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Overview of the Clinical Development Decision-Making Process

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Drug Development Label Driven

"We Sell Only the Package Insert,

We Give Away the Product !"

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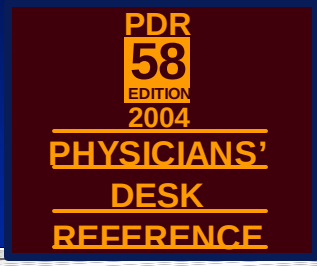
The Outcome Measure



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A Decision is...

- An allocation of RESOURCES
  - *Add Resources*
  - *Remove Resources*
  - *No change in Resources*

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Clinical Projects WILL Fail, so...

✓ Fail early *BEFORE* going into the clinic

✓ Fail *EARLY* in the development cycle

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Critical Decisions

- Therapeutic areas?
- Disease state?
  - Dx, Px, Rx. Tx
- Screens? Predictiveness?
  - Activity? Safety? ADME? Value?
- *Differentiation targets?*
- *Data for candidate selection?*
- *Data for proof of concept/differentiation?*
- *Global development & regulatory strategy?*

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Very Critical Decisions

- ✓Differentiation
- ✓Dose
- ✓Dose regimen
- ✓Patient populations
- ✓Cost per treatment day

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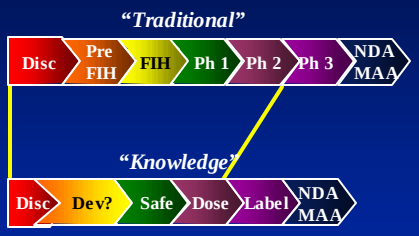
Paradigm Shift: Knowledge Based



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Where Can We Learn Drug Development?

- Courses-PERI, CDDS, FDLI, NIH
- FDA Advisory Committee Mtgs.
- FDC "The Pink Sheets"
- FDC "Drug Approval Monthly"
- Analyze Package Inserts

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Clinical Development Rules

1. Manage the failures.
2. Time is the enemy.
3. Keep your eye on where the puck is going to be.
4. Differentiate.
5. It takes a village to develop a drug.

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Rule # 1

- Manage the failures.
  - –The successes will take care of themselves--but not all of the time

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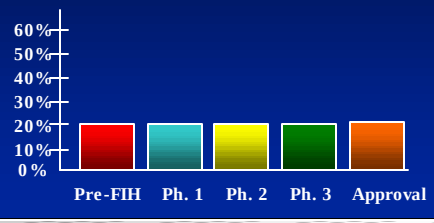
Impact of Established Decision Criteria

(All drugs are created equal)

Attrition Distribution



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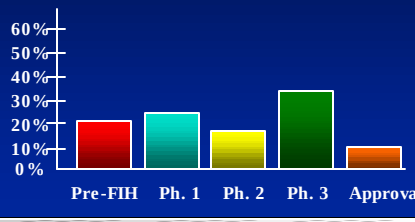
Impact of Established Decision Criteria

(Too busy for decision-making)

Attrition Distribution



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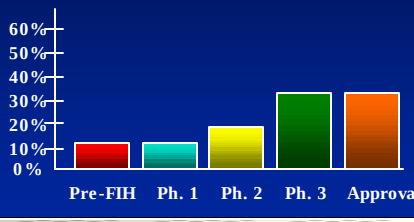
Impact of Established Decision Criteria

(Never met a drug they didn't like)

Attrition Distribution



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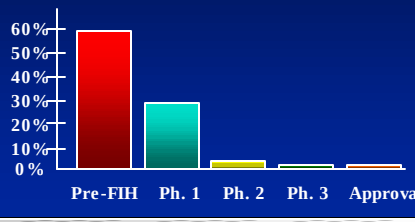
Impact of Established Decision Criteria

(Management of the failures)

Attrition Distribution



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Overview of the Medications Development Process

- ✓ Overview
- Portfolio Design, Planning and Management
- Decision Points Concept

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Rule # 2

- Time is the enemy.
  - –Nothing beats a well designed drug development strategy.

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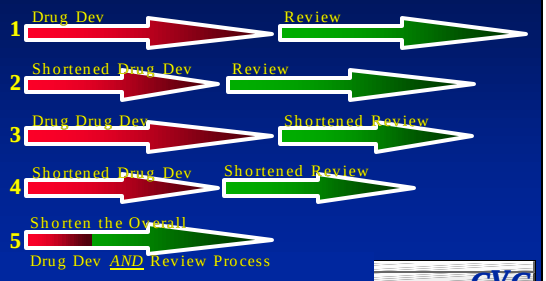
Shortening the Overall Process



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Rule # 3

- Keep your eye on where the puck is going to be.
  - Drug development is a highly regulated process.

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Definition of: "A New Drug"

- "...any drug that is not generally recognized as safe and effective under the conditions prescribed, recommended, or suggested in the labeling..."
  (*marketed after 1939*)
  Section 201 (p)--Federal Food, Drug and Cosmetic Act of 1938, As Amended

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Definition of: "A New Drug"

- ✓ NME (NCE) / NBE ?
- ✓ New Combination ?
- ✓ New Formulation ?
- ✓ New Indication ?
- ✓ Rx to OTC Switch ?

