UCSF-CTSI
Drug Development and Regulatory Sciences Seminar Series

Drug Development Decision Points

- Lead identification
- Lead optimization
- Evaluate
- Drug development
- Regulatory review
- Scale up & launch
- Post market

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&
Center for Drug Development Science--UCSF-DC

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Drug Development Decision Points

Objectives

1. How can we make better decisions?
2. Understanding the probabilities associated with new drug development
3. How to improve the probabilities associated with new drug development?
4. How do we create a better product than our competition?
5. Why are some companies more successful than others?
6. Why are our timelines never good enough for our management?

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How Can I Learn More About Drug Development?

- Courses - PERI, ECPM, EUFEPS, CDDS, CSDD, DIA, NIH
- FDA Advisory Committee Meetings
- FDC Reports “The Pink Sheets”
- FDC Reports “Pharmaceutical Approvals Monthly”
- FDA and EMeA web sites
  - Drugs@FDA; FDA and ICH Guidances
- Analyze Package Inserts
Drug Development Regulation

- **EMEA (EMA)**
  - [www.emea.org](http://www.emea.org)
  - [www.emea.europa.eu](http://www.emea.europa.eu)

- **ICH**
  - [www.ich.org](http://www.ich.org)
EMEA launches updated medicines-information database
Published 25/05/2007

- A second version of the EudraPharm database of information on medicinal products approved within the European Union has been released today. The main new benefits of this update are:
  - Inclusion of product information documents in all available EU languages
  - Inclusion of maximum-residue-limit information for veterinary products
  - Inclusion of an advanced search function to make information searches more accurate
  - Inclusion of a new site map to improve navigation.
- EudraPharm is a long-term project being funded by the European Commission and implemented by the EMEA, in close cooperation with the medicines agencies of each EU Member State, to provide information about all medicines for human or veterinary use authorised in the EU.

http://www.emea.europa.eu/
Drug Development Regulation

- MHRA
  - Medicines and Healthcare products Regulatory Agency
  - An executive agency of the Department of Health


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Drug Development Regulation

• FDA
  ➢ www.fda.gov
  ➢ www.fda.gov/cder
  ■ Advisory Committees
  ➢ drugs@fda

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Drug Development Courses

- **PERI**
  - www.peri.org

- **ECPM**
  - www.ecpm.ch

- **MSc Pharmaceutical Medicine**
  - www.hiberniacollege.net
Drug Development Courses

- European Regulatory Affairs course sponsored by the SIR Institute for Pharmacy Practice and Policy
  - [www.stevenshof.nl](http://www.stevenshof.nl)
Drug Development Courses

- **DIA**
  - [www.diahome.com](http://www.diahome.com)

- **CDDS**
  - [cdds.ucsf.edu](http://cdds.ucsf.edu)

- **CSDD**
  - [csdd.tufts.edu](http://csdd.tufts.edu)

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Drug Development Meetings

- EUFEPS
  - www.eufeps.org
- ASCPT
  - www.ascpt.org
- AAPS
  - www.aaps.org
- DIA
  - www.diahome.org

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Pharmaceutical Manufacturing Associations

• EphMRA
  ➢ http://www.ephmra.org/main.asp?page=0

• PhRMA
  ➢ http://www.phrma.org/
10 year Trend in Biomedical R&D Spending

Adapted from J. Cossman: “The Critical Path Institute” 2007 & FDA Critical Path Initiative 2004

Slide courtesy of Carl Peck
Trends in R&D Spending vs. New Drug & Biologic Applications

Source: GAO Analysis of PhRMA and FDA data

Slide courtesy of Carl Peck
10 year Trend in New Applications to FDA

- Total NMEs Rec'd by FDA
- Original BLAs

Adapted from J. Cossman: “The Critical Path Institute” 2007 & FDA Critical Path Initiative 2004

Slide courtesy of Carl Peck
The Product(s) of Global Pharma R&D

Addressing Unmet Medical Needs

a. Drug
b. Biologic
c. Device
d. Diagnostic
e. Combo of any of the above

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Overview of the Drug Development Process:

Topic 1
How can we make better decisions?
Which Path Forward?
What should be on the signs?
Top Ten Most Common Drug Development Errors
NDA Partners has inventoried the 10 Most Common Drug Development Errors

