Process Research and Development in Pharmaceutical Industry

- An Introduction

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Outline

♦ Overview of Pharmaceutical Industry
  – What Does It Take to Develop a Drug?
  – What Is the Current Status of Pharmaceutical Industry?
  – How Are (Should) Decisions (Be) Made During the Development?

♦ Introduction of Gilead Sciences

♦ What a Chemist Can Do in Pharmaceutical Industry

♦ Process Research and Development
  – Science, Business and More
Overview of Pharmaceutical Industry
- What Does It Take to Develop a Drug?
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What a Chemist Can Do in Pharmaceutical Industry

Process Research and Development
- Science, Business and More
From Idea to Approval

Discovery and Preclinical Research and Development

- Discovery
- Preclinical

Clinical Trials

- Phase I
- Phase II
- Phase III

Surveillance

- Up to 7 Years

- NDA Review and Approval

- Phase IV

1-3 Years

2-10 Years

30 days Safety Review IND

Short-term Animal Testing

Long-term Animal Testing

Medicinal Chemistry, Biology, Pharmacokinetics, Toxicologics

Chemical Development, Formulation/Drug Delivery, Packaging, Pharmacokinetics, Pharmacology, Clinical Research, Regulatory, Commercial Strategy, Portfolio Management, Commercial/Marketing

Compliance with Regulatory Requirements, Continual Interactions with Regulatory Bodies
Discovery

1. Identify and define medical needs

2. Research on disease mechanisms: identify and validate targets (receptors) involved in disease processes

3. Search for lead compounds that interact with targets

4. Optimize the properties of the lead compounds to generate potential drug molecules

5. Perform drug development and preclinical studies (in vitro and in vivo studies)

- Most situations: proteins or receptors (exception: antisense and RNA interference, gene therapy)
- Receptors: enzymes, intracellular, cell surface
- Binding is specific, at particular sites in the target molecule, reversible
- Idea Drug: potent, efficacious, specific
HIV Virus Life Cycle and AIDS

- Human Immunodeficiency Virus (HIV)
- Greatest scourge in humankind in recorded history
- HIV attack your immune system
- Acquired immunodeficiency Syndrome (AIDS), immune system failure
HIV Therapy

- First Anti-HIV Drug, Retrovir® in 1987, since the discovery of HIV in 1984
- Four Classes (Nat Rev Drug Discov. 6(12):1001-18, 2007)
  - Viral entry inhibitors
  - Reverse transcriptase inhibitors
  - Integrase inhibitors
  - Protease inhibitors
- 26 compounds, 33 brands
  - Used singly, not capable of suppressing virus replication
  - Three combo, HAART (like Gilead’s Atripla and Complera)
Preclinical Studies

♦ Initial development process takes place in the lab using *in vitro* methods (e.g. Ames test) and *in vivo* tests in animals to study:
  ♦ Pharmacological responses of the compound
    ♦ Pharmacodynamics (PD)
    ♦ Pharmacokinetics (PK)
  ♦ Toxicological effects, including toxicity, carcinogenicity, mutagenicity, and reproductive development.
    ♦ Two types of study: single dose acute toxicity and Repeated dose
    ♦ Two different routes of administration: intended route for clinical trials, and intravenous injection
    ♦ Two mammalian species: a rodent (mouse or rat) and a nonrodent (rabbit, dog)
PD and PK

♦ PD: actions of the drug on the target disease and other responses, such as heart rate, enzyme levels, antibody production, or muscle relaxation/contraction
  ♦ Provide information for the potency, effectiveness and safety margin

♦ PK: actions of the body on the drug, i.e. what happens during the transportation of the drug to the specific site for the drug-receptor interaction
  ♦ Kinetics of ADME (absorption, distribution, metabolism and excretion)
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Preclinical Studies – Tox Dose Guideline

<table>
<thead>
<tr>
<th>Duration of Clinical Trials</th>
<th>Rodents</th>
<th>Norodents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose</td>
<td>2-4 weeks</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Up to 2 weeks</td>
<td>2-4 weeks (1 month)</td>
<td>2 weeks (1 month)</td>
</tr>
<tr>
<td>Up to 1 months</td>
<td>1 month (3 months)</td>
<td>1 month (3 months)</td>
</tr>
<tr>
<td>Up to 3 months</td>
<td>3 months (6 months)</td>
<td>3 months (3 months)</td>
</tr>
<tr>
<td>Up to 6 months</td>
<td>6 months</td>
<td>6 months (chronic)</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>6 months</td>
<td>6-9 months</td>
</tr>
</tbody>
</table>
Is the Lead Developable
Preclinical Studies and IND

