Design of Clinical Drug Development Programs*

* For Smarties

Dr Christopher D Breder 4/03/14
Disclaimer

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

• To give the audience a general idea of the pharmaceutical development strategies used in the process of filing a US marketing application and of increasing the value of the approved asset
Where do New Drug Products come From?
## Development Lead Selection

<table>
<thead>
<tr>
<th>New Molecular or Chemical Entities *</th>
<th>Biologics</th>
<th>Reformulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Synthesis</td>
<td>Antibodies</td>
<td>Formulation +</td>
</tr>
<tr>
<td>Structure Activity Relationships</td>
<td>Oligonucleotides</td>
<td>Modified Release including</td>
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<tr>
<td>“Fishing”</td>
<td>Enzymes</td>
<td>Controlled and</td>
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<tr>
<td>Fortuitous Finds</td>
<td>Replacement proteins</td>
<td>Extended release</td>
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<tr>
<td>Etc...</td>
<td>Etc...</td>
<td>Etc...</td>
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</tbody>
</table>

* A drug where no active moiety has been approved through Sec. 505(b) of the FD&CA

**High Throughput Screening**
Development Lead Selection.2

4 Chemical Candidates, A, B, C & D

Receptor Binding
A = 23 nM; B=45 nM; C=67 nM; D=120 nM

Off target < 500nM
A = 5HT2B Ag; B = M1; C = Mu Ag; D=CCK

Oral (+/- SQ, INT) Bioavail.
B = ++++, C= +, D= +++

In Vivo PD Screen
B = ++++, C= ++, D= ++++

Preliminary tox
B ~ D

Extras...ADME, PgP, etc
B “-“; D= CYP3A4 inh, PgP subs.

B goes to “IND enabling” program; SAR focus on B like molecules
The Goal

Data from these studies obtained prior to Ph3
Aim of Drug Development

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

- **Nonclinical [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.
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/
The Basis of Efficacy

• SEC. 505. [21 USC §355] New Drugs
• (e), "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations,... [that] drug will have effect it purports or represented to have under conditions of use prescribed, recommended, or suggested in labeling or proposed labeling thereof. If 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 preceding sentence.
Adequate and well-controlled studies.

- Clinical investigations of a drug distinguish effect of drug from other influences, such as spontaneous change in course of disease, placebo effect, or biased observation.

- Adequate and well-controlled studies have following:
  - clear objectives; summary of methods
  - a valid comparison with a control
  - assurance [subjects] have the disease or condition being studied
  - The method of assigning patients to treatment and control minimizes bias
  - Adequate measures are taken to minimize bias
  - Methods of assessment of subjects' response well-defined
  - adequate analysis to assess the effects of the drug
Conclusion 1. Efficacy Requirements

• So, unless you have contributory evidence, you should plan on doing two adequate and well controlled trials (AWCT).
  – “Phase 3”, “Pivotal”, “Registrational”, or “Confirmatory”

• Exceptions?

*Coming soon….How to get to your 2 adequate and well controlled Phase 3 trials.*
Patient / Metabolism Specific Studies

• Some studies you should do prior to Phase 3
  – Renal or Hepatic Impairment PK (RIPk or HIPk)
    • Depending on the metabolism, population
    • The results may effect whether you include this population or dose adjust in Phase 3
  – Drug Drug Interaction Studies (DDI)
    • Depending on the In Vitro Metabolic Profile
    • The results may effect whether you include this population or dose adjust in Phase 3

• Very often these subjects are excluded from Phase 2 because these studies have not been performed.
  – Usually dose not effect your overall dose / efficacy.safety exploration
    • Often want to determine if drug efficacious before investing in these studies
Clinical Development Path ....so far

- 2 AWCT Ph3
- NDA

Data from these studies obtained prior to Ph3
How do I get to my 2 AWCT

• What do I need to know to conduct these AWCTs?
  – Right dose in terms of efficacy and safety, from...
    • Phase 2b trials – effect of dose range on efficacy and safety
Phase 2, the Lone Unloved Development Phase

• Not strictly required by regulations
  – However, a case may be made for conduct of Phase 3 based on thorough understanding of the dose / efficacy or relationship
  – E.g., for drugs with toxicities, may ensure the lowest efficacious dose is used.