1. **Poor product differentiation during planning**
   - Not properly characterizing “Market Advantage”
   - Not developing Target Product Profile (TPP) and Draft Target Labeling to identify Key Development Decisions

2. **Not challenging fundamental assumptions**
   - Not continuously assessing new knowledge to evaluate the validity of the fundamental assumptions that originally supported the project

3. **Wrong questions**
   - Not taking into account during CMC, animal and clinical study design
   - What are the Key Decisions/Decision Criteria are that need to be informed by new knowledge
NDA Partners has inventoried the 10 Most Common Drug Development Errors

4. **Wrong form of the drug and/or Wrong dosage form**
   - Initiating development with the wrong form of the drug substance (i.e., wrong salt, wrong ester, the racemate instead of the pure enantiomer)
   - Initiating development with the wrong dosage form (i.e., unpredictable or inconsistent BA)

5. **Poor contingency planning**
   - Not considering contingency plans [i.e., only planning for success and then not knowing what to do when preclinical, CMC or clinical results don't come out as expected]

6. **Too much reliance on the preclinical rationale**
   - Trying to answer too many questions about a drug's prospects preclinically (at some point the drug developer needs to conduct the relevant studies in man)
NDA Partners has inventoried the 10 Most Common Drug Development Errors

7. Regulatory aversion
✓ Inability to understand and/or accept regulatory input from regulatory agencies/experts

8. Inadequate “Learnings”
✓ Improper use of a “Confirming Design” and analysis where “Learning” is required

9. Study designs not informed
✓ Failure to adequately use prior information
✓ Not fully extracting relevant information from data already gathered

10. Not enough team input
✓ Too much reliance on only each individual’s past experience
What is a “Decision?”

A. A decision is a commitment of resources

B. Decision-making criteria must be prespecified

C. Project progress must be effectively reviewed against:
   ✓ Predefined specifications
   ✓ Agreed upon timelines
   ✓ Allocation of required resources
Drug Discovery & Development Decisions

- **Key decision points**
  - Lead identification
  - Enter development
  - First in humans (FIH) *(What dose?)*
  - Proof of mechanism (PoM)
  - Proof of concept (PoC)
  - Phase 2/3 transition *(Differentiation)*
  - Submission
  - Approval, Risk Management Program, Pricing and Launch
  - Post-market program
  - Post-market surveillance
  - Next generation products

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Drug Discovery, Development & Review

~$ 0.8–1.5 Billion / 4-6 Years
Decision Assessment Tools

- Biomarkers
- Surrogate **Endpoints**
- Regulatory definition
- Clinical outcomes
- Clinical benefits
Drug Discovery, Development & Review

~$ 0.8-1.5 Billion / 4-6 Years

Biomarker Surrogate Endpoints Clinical Effect Clinical Outcomes

Inhibit LDL Enzyme

↓ LDL Levels

↓ CV Disease

↓ Morbidity & Mortality

SAFETY?

Decisions: Lead ID Enter Development FIH PoM PoC Ph 2/3 Trans. Submission Post-Market Approval

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How Companies are Organized

• Target
• Identification
• Optimization
• Evaluation
• Development
• Review
• Launch
• Post-Market
Decisions

- Classic flowchart with these elements:
  - Identification
  - Optimization
  - Evaluation
  - Development
  - Review
  - Launch
  - Post-Market
Decisions

- Elements that make up the identification of a “lead:
  - Drug discovery
  - Biotechnology
  - Genomics & proteomics
  - High throughput screening (including the use of combinatorial library to optimize the lead)
Drug Discovery, Development & Review

~$ 0.8-1.5 Billion / 4-6 Years

Genomics & proteomics

Biotech

Drug Discovery

Lead identification

Lead optimization

Evaluate

Drug development

Regulatory review

Scale up & launch

Post Market

High throughput screening

Decisions:

Lead ID

Enter development

FIH

PoM

PoC

Ph 2/3 Trans.

