
<tr>
<td>Anti-Smoking Products</td>
<td>$501</td>
<td>$504</td>
<td>$492</td>
<td>$493</td>
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<tr>
<td>Cough/Cold and Related</td>
<td>$3,542</td>
<td>$3,639</td>
<td>$4,107</td>
<td>$4,172</td>
</tr>
<tr>
<td>Eye Care</td>
<td>$422</td>
<td>$442</td>
<td>$459</td>
<td>$474</td>
</tr>
<tr>
<td>First Aid</td>
<td>$604</td>
<td>$628</td>
<td>$649</td>
<td>$655</td>
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<tr>
<td>Foot Care</td>
<td>$352</td>
<td>$355</td>
<td>$347</td>
<td>$334</td>
</tr>
<tr>
<td>Heartburn (includes anti-gas)</td>
<td>$1,247</td>
<td>$1,264</td>
<td>$1,242</td>
<td>$1,277</td>
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<tr>
<td>Laxatives</td>
<td>$708</td>
<td>$762</td>
<td>$810</td>
<td>$822</td>
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<tr>
<td>Lip Remedies</td>
<td>$369</td>
<td>$410</td>
<td>$415</td>
<td>$408</td>
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<tr>
<td>Oral Antiseptics and Rinses</td>
<td>$687</td>
<td>$730</td>
<td>$744</td>
<td>$727</td>
</tr>
<tr>
<td>Sunscreens and Blocks</td>
<td>$366</td>
<td>$415</td>
<td>$477</td>
<td>$499</td>
</tr>
<tr>
<td>Toothpaste</td>
<td>$1,216</td>
<td>$1,247</td>
<td>$1,254</td>
<td>$1,264</td>
</tr>
<tr>
<td>All Others</td>
<td>$2,141</td>
<td>$2,394</td>
<td>$2,515</td>
<td>$2,525</td>
</tr>
</tbody>
</table>

Source: The Nielsen Company (total U.S. - food, drug, and mass, excluding Wal-Mart)

http://www.chpa-info.org/pressroom/Sales_Category.aspx
OTC Drug Products

General Concepts

• Need to ensure that consumers can:
  – Diagnose the underlying condition
  – Determine whether drug is appropriate for them
  – Self-administer safely and effectively
  – Avoid potential serious consequences
  – Recognize when to see a physician or seek emergency assistance

• Label comprehension is key to approval
  – All labeling directed to the consumer
Generic Drugs

Generics: A $90 Billion Opportunity

Western Europe: $17bn
US, Canada: $50bn
China: $3bn
Latin America: $2bn
Eastern Europe & Russia: $10bn
Japan: $4bn
Rest of World: $4bn

Total World Pharmaceutical Sales: $600bn
Source: TS Research, IMS Health, VCI Pharma Handbook

Definition of Generic Drug

• “Same” as a drug product listed in the Orange Book (“listed drug”)
  – active ingredient(s)
  – route of administration
  – dosage form
  – strength
  – conditions of use recommended in labeling

  OR. . .

• Certain changes from a listed drug if FDA has approved a suitability petition

• Labeling same as reference listed drug except for
  – Manufacturer/distributor
  – Indications protected by patent or exclusivity
Summary

• Clinical Development is the portion of the program with an aim to provide information about the dose relationship of safety and efficacy and to provide evidence for risk benefit considerations
• The Clinical Pharmacology portion is driven by specific questions about the drug:patient interactions
• The Efficacy considerations should be directed at testing a clinically meaningful hypothesis in the target population
• Postmarketing planning should be in parallel with the registrational program and execution and execution should