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Critical Decisions

- Therapeutic areas?
- Disease state?
  - Dx, Px, Rx, Tx
- Screens? Predictiveness?
  - Activity? Safety? ADME? Value?
- *Differentiation targets?*
- *Data for candidate selection?*
- *Data for proof of concept/differentiation?*
- *Global development & regulatory strategy?*

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Prove & Convince

- ✓ Select Lead
- ✓ Assess Safety
- ✓ Identify Subjects Differentiation & POC/POP
- ✓ Select Dose & Select Dose Regimen
- ✓ *Convince whom first ??*

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Prove & Convince

- ✓
- ✓ Regulatory Agencies
- ✓ Purchasers
- ✓ Prescribers
- ✓ Patients

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Medications Development

The process of generating the scientific and technical data to…

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Development Data For NDA / PLA / MAA Review

- ✓ Preclinical Data
- ✓ Chemistry Manufacturing Controls (CMC) Data
- ✓ Clinical Data
- ✓ Biopharmaceutical Data
- ✓ ???

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The Gold Standard

Clinical Data to Support FDA NDA/BLA and BoH/MAA Approvals

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The Platinum Standard

The Clinical Data to Support Reimbursement

- → Outcomes
- → Differentiation
- → Cost of New Medication Vs.

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Overview of the Medications Development Process

- Overview
- ✓ *Portfolio Design, Planning and Management*
- Decision Points Concept

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A Portfolio is…

The combination of *all* R&D projects, that based on past company, industry and regulatory performance, *will predictably yield valuable new products at the rate needed* to support the planned growth of the organization.

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Why ?

- Design the future
- Increase the odds
- Maximize success

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What Happens to My Project ?

5-10 INDs

?	?	? NO	? NO	?
ANIMAL SAFETY	CLINICAL SAFETY	CLINICAL EFFICACY	COMMERCIAL INTEREST	NDA

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The Outcome of R&D

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Drug Development Process: Probability of Success

Milestone	Probability of Approval
Lead ID	≤ 5%
Enter Development	10%
First in Man	15%
Proof of Concept	40%
Phase 2/3 Transition	80%
Regulatory Submission	90%

Pharmaceutical Project Management, Tony Kennedy, Drug & Pharm. Science, Vol. 86

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Drug Development Process: Reasons for Research Abandonment INDs filed 1985-1989

Efficacy	41%
Safety (Human & Animal)	26%
Economics	29%
Other	4%

J. DiMasi, *Clinical Pharmacology and Therapeutics*, July 1995, pages 1-14

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Drug Development Process: Success Rates Self-Originated INDs filed 1970-1974

Antineoplastic	44%
GI	33%
Respiratory	30%
Analgesic/anesthetic	24%
Antiinfective	22%
Endocrine	16%
CNS	13%
Cardiovascular	12%