Submission

Post-Market

Approval

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Decisions

✓ Toxicity testing
  ✓ Safety, NOAEL, target organs, differentiation, immunogenic, adjuvants, vehicle

✓ Chemistry/Formulation
  ✓ COGs, facilities, IP, stability, routes of administration, cell bank(s) characterization, adventitious agent testing, potency, sterility, bioburden

✓ ADME
  ✓ Absorption, Distribution, Metabolism & Elimination, CYP-450, DDI

✓ Clinical trials
  ✓ Safety, patients, special pops, DDI, combinations
Drug Discovery, Development & Review

~$ 0.8-1.5 Billion / 4-6 Years

- Lead identification
- Lead optimization
- Evaluate
- Drug development
- Regulatory review
- Scale up & launch
- Post Market

Chemistry & ADME

Decisions:
- Lead ID
- Enter Development
- FIH
- PoM
- PoC
- Ph 2/3 Trans.
- Submission
- Post-Market

Approval
© Charles Grudzinskas 2007
Decisions

• The continuum of development through review, approval, launch, and the post-marketing stages:
  ✓ Global regulatory interactions
    ✓ Subpart E/H, accelerated, priority, rolling NDA, risk assessment & management plans
  ✓ Document preparation
    ✓ Strategy, outsource, web-based, reviewer friendly
  ✓ Bulk and finished product manufacturing
    ✓ Facilities, timelines, PAI
Drug Discovery, Development & Review

~$ 0.8-1.5 Billion / 4-6 Years

- Lead Identification
- Lead Optimization
- Evaluate
- Drug Development
- Regulatory Review
- Scale up & Launch
- Post Market

Decisions:
- Lead ID
- Enter Development
- FIH
- PoM
- PoC
- Submission
- Ph 2/3 Trans.
- Post-Market

Approval

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Decisions

- The integration all of the elements that are the continuum of:
  - Discovery
  - Development through review
  - Approval and launch, and
  - Post-marketing stages
Drug Discovery, Development & Review

Planning

Work

~$ 0.8-1.5 Billion / 4-6 Years

Drug Discovery

Biotech

Genomics

Toxicity Testing

Regulatory Interactions

Document Preparation

Lead Identification

Lead Optimization

Evaluate

Drug Development

Regulatory Review

Scale up & Launch

Post Market

High Throughput Screening

Chemistry & ADME

Clinical Trials

Bulk & Finished Prod. Manufacturing

Decisions:

Lead ID

Enter Development

FIH

PoM

PoC

Submission

Ph 2/3 Trans.

Post-Market

Approval

Planning © Charles Grudzinskas 2007
Prove & Convince

5 ______________________
Prove & Convince

5 Ourselves
5 Regulatory Agencies
5 Purchasers
5 Prescribers
5 Patients

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Drug Discovery, Development & Review Stages

• The **stages** of drug development & review include:
  
  • **Identification** (Drug discovery)
  • **Optimization** (Lead selection)
  • **Evaluation(s)** (Proof of mechanism)
    (Proof of principle/concept)
  • **Development** (Evidence) **Safety/Effectiveness**
  • **Review** (Regulatory review)
  • **Launch** (Product introduction)
  • **Post-Marketing** (Market expansion)

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Overview of the drug development process

Topic 2:

Understanding the probabilities associated with new drug development

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The Drug Development Product

• Safety

• Effectiveness

• Quality

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Increasing the Probability of Success & Predictiveness of Regulatory Risk

Uncertainty about which NCE
- Developability
- Dose & Schedule
- Safe & Effective
- Vs. Placebo
- Vs. Competitor

Uncertainty about Development Program
- Yield of useful information
- Internal decisions
- Regulatory
- Commercial

Uncertainty about Market
- Demand for various product attributes
- New competitors
- New therapies

Only 1/12 NCEs in development make it to market!

2/3 to 5/6 clinical trials produced no useful Knowledge for FDA!

Most drugs fail to meet commercial expectations!
How safe is the new drug in humans?

How does the Human body handle The new drug (PK & ADME)?

Can we reliably formulate the new drug for delivery to humans?

Can we reliably make the new drug?

A Successful New Drug

Deliver it?

Safe?

Make it?

How well does the new drug work in humans?

Can we reliably make the new drug for delivery to humans?

Safety, Effectiveness & Quality
Risks, Reasons & Resources
## EXHIBIT 5
Probability Of Market Entry, Durations, And Costs For New Drugs, By Disorder And Primary Indication

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Adams, Christopher, Health Affairs, 25:2, 2006, page 425

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“US-IND” (not all FIHs) to NDA

Previous Clinical Data  Not Innovator

1/3

INDs  NDAs

Previous Clinical Data  Innovator

1/6

INDs  NDAs

No Previous Clinical Data  Innovator

1/12

INDs  NDAs

J. DiMasi (Tufts) Clinical Pharmacology & Therapeutics May 2001
Reasons for IND Terminations

J. DiMasi, Clinical Pharmacology & Therapeutics, page 297, May 2001
Qualitative True Cost of a NME

• In 2004, 24 new NMEs approved
• 2004 Reported pharma R&D spend = $38,000,000,000 ($38B)

• An estimate of $1.6B per NME!