• These trials are almost as long and expensive in certain designs as the Phase 3 studies
  – Can they be used as registrational?

• In certain cases, you can make argument for not doing
  – Modified release formulations with well behaved PK
Aim of Drug Development

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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>
</tr>
<tr>
<td>25 mg</td>
<td>11/5</td>
</tr>
<tr>
<td>50 mg</td>
<td>10/6</td>
</tr>
<tr>
<td>75 mg</td>
<td>11/6</td>
</tr>
</tbody>
</table>
Phase 2: 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 efficacious dose (MED) that gives a significant effect
  – The shape of the curve leading up to the MED
  – The effect of titration on the drugs tolerability
Clinical Development Path ....so far

Phase 2b → 2 AWCT Ph3 → NDA

Data from these studies obtained prior to Ph3
How Do I Get to Study My Drug in Patients (Phase 2)?

• What information do I need to start studying my drug
  – For extended periods?
  – In large numbers of subjects?
  – In people with different medical vulnerabilities?
  – In people on concomitant therapies?

• Answer
  – Reasonable steps in trial size and duration
  – Well characterized clinical pharmacology
Clinical Pharmacology Trials Before Phase 2

- First in Human (FIH) or Single Ascending Dose (SAD)
  - Prerequisites: IND enabling nonclinical studies per ICH M3R2 (see slide 21)
  - What it gives you
    - Tolerability/Safety bridge to tox data
    - Approximate (overestimates) – repeat dose tolerability
    - Data for PK modeling
  - Allows: MAD, Potentially other SD studies (though determination of the MTD in the MAD is best done early)
Single Ascending Dose Study

- **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

![Single Dose (SD) PK Curve](source: www.medscape.com)
Clinical Pharmacology Trials Before Phase 2

- Multiple Ascending Dose Study (MAD)
  - Prerequisites: SAD, Nonclinical repeat dose studies of appropriate duration and population (as applicable)
  - What it gives you
    - Maximal Tolerated Dose ~ top clinical dose
    - Tolerability/Safety data at or > clinical doses
    - Critical PK data – $C_{\text{min}}$, accumulation etc.
  - Allows:
    - Dose selection for Phase 2,
    - Studies where you need to know the top clinical dose (e.g., QT study, Food Effect study)
Multiple Ascending Dose Study

- **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
Clinical Development Path ....so far

Data from these studies obtained prior to Ph3
Other Supportive Clinical Pharmacology Studies

- Thorough QT
- Food Effect
- Dose Linearity
- Dose Proportionality
- Mass Balance
Thorough QT Study (TQT)

- A thorough QT study is performed to determine potential of drug to prolong the QT interval of EKG.
  - This effect has been linked to a ventricular arrhythmia, Torsades de Pointes, which may lead to sudden cardiac death.
  - The study is done with the new drug, a placebo and a positive control known to induce QT prolongation.
  - Primary endpoint: Upper bound of 90% confidence interval in the change from baseline of a time series of EKGs cannot include 10 ms
Food-Effect Study

- Objective – Determine effect of food (high fat meal) on drug absorption
  - A crossover study of fed vs fasted state
  - Primary endpoint - This is a bioequivalence study (Exposure in the fasted state should be BE to that in the fed state)
  - If not BE, labeling or reformulation depending on circumstances

BE = bioequivalent or bioequivalence depending on the context
Timing Considerations of Clinical Pharmacology Studies

• Thorough QT
  – often done after efficacy determined unless there is a prior signal of concern
    • hERG assay; CV safety pharmacology study, Ph1 EKG

• Food Effect
  – Optimally precedes Ph2; trials prior done fasted
  – May consider doing a pilot study of one or two subjects fed in early studies (SAD or SD in modified-release program) to check for gross food effects that would make one consider reformulating
Dose Linearity

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

• Primary endpoint: 

Dose Proportionality

- **Objective – Proportionality of Dosing Units**
  - E.g., compare 4x1 mg, 2x2mg and 1x4 mg
  - Needs to know from Ph-2 studies, what dose-range to be investigated in Ph-3 and how to escalate dosing (titration to higher doses); this will determine what dosage units are needed.