J. DiMasi, *Clinical Pharmacology and Therapeutics*, July 1995, pages 1-14

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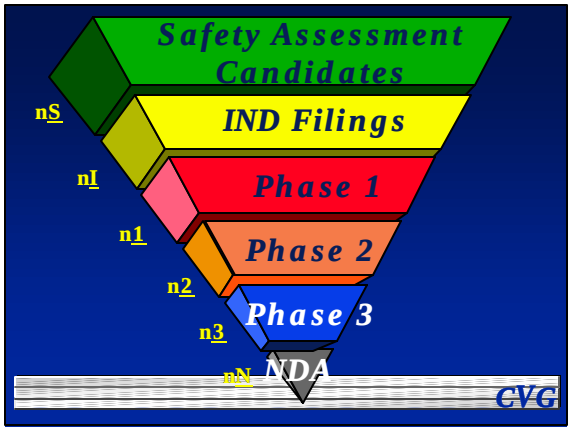
Safety Assessment Candidates
nS
IND Filings
nI
Phase 1
n1
Phase 2
n2
Phase 3
n3
nN
NDA
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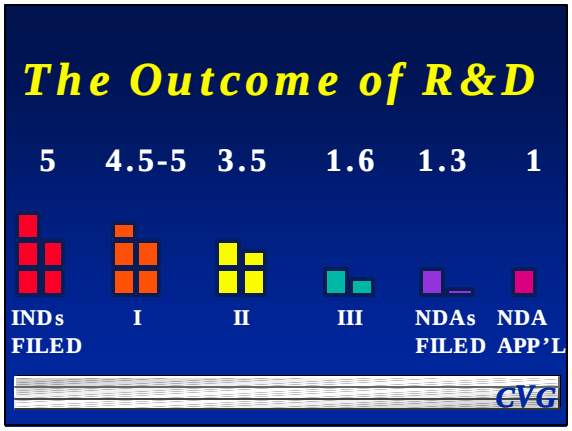
The Outcome of R&D
5
4.5-5
3.5
1.6
1.3
1
INDs FILED
I
II
III
NDAs FILED
NDA APP'L
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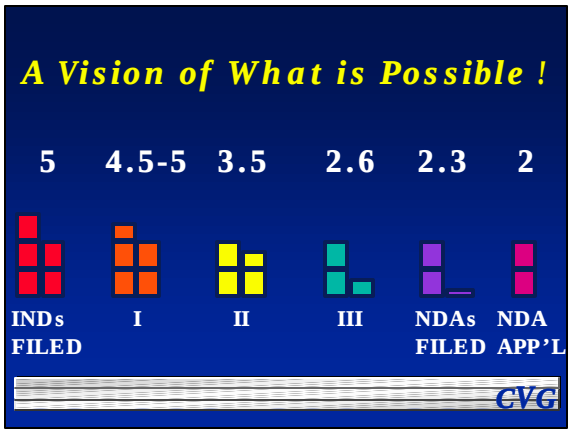
A Vision of What is Possible !
5
4.5-5
3.5
2.6
2.3
2
INDs FILED
I
II
III
NDAs FILED
NDA APP'L
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Overview of the Medications Development Process
Overview
Portfolio Design, Planning and Management
Decision Points Concept
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Key Decisions in Clinical Development
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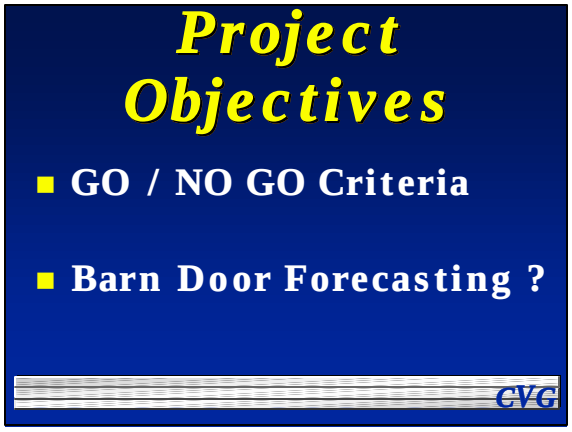
Project Objectives
GO / NO GO Criteria
Barn Door Forecasting ?
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Drug Development: Activity-Based Process

- ✓ Discovery
- ✓ Preclinical Development
- ✓ Clinical Development
- ✓ Registration
- ✓ Post-Marketing

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Drug Development: Activity-Based Process

0.5-3 yr. 0.5 -1 yr. 2-5 yr. 1 mo.-1 yr.

~$300-500 Million

4-10 Years

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Drug Development: Knowledge-Based Process

- ✓ Lead Identification
- ✓ Enter Development
- ✓ First in Humans (FIH)
- ✓ Proof of Concept (Principle) (POC)
- ✓ *Phase 2/3 Transition*
- ✓ Submission
- ✓ Approval and Launch

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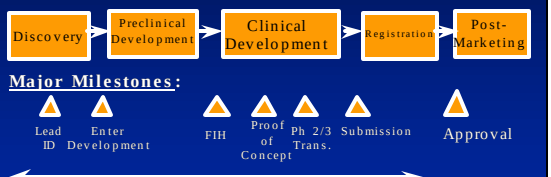
Drug Development: Knowledge-Based Process



~$300-500 Million

4-10 Years

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Drug Development: Knowledge-Based Process

- Biomarker
- Surrogate marker
- Clinical benefit
- Clinical outcome

- *Lead identification*
- *Proof of principle*
- *Phase 2/3 transition*
- *Market success*

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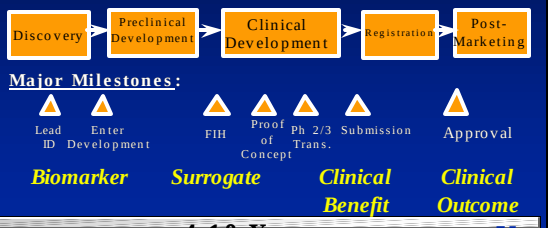
Drug Development: Knowledge-Based Process



4-10 Years

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Go Criteria at Major Milestones

Lead Identification

- Pharmacological Activity
- In vitro and in vivo potency & selectivity
- Viable synthesis or production possible
- Patentable
- Metabolic resistance
- ???

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Go Criteria at Major Milestones

Enter Development (Safety Assessment Candidate):

- In vivo activity in disease model
- Estimate of cost of goods
- Pilot toxicity results
- Preliminary metabolism data
- ???

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Go Criteria at Major Milestones

First in Human (FIH):

- Adequate rationale and data from animal models to expect beneficial result in therapeutic target
- Adequate safety margin in animals to proceed into initial clinical study

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Go Criteria at Major Milestones

Proof of Concept/Principle:

- Evidence of expected pharmacologic activity in humans
- Acceptable therapeutic index (benefit/risk)

→ *Desired differentiation*

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Go Criteria at Major Milestones

Phase 2/3 Transition:

- Pharmacological effect (not efficacy) proven
- Dose response characterized

→ *Desired differentiation*

- Acceptable benefit risk profile

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Go Criteria at Major Milestones

Phase 2/3 Transition:

- Acceptable competitive situation (emerging profile similar to target profile, no surprises from competitors)
- Acceptable cost of goods
- No major manufacturing issues
- ???