• However, a large portion of R&D spend (~50%) is on follow-on products*
  - Line extensions
    - Risperdal Consta
  - Optical isomers
    - Prilosec → Nexium
  - Metabolites
    - Claritin → Clarinex

• An estimate of $0.8B per each NME!

*Changing Patterns of Pharmaceutical Innovation, The National Institute for Health Care Management, Research and Educational Foundation, May 2002
Overview of the drug development process

Topic 3:

How to improve the probabilities associated with new drug development

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Learning & Confirming


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Learning & Confirming-1

• Drug development consists of three design choices
  1) Assignment
  2) Observation
  3) Analysis
Learning & Confirming-2

- A cascade of “learning” and “confirming” cycles
Learning & Confirming-3

- **Identification of need***
  - What question(s) do you need to answer?
  - What do you want to do with the answer(s)?
  - How well do you need to know the answer(s)?

- **Prioritization of needs**
- **Implementation**

* Lewis Sheiner, UCSF
L & C Development Program

- **Phase 1 Learning**
  - Healthy Volunteers
  - Safety & tolerance, PK-ADME, drug-drug interactions

- **Phase 2 Learning**
  - Patients
  - PK-ADME & PK-PD in patients

- **Phase 3 Confirming**
  - Patients
  - Evidence of safety
  - Evidence of effectiveness

- **Phase 4 L & C Market**
  - Expansion & life-cycle management

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Phase 1: Learning
In Healthy Volunteers

- Safety & tolerance, PK-ADME, drug-drug interactions
  - Single dose: healthy?
  - Multiple dose: healthy?
  - PK-ADME with food, age, gender, disease state
  - PK in liver, renal, etc.
Phase 2: Learning
In Patients

• PK-ADME & PK-PD in patients
  ➢ Dose-exposure-response in tumor A
  ➢ Dose-exposure-response in tumor B
  ➢ Use in combinations
Phase 3: Confirming
In Patients

- Evidence of safety and effectiveness
  - Pivotal trial(s)
  - Long-term safety
Phase 4: Learning & Confirming

• Market expansion & life-cycle management
  ➢ New indications
  ➢ Pharmacovigilance
  ➢ New formulations
  ➢ Combinations
  ➢ New regimens
Reinventing the “Drug Creation Process”

Drug Creation Process
Learn and Confirm, a New Paradigm for Clinical Development at XYZ

XYZ recognizes that a new pharmaceutical environment has arrived, one characterized by stronger pricing pressure for prescription drugs, greater involvement of state and federal governments, stronger regulatory and compliance requirements, and greater consumer choice. In response, XYZ has launched a transforming initiative to develop the best clinical development model for the 21st century. We believe this will position XYZ for success in this new environment.

The overarching theme of the team’s actions is that XYZ cannot adequately respond to the needs of the new and evolving environment using a traditional phased approach to clinical development and instead must adopt a "Learn and Confirm" paradigm as our Clinical Development Model of the Future. The concept of Learn and Confirm emerged from our discussions with the Food and Drug Administration (FDA) and from a paper published in 1997 by L.B. Sheiner. In this paper, Sheiner identified two distinct activities in clinical development, Learning and Confirming. The goal of Learning is to focus on how to use a drug in representative patients to make an acceptable benefit/risk profile likely, while the goal of Confirming is to demonstrate, in a large and representative patient population, that an acceptable benefit/risk profile is achieved.

http://www.wyeth.com/research/drugprocess

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What is your drug’s “Knowledge-Phase?”
“Knowledge-Phase”

• “Knowledge-Phase” refers to the actual knowledge-base that exists for the new drug, rather than the “apparent phase” of drug development.

• An example would be a drug in Phase 3 clinical trials with the effectiveness dose and dose frequency having not yet been fully established prior to the initiation of the Phase 3 clinical program.

• This drug’s effectiveness “Knowledge-Phase” is therefore Phase 2.