- If one uses multiple tablets to make up a certain dose (your top clinical dose is greater than your top dosage strength), then this study should be done prior to Ph-2A.
Metabolism Studies

• Objective – metabolism in vivo
  – track metabolites in all PK studies once metabolites established

• Objective – characterize excretion
  – Mass Balance Study - Same mass balance experiment as in animals ...no cage
  – only way to know what metabolites are in man and have measureable exposure -
    microsomes and hepatocytes don’t fully inform with respect to this.
  – Essential for downstream studies
Timing of Other Clinical Pharm Studies.

- **Mass Balance**
  - "as early as possible"
  - Many advocate this study should be the 3rd study conducted (after FIH and MAD study). Due to improvements in analytical capabilities, this study is now usually done much later in the development program. Today, plasma and urine samples from FIH can be analyzed for metabolites without 14C material as they can utilize the mass spectrometer to scan for potential metabolites. However, it is important to confirm findings once the compound is worthy of Phase 3 development.

- **Dose Linearity**
  - Before Phase 2A, you should have an idea of this information.

- **Dose Proportionality**
  - Pivotal study with to be marketed formulation before Phase 3
Distribution in 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
Clinical Development Path ....so far

SAD (DL preliminary) → MAD → Phase 2b → 2 AWCT Ph3 → NDA

TQT*, DL DP DDI

MB

RIPk HIPk DDI

Data from these studies obtained prior to Ph3
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What is Ultimately Required for Safety

• Number treated for 6 months at intended clinical doses should be adequate to characterize the pattern of ADEs over time. Usually 300 to 600 patients adequate;

• Some patients should be treated with drug for 12 months. 100 patients for minimum of one-year is acceptable

• It is anticipated that total number treated with drug, including short-term exposure, will be about 1500.

• Filing for approval usually possible based on data from patients treated 6 months. Data on patients treated through 12 months should be submitted as soon as available and prior to approval in USA. In the USA, initial submission for drugs designated as priority drugs must include the 12 month patient data.

• Reasons for exceptions [i.e larger databases] exist

Conclusion 2. Safety Requirements

- As a first approximation, you will need at least 1500 subjects exposed to drug
  - 300 for 6 months
  - 100 for 1 year
- If there are any of a variety of safety concerns, these numbers could go more (# subjects) or longer (duration of exposure)

Coming soon... How to get to your adequate exposure database.
Long Term Extension Studies (LTES)

- **Objective:**
  - Long term safety data, more subjects for longer
    - Allows observation of AEs that take longer or are less frequent than the duration and sample size of the RCT
  - Continuation of therapy from RCTs until marketing
  - Marketing claims – typically need controlled data (not OL)

- **Design**
  - *Usually* open label
    - Allows Investigators to flexibly dose to effect or based on tolerance
    - Harder to characterize safety without control group
  - Can either be associated with a specific, blinded RCT or you can have one LTES that “catches” subjects from multiple trials
  - Visits and evaluations *usually* less frequent than double blind (DB) RCT used for demonstrating efficacy
In this example, subjects are enrolled in the LTES from a preceding DB RCT or are drug naïve.

At the end of the DB RCT treatment period, subjects are titrated to a common dose. After achieving that dose, the Investigator is allowed to flexibly change their dose level throughout the trial, to a dose that is usually between a subject’s minimally effective (Z) and maximally tolerated (W) dose.

Various rules are applied as to the common dose, the frequency of dose changes, the speed of titration and the minimum and maximum allowable dose. Note the study visits are less frequent.
Clinical Development Path ....so far

- SAD (DL preliminary)
- MAD
- Phase 2b
- 2 AWCT Ph3
- OLES
- NDA

Data from these studies obtained prior to Ph3
Modifed Release

Extended Release

Delayed Release

Controlled Release

Source: Pharmacotherapy © 2003 Pharmacotherapy Publications
Extended Release (ER) versus Immediate Release (IR) Plasma Profiles

![Graph showing plasma profiles for Tramadol]