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Go Criteria at Major Milestones

Regulatory Submission:

- **PROOF of efficacy and safety**
- **Validation of substance and product manufacturing processes**

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Go Criteria at Major Milestones

Regulatory Approval:

- **CONVINCING PROOF of safety and efficacy**

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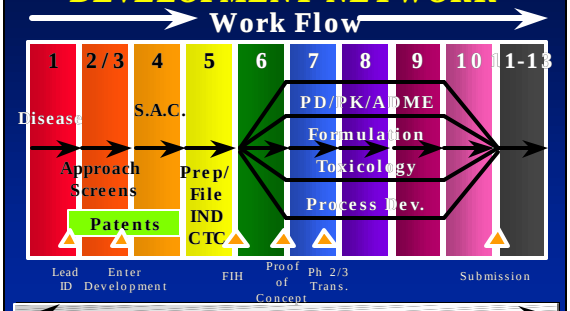
DRUG DISCOVERY / DEVELOPMENT NETWORK



4-10 Years

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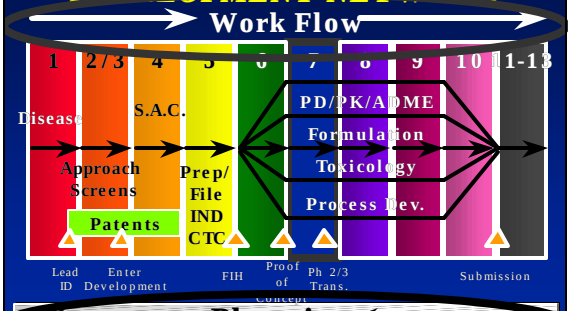
DRUG DISCOVERY / DEVELOPMENT NETWORK



Planning

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Future R&D Costs

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Rule # 4

- **Differentiate.**
  - **–Learn from others' successes and failures.**
  - **–It's OK to raise the bar for the other guy.**

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Label Driven Development Plans

(As *The* Planning Tool)

- Indications and Usage
- Clinical Pharmacology
- Dosage and Administration
- Adverse Effects
- Precautions

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Label Driven Development Plans

(As *The* Planning Tool)

- Label
  - Indications & differentiation
    - Patient populations
    - Dose & dose regimen determination
    - PK/PD profile
    - Safety profile

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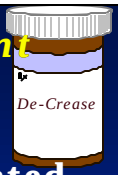
Drug Development Label Driven



De-Crease is indicated for first-line therapy for reducing excess drinking episodes by those with a history of alcohol abuse.

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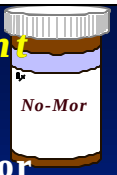
Drug Development Label Driven



No-Mor is indicated for first-line therapy for initiating and maintaining alcohol abstinence by those with a history of alcohol abuse.

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Drug Development Label Driven

NorMal is indicated for first-line therapy for initiating and maintaining normal alcohol consumption by those with a history of alcohol abuse.

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Differentiation

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Differentiation:
"After menopause, women have a new choice to prevent osteoporosis."

- ♀ **"Evista is for the prevention of osteoporosis in postmenopausal women."**
- ♀ **"Evista is not a traditional hormone. It is a SERM: Selective Receptor Modulator... "**

Reader's Digest Ad, June 1998 CVG

Differentiation:
"After menopause, women have a new choice to prevent osteoporosis."

- ♀ **"Importantly, women taking Evista had no increased risk of breast or uterine cancer in studies up to three years. And most women didn't get the bleeding, bloating, and breast tenderness often associated with estrogen replacement."**
- ♀ **"Evista can even increase bone mass - although not as much as estrogen replacement."**

Reader's Digest Ad, June 1998 CVG

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 CVG

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 CVG

Reimbursement

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EXPANDED REIMBURSEMENT
"HCFA Reimbursement For Epogen, Takeover Talk Help Amgen Grow in June"

- **"A second increase in the Health care Financing Administration reimbursement rates for Epogen has aided in increasing the valuation of Amgen in the financial community."**
- **"On June 19, HCFA issued a program memorandum to payors that directed payment of claims for Epogen (erythropoietin alfa) in patients whose hematocrit levels reach as high as 37.5%"**

"The Pink Sheet" 7/6/98 page 20 CVG

EXPANDED REIMBURSEMENT

"HCFA Reimbursement For Epogen, Takeover Talk Help Amgen Grow in June"

- On June 24, Gruntal & Co. analyst David Saks predicted that the new reimbursement policy could result in a 10% increase in use; Epogen sales in 1997 were about $1.07 bil. and Amgen's total revenues were $2.4 bil. Gruntal upgrades Amgen from "buy" to "strong buy."

"The Pink Sheet" 7/6/98 page 20

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Competitive Advantage

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"Anti-impotence drug maker Vivus Inc. said Tuesday it was considering strategic alternatives including selling the company after harsh competition from Pfizer's Viagra."