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“Knowledge-Phase”

Learning

- Evaluating prior to FIH
- Evaluating in healthy volunteers (HV)
- Evaluating in patients

Pre-FIH      Phase 1      Phase 2      EoP2

End of Phase 2

Confirming

- Developing in patients

Phase 3
Confirming Evaluating in healthy volunteers (HV) Phase 1 Evaluating in patients Phase 2 Developing in patients Phase 3 Learning "Knowledge-Phase" How safe is the new drug in humans? How does the Human body handle The new drug (PK & ADME)? Can we reliably formulate the new drug for delivery to humans? Can we reliably make the new drug? How well does the new drug work in humans? A Successful New Drug
What is your drug’s “Knowledge-Phase?”
What is Reliable & Convincing Evidence?

Phase 2

Drug does work

True

False

False

Drug doesn’t work

True

False

+  -  +  -
Phase 2 Goals:

What Do We Want to Learn?

- Who is likely to respond?
  - Tumor type?
  - Performance status?
  - Previous treatment?
  - Additional—e.g., receptor status
- What type of response?
- Dose
  - What will be the “response-rate dose relationships?”
- Dose regimen & interval (US vs. Europe...)
- Dose duration
- Dose combinations—proper sequencing?
Overview of the drug development process

Topic 4:

How do we create a better product than our competition?

First in class? Best in class?
Differentiation: Oncology

- **Better effectiveness profile**
  - Imatinib Mesylate (Gleevec™)

- **Better safety profile**
  - Epirubicin (Ellence™)

- **Better patient persistence (compliance)**
  - Less chair-time?
  - Oral paclitaxel?
Tools for Success

- **Target:**
  - Product Profile (TPP)
  - Package Insert/Summary of Product Characteristics (TPI)/TSPC)

- **Comparative PI/SPC elements**
  - Marketed
  - In development--future competition
Target Product Profile

• Meets ICH guidances

↑ The “optimal” target

↓ The “threshold” target
  ➢ Below which we will not launch!!

• Must be measurable (metric)
Overview of the drug development process

Topic 5: Why are some companies more successful than others?
Value-Drive Decision Criteria

1. **TPP**
2. **Target PI/SPC**
3. **Draft PI/SPC**
4. **Draft CSE & CSS**
5. **Master Plan**
6. **Prespecified decision-making criteria**
7. **CDP (Clinical Dev. Plan)**
8. **Non-CDP**
If the project is doomed--

- Terminate Wisely!
- Terminate Early!
- Terminate Cheaply!
If the project is doomed--

- Critical Success Factors? (CSFs)
- Critical Failure Factors? (CFFs)

⇒ The intent here is to conduct the “killer experiments” early to identify as soon as possible projects that normally would be failing later in the clinical development process.
Potential Positive Impact of Established Decision Criteria

Ideal Attrition Distribution

TPP

Work

Planning

None!

Pre-FIH  Ph. 1  Ph. 2  Ph. 3  Approval

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Overview of the drug development process:

Topic 6
Why are our timelines never good enough for our management?

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

Years Between Drug Launch and First Competitor

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• Increased competitiveness
• Must maximize opportunity from day one

Adapted from A.T. Kearney, The Economist 09/20/97

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Drug Discovery, Development & Review

Planning

Work

~$ 0.8-1.5 Billion / 4-6 Years

Biotech

Drug Discovery

Genomics

Toxicity Testing

Drug Development

Regulatory Review

Scale up & Launch

Post Market

Lead identification

Lead Optimization

Evaluation

Drug Development

Regulatory Review

Post Market

High Throughput Screening

Chemistry & ADME

Clinical Trials

Bulk & Finished Prod. Manufacturing

Decisions:

- Lead ID
- Enter Development
- FIH
- PoM
- PoC
- Submission
- Ph 2/3 Trans.
- Post-Market

Approval

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Overview of the drug development process

Objectives

1. How can we make better decisions?
2. Understanding the probabilities associated with new drug development
3. How to improve the probabilities associated with new drug development?
4. How do we create a better product than our competition?
5. Why are some companies more successful than others?
6. Why are our timelines never good enough for our management?
10 year Trend in New Applications to FDA

- Total NMEs Rec’d by FDA
- Original BLAs

Adapted from J. Cossman: “The Critical Path Institute” 2007 & FDA Critical Path Initiative 2004

Slide courtesy of Carl Peck
Can we reverse the 10 year Trend in New Applications to FDA