- **ULTRAM ER Tablets, 200 mg q.d.**
- **ULTRAM Tablets, 50 mg q.d.**

a. Tramadol
How does the **Development 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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Dosing</th>
<th>FPFV-Topline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol dumping</td>
<td>Test for alcohol dumping in reaction vessel; May need human study depending on results</td>
<td>SD</td>
<td>1Q each</td>
</tr>
<tr>
<td>SD</td>
<td>Test a # formulations vs IR; Pilot fed arm</td>
<td>SD, X-over</td>
<td>1 Q</td>
</tr>
<tr>
<td>MD</td>
<td>Test top 1-2 candidates vs IR; Final candidate choice</td>
<td>Steady State, X-over</td>
<td>2Q+</td>
</tr>
<tr>
<td>Relative Bioavailability</td>
<td>Top clinical dose MR vs IR; Gives good picture of tolerability; May add Pbo</td>
<td>Steady State, X-over</td>
<td>3-4Q</td>
</tr>
<tr>
<td>Dose proportionality</td>
<td>As per IR</td>
<td>SD, X-over</td>
<td>1 Q</td>
</tr>
<tr>
<td>Dose linearity</td>
<td>As per IR</td>
<td>SD, X-over</td>
<td>1 Q</td>
</tr>
<tr>
<td>Food Effect</td>
<td>As per IR</td>
<td>SD, X-over</td>
<td>1 Q</td>
</tr>
<tr>
<td>Bridging GMP</td>
<td>Detect changes in performance with scaleup; As per IR</td>
<td>SD, X-over</td>
<td>1 Q</td>
</tr>
</tbody>
</table>
# Prototypic Clinical Development Plan

(Modified Release Type)

<table>
<thead>
<tr>
<th>Study</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
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<tbody>
<tr>
<td>Pilot SD (w pilot Fed arm)</td>
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<tr>
<td>Pilot MD</td>
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<td>Rel BA</td>
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<td>Dose Prop</td>
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<td>Dose Lin</td>
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<td>Food Effect</td>
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<td>Bridge API</td>
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<tr>
<td>Peds PK</td>
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<td>Launch</td>
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</tbody>
</table>
Logical Studies Flow - Biologics

FIH/SAD: Based on NOEL; Often in HNV (depends on effect)
MAD: Often in HNV (depends on effect)
Duration of Effect: How often do you need to dose in terms of EFFECT
Titration: How fast can you get there; Can you go higher if slower

Phase 2
Phase 3

Other Studies: TQT, Drug Interaction, Special populations, etc

HNV: Healthy Normal Volunteer; MTD: Maximal tolerated dose; NOEL: No Observed Effect Level; TQT: Thorough QT Study
The After-Life: Postmarketing Development

New Indications

Formulations / Follow On

Generic

Pediatrics

Partner?

OTC
How Companies Plan to Counter Generics

Life Cycle Management ROI

Dollars Earned Per $1 Spent

- Pediatric Exclusivity
- New Indication
- New Formulation
- Next Generation Product
- Authorized Generic
- Strategic Pricing

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
Pediatrics - 3 Flavors

Study
- Epilepsy
- Asthma

Defer
- Depression
- Type 2 Diabetes

Waiver
- ALS
- Parkinson's

Some diseases have distinct Adult and Pediatric Indications but a pure adult program may not be allowed if it is expected that pediatrics will be prescribed the medication.
Pediatric Programs

• Nonclinical "Juvenile Tox Study (-ies)"
  – Designed in conjunction with review body including items of special interest given drugs mechanism

• Clinical Program - An example (there are many ways to do this)
  – Phase 2A study
    • Main goal is PK, tolerability leading to dose selection with Pharmacodynamic secondary endpoints
  – Phase 3
  – Issues
    • Weight based dosing
    • Placebo
    • Ethics - Subpart D
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>
</tr>
<tr>
<td>Analgesics, External</td>
<td>$314</td>
<td>$318</td>
<td>$321</td>
<td>$307</td>
</tr>
<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>
</tr>
<tr>
<td>Cough/Cold and Related</td>
<td>$3,542</td>
<td>$3,639</td>
<td>$4,107</td>
<td>$4,172</td>
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<tr>
<td>Eye Care</td>
<td>$422</td>
<td>$442</td>
<td>$459</td>
<td>$474</td>
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<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>
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<tr>
<td>Toothpaste</td>
<td>$1,216</td>
<td>$1,247</td>
<td>$1,254</td>
<td>$1,264</td>
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<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

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
  – “Voluntary” pieces of approved labeling
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