Reuters, August 24, 1998

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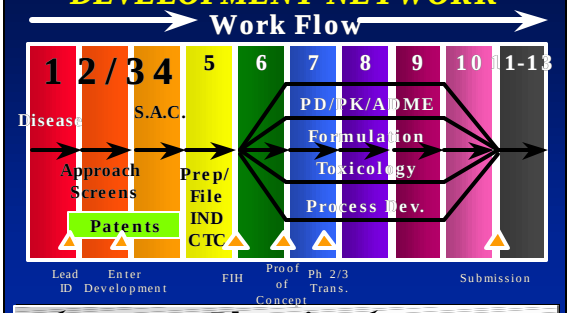
DRUG DISCOVERY / DEVELOPMENT NETWORK



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Lead Identification

1. WHAT DISEASE ?

- Technology Driven ?
- Medical Need Driven ?
- Types of Patients / Subjects ?
- Differentiation !

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SIGA Announces Identification of Lead Antibiotic Compound

- ``This compound, an inhibitor of pilus assembly, represents a new class of anti-infectives that may circumvent resistance to conventional antibiotics."
- Pili are structures on the surface of gram-negative bacteria, such as E. coli and Salmonella, that are required for the attachment of bacteria to human tissue, the first step in the infection process.

BW HealthWire, September 8, 1998

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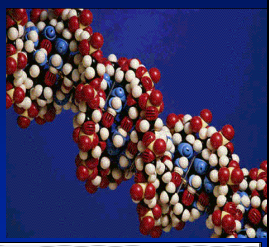
Lead Identification
2. WHAT APPROACHES ?

- Treat ?
  - Stabilize
  - Slow Progression
  - Prevent Relapse
- Cure ?
- Prevent ?
- Diagnose ?



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Theragenics

- In a related development for Herceptin, it may soon be easier to target patients who will benefit most from the drug.
- Danish firm DAKO A/S, which licensed Genentech's HER2 technology, has filed for FDA approval of a test for the gene that causes overexpression of the HER2 receptors. Another FDA advisory panel will meet Sept. 4 on that test.

Reuters, August 27, 1998

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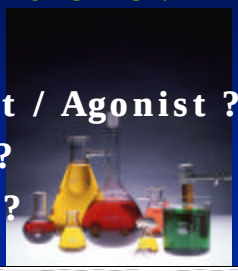
Lead Identification
2. WHAT APPROACHES ?

- Enzyme ?
- Replacement / Agonist ?
- Antagonist ?
- Modulation ?



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Lead Identification
3. WHAT SCREENS ?

- Receptor Based ? Combinatorial ?
- Biomarker & Surrogate End Points ?
- In Vivo ? (What Animal & Species ?)
- Source(s)
- Relevance to Human Condition ?

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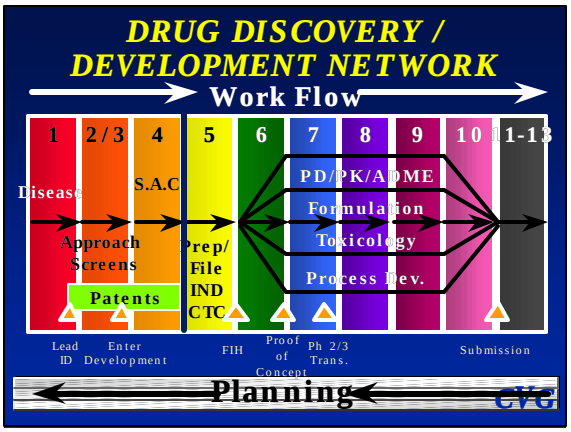
DRUG DISCOVERY / DEVELOPMENT NETWORK



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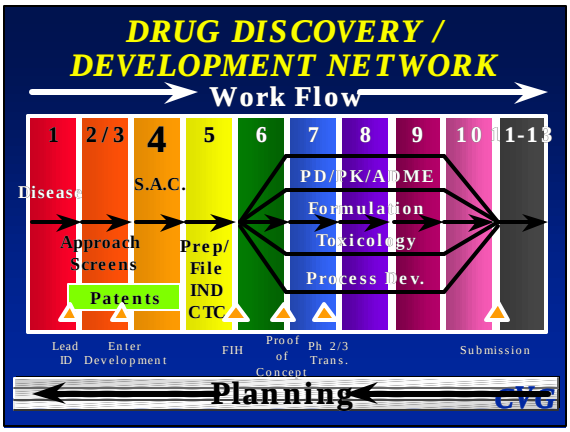
DRUG DISCOVERY / DEVELOPMENT NETWORK



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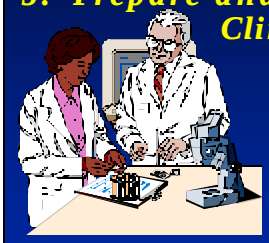
Enter Development
(Safety Assessment Candidate)
5. Prepare and File IND/CTC(X)?
Clinical



- Clinical
- Preclinical
- Formulation
- Bulk Active

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"AND THE BAND PLAYED ON "

- I THINK ?
- I KNOW ?
- I CAN PROVE !

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Enter Development
(Safety Assessment Candidate)
5. Prepare and File IND/CTC(X)?
Clinical

- Outcome Measures/Surrogates
- Subject Populations
- Duration of Treatment
- Number of Subjects (Why ?)
- Method of Analysis

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Enter Development
(Safety Assessment Candidate)
5. Prepare and File IND/CTC(X)?
Clinical

- Route(s) of Administration
- Dose/Dose Regimen
- Protocol
- Investigators

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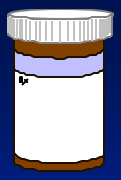
Dosage & Administration



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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

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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

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Enter Development (Safety Assessment Candidate)

5. Prepare and File IND/CTC(X)? Preclinical

- Rationale for Use
- Rationale for Surrogates
- Pharmacology/Species (Why ?)
- Toxicology/Species (Duration; No Effect Level)
- Route(s) of Administration

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Enter Development (Safety Assessment Candidate)

5. Prepare and File IND/CTC(X)? Preclinical

- Dose/Dose Frequency
- ADME/CYP-450
- Concomitant Meds

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Drug Interactions

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Forest Celexa Metabolism May provide Marketing Distinction for Fifth SSRI

- Forest/W-L's SSRI Celexa metabolism minimally involves the liver CYP-450 isoenzyme 2D6, which may result in fewer drug-drug interactions than other SSRIs.

"The Pink Sheet," 7/27/98

CVG

Forest Celexa Metabolism May provide Marketing Distinction for Fifth SSRI

- "Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers...suggesting that coadministration of Celexa with a drug that inhibits 2D6 is unlikely to have significant effects on citalopram metabolism," labeling reads.

"The Pink Sheet," 7/27/98

CVG

Forest Celexa Metabolism May provide Marketing Distinction for Fifth SSRI

- Drugs that pass through the 2D6 pathway include tricyclic antidepressants, phenothiazine tranquilizers, beta blockers and type 1C antiarrhythmics such as propafenone, encainide and flecainide.

"The Pink Sheet," 7/27/98 CVG

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 CVG

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 CVG

Enter Development (Safety Assessment Candidate)

5. Prepare and File IND/CTC(X)?

Formulation

- Routes of Administration
- Doses
- Manufacturing Sites
- Stability Needed
- Packaging

CVG

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* CVG

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* CVG

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*

CVG

Enter Development (Safety Assessment Candidate)

5. Prepare and File IND/CTC(X)? Bulk Substance

- Quantity Needed
- Synthesis
- Sources of Ingredients
- Manufacturing Sites
- *Cost of Goods (COGs)*

CVG

Development Decision Points

6. PHASE 1 (POC/POP)?
7. PHASE 2 ?
8. END OF PHASE 2 (Go / No Go) ?

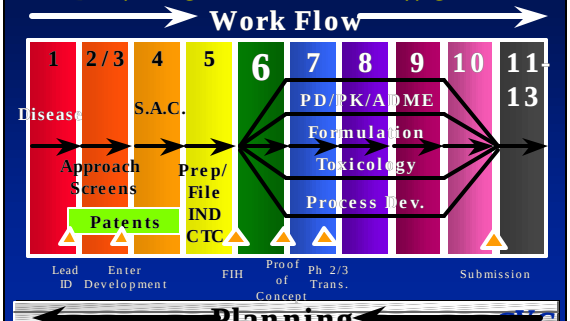
CVG

Development Decision Points

9. NON-CLINICAL ?
10. CLINICAL TRIALS ?

CVG

DRUG DISCOVERY / DEVELOPMENT NETWORK



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First in Human/Proof of Principle

6. First in Humans

- PD (Pharmacodynamics)
  - What the ***Drug*** does to the *Body*
- PK (Pharmacokinetics)
  - What the ***Body*** does to the *Drug*

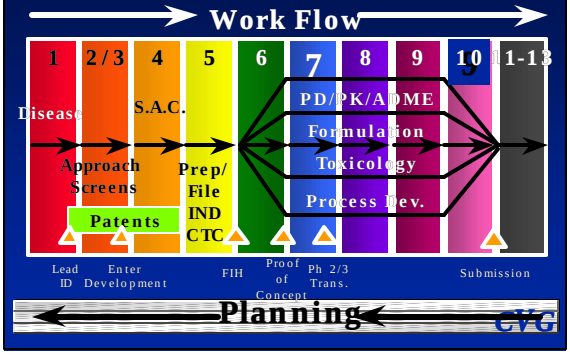
CVG

First in Human/Proof of Principle
6. First in Humans

- What is the t 1/2?
  - *–Physical & pharmacological*
- Food effect?
- Absorption profile?
- First pass metabolism?
- Where is the drug absorbed?

CVG

DRUG DISCOVERY / DEVELOPMENT NETWORK



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First in Human/Proof of Principle
7. Proof of Principle

- Critical Design Success Factors
  - ✓ Mechanism of Action ?
  - ✓ Disease State ?
  - ✓ Outcome Measures ?

CVG

First in Human/Proof of Principle
7. Proof of Principle

- Target Population
- Comparator / Placebo ?
- Dose Ranging
  - ✓ Optimal Therapeutic Effect
  - ✓ Side Effects

CVG

First in Human/Proof of Principle
7. Proof of Principle

- Dose Frequency
  - ✓ Optimal Therapeutic Effect
  - ✓ Side Effects
- *Dose / Dose Regimen*
- Benefit / Risk Ratio

CVG

First in Human/Proof of Principle
7. Proof of Principle

- Patient Population Subsets
  - → Drug Abuse
    - → Heavy, Moderate, Light Abuse
    - → Dual Diagnosis
      - → ADD, Depression, Schizophrenia, ASPD

CVG

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."
- "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.."

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

CVG

PATIENT POPULATION
Broad range of Subpopulations

- "In a study involving 178 spinal cord patients, 83% reported improved erections on Viagra vs. 12% on placebo… "
- "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

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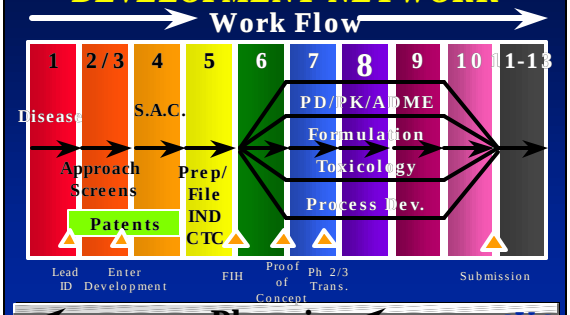
DRUG DISCOVERY / DEVELOPMENT NETWORK



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Rule # 5

- It takes a village to develop a drug.
  - –Heavy-weight teams are a must.
  - –There is no "I" in "team."

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Phase 2/3 Transition
8. EOP2 Meeting

- FDA / Company Conference
  - ? Acute / Chronic Safety
  - ? Dosage Form
  - ? PD / PK / ADME / CYP-450
  - ? Dose / Dose Regimen / Subjects

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Phase 2/3 Transition
8. EOP2 Meeting

- FDA / Company Conference
  - ? Phase 1 Safety
  - ? Phase 2 Safety / Activity
  - ? Phase 3 Development Plan
  - ? *Contract with FDA & BoHs*

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Phase 2/3 Transition
8. EOP2 Meeting

- Decision on How to File in Europe

CVG

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

CVG

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

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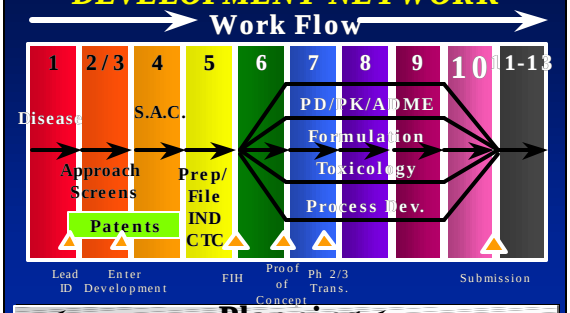
DRUG DISCOVERY / DEVELOPMENT NETWORK



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Phase 2/3 Transition
10. Clinical Development

- Patient Populations ?
- Primary Outcome Measures of Efficacy ?
- Surrogate Markers ?

CVG

Phase 2/3 Transition
10. Clinical Development

- Comparator ?
- Concomitant Medications (CYP-450) ?
  - Which Ones ?

CVG

REVISED LABELING
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 CVG

REVISED LABELING
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 CVG

Phase 2/3 Transition
10. Clinical Development

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

CVG

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 CVG

Phase 2/3 Transition
10. Clinical Cut-Off Date

- Evaluated ?
- Treated ?
- Data Collected ?
- Data In House ?
- Data Resolution ?
- Data Tables ?
- Stat Tables ?
- Final Report ?

CVG

Phase 2/3 Transition
10. Clinical Cut-Off Date

- Forward Motion ?
- Snapshot
- Videotape / CD ROM
- *Intervention*

CVG

Registration
12. Decision to File

Do we really have a drug??

- ? Efficacy in target population
- ? Adequate safety profile
- ? Acceptable dose regimen
- ? Competitive advantage *(differentiation)*
- ? Restrictions/warnings
- ? Concomitant medications
- ? Human PK
- ? Animal safety data
- ? Controlled manufacturing (GMP)

CVG

SAFETY
Launch Delay
Submission of Follow-Up Safety Data

- ⦸ The launch of Roche's Xenical will occur in mid-1999 at the earliest the company indicated following a May 12 "approvable" letter for the anti-obesity agent.
- ⦸ "Final approval is subject to certain conditions including submission of follow-up safety data from Xenical's ongoing clinical programs and agreement on final labeling." Roche said.

"The Pink Sheet" 5/18/98 page 6 CVG

SAFETY
Launch Delay
Submission of Follow-Up Safety Data

⦸ However, the launch of Xenical (orlistat) will now come at least two years later than Roche had hoped when it made the anti-obesity agent its top research priority.

"The Pink Sheet" 5/18/98 page 6 CVG

Registration
13. Review

- NDA/BLA/ MAA Review
- Refuse to File ?
- CANDA / CABLA
- Priority (P/S)
- Accelerated; Expedited; Rolling NDA

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Priority Review

Monsanto shares jumped 5 percent Monday after the U.S. Food and Drug Administration granted "priority review" to its G.D. Searle unit for the arthritis drug Celebra.

CBS Market Watch, August 24, 1998 CVG

Registration
13. Review--How Frequently?

- TID, BID, OD ?
- Weekly, Monthly ?
- Intermittently ?
- Continuously ?

In Whom Was it Studied ?

CVG

Registration
13. Review--How Administered?

- Oral, SL, Controlled Release
- Transdermal, Topical
- IV, IM, SC
- Suppository
- Diluents / Compatabilities

In Whom Was it Studied ?

CVG

Registration
13. Review--What Indications?

"We Sell Only the Package Insert,

We Give Away the Product !"

CVG

Registration
13. Review--What Indications?

- Decision to Launch
  - ✓ Indications
  - ✓ Patient Populations
  - ✓ Sub-Types
  - ✓ Frequency of Dosing
  - ✓ Restrictions / Warnings
  - ✓ Concomitant Medications

CVG

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

CVG

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

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Registration
13. Review--What Indications?

- Economics
  - –Indications
  - –Margin
  - –Cost of goods (COGs)
    - •Patents & royalties
- Advertising/promotional costs

CVG

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*."

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

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

- "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 CVG

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 CVG

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 CVG

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 CVG

Orthofix Receives FDA Approval to Modify Labeling on Bone Growth Stimulators

- Orthofix Inc., announced today (8/11/98) that it has received notification from the Food and Drug Administration (FDA) that labeling for Physio-Stim(R) Lite Bone Growth Stimulators may be modified, ***thereby removing the requirement that surgeons wait a minimum time before prescribing the devices.*** Physio-Stim Lite is the brand name for a line of bone growth stimulators that are used for patients with non-healing fractures, commonly known as non-unions.

PR Newswire 8/11/98 CVG

EXPANDED PATENT LIFE
"Abbott Tricor Micronized Fenofribrate Patent Runs For Next Decade"

- **"Abbott/Fournier's micronized formulation of fenofibrate, *Tricor*, will have patent protection for at least a decade beyond that of the originally approved fenofibrate formulation *Lipidil*."**
- **"Lipidil has never been marketed in the U.S., although FDA approved the compound Dec. 31, 1993 after an NDA review of nearly 10 years."**

"The Pink Sheet" 7/15/98 page 14 CVG

EXPANDED PATENT LIFE
"Abbott Tricor Micronized Fenofribrate Patent Runs For Next Decade"

- **"The Lipidil patent will expire on Dec. 31 making it an unattractive promotional candidate. The newer formulation, however, is protected by at least one patent that runs well into the next decade."**

"The Pink Sheet" 7/15/98 page 14 CVG

Overview of the Medications Development Process

- ✓ Overview
- ✓ Portfolio Design, Planning and Management
- ✓ Decision Points Concept

CVG

Case Studies

- ✓Siga's antibiotic (Novel mechanism)
- ✓Lilly's Evista (Differentiation-SERM)
- ✓BM-S's Pravachol (Px first MI)
- ✓Amgen's Epogen (Reimbursement)
- ✓DAKO A/S's Her-2 Dx (Theragenics)
- ✓Forest's Celexa (5th SSRI)

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Case Studies

- ✓Pfizer's Zyrtec (Patient age groups)
- ✓HMR's fexofenadine (CYP-450)
- ✓Inhale's insulin (Novel delivery system)
- ✓Pfizer's Viagra (Sub-populations)
- ✓Merck's Singulair (Exercised induced)
- ✓Roche's Posicor & Xenical (Safety)
- ✓Janssen's Propulsid (CYP-450--Safety)

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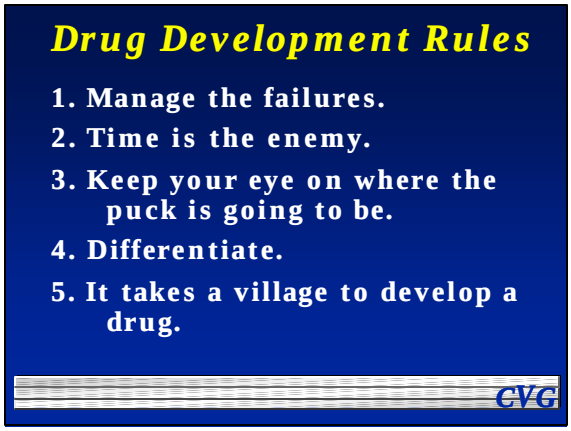
Case Studies

- ✓Merck's Omeprazole (CYP-450)
- ✓Wyeth-Ayerst's Naperlan (Population)
- ✓Orthofix's Physio-Stim (+ Indication)
- ✓Abbott's Lipidil (Patent extension)
- ✓Wyeth-Ayerst's Verdia (Safety)

CVG


Drug Development Rules
1. Manage the failures.
2. Time is the enemy.
3. Keep your eye on where the puck is going to be.
4. Differentiate.
5. It takes a village to develop a drug.
CVG