- PD, PK and Toxicity (short term and long term) information from preclinical studies provide us with confidence in the safety aspect of the potential drug, and enable the dose and dosing regimen

- IND is submitted
  - Preclinical data
  - CMC
  - IB
  - Protocol – study design

Very important enabling facts: Drug substance and drug product process development and manufacturing
Phase 1 Clinical Trials

- First studies in humans: “Entry into Man”
- Subjects: 10 - 100 healthy volunteers (or a specific disease group)
  - Single ascending dose (SAD)
  - Multiple ascending dose (MAD)
- Determine:
  - Safety/Toxicity and Tolerability
  - Dose range finding - highest tolerable dose
  - Pharmacokinetics
    - Absorption, Distribution, Metabolism, Excretion (ADME)
- Other types of Phase 1 studies:
  - bioequivalence, food effect
  - drug-drug interactions
  - PK in special populations (e.g. kidney failure)
- Phase 1 / 2 (include initial efficacy assessments)
  - conducted in the intended patient population
  - allow for more expedited development
- Months to 1 year, 50-70% compounds are abandoned

Obtain sufficient safety, PK, and pharmacologic data to design well-controlled, scientifically valid Phase 2 studies
Phase 2 Clinical Trials

- First studies in the patient population – targeted disease state (often placebo-controlled, some time active controlled)
- Subjects: 50 - 500 patients
- Determine:
  - Dose response (establish Min/Max effective dose and Max safe dose)
  - PK : correlate blood levels with pharmacologic effects/adverse effects
  - Safety, tolerability and efficacy
- 2 years or more, success rate: 30%

Obtain sufficient information to justify larger extended clinical trials to demonstrate a good risk-benefit ratio
Phase 3 Clinical Trials

- Expanded controlled clinical trials (pivotal studies) using the anticipated dosage form to evaluate overall risk-to-benefit ratio
- Subjects: 500 - 2000 patients
- Determine:
  - Dose associated with efficacy
  - Accumulate adequate safety database
- 3-5 years, 4-10% success rate of drug entering clinical trials

- NDA, EMEA, other regulatory submission

Provide sufficient info about safety & efficacy to demonstrate that the benefits outweigh the risks and provide adequate basis for labeling instructions (achieved TPP?)
<table>
<thead>
<tr>
<th>Product</th>
<th>Target Product Profile (Example)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Market</strong></td>
<td>e.g. All HIV-infected patients</td>
</tr>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td>QD, can be co-formulated into a single tablet</td>
</tr>
<tr>
<td><strong>Pill Burden</strong></td>
<td>1 pill</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>≤ 50 mg</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Non-inferior to SOC in Phase 3</td>
</tr>
</tbody>
</table>
| **Safety**       | Bone: Superior to SOC in bone mineral density (BMD) loss xxx% decrease/increase…  
|                  | Renal: Superior to SOC in eGFR reduction |
| **Tolerability** | Similar or better than SOC       |
| **Drug-Drug Interactions** | Similar to SOC       |
| **Resistance**   | Target…                         |
| **Food/Meal Restriction** | Without regard to food  |
| **Pregnancy Category** | Similar to SOC                 |
Phase 3b/4 Clinical Trials/Surveillance

- **Phase 3b**
  - Conducted while NDA pending approval
  - Additional safety data & additional indications or special populations

- **Phase 4**
  - Post-NDA approval
  - May be required by FDA as a condition for approval
  - Investigator-initiated studies to expand market
  - Post-marketing surveillance and epidemiology studies

- **Expanded Access/Compassionate Use**
  - No available treatment/ life threatening illness/sufficient human data to suggest safety & efficacy
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Number of NMEs Approved by FDA
Number of NMEs Approved by FDA in Last 60 Years

Total Number of NMEs Approved Annually by FDA between 1950 to 2010

Number of NMEs Approved Per Year

Year
Many Players, Few Winners

- > 4,300 companies that are engaged in drug innovation currently
- Only 261 organizations (6%) have registered at least one NME since 1950
- Of these, only 30 (11%) have been in exist for the entire 60-year period
- The remaining organizations have failed, merged, been acquired
Capitalized Cost per NME and Success rate

- ~30,000 synthesized and tested
- ~2,000 to the preclinical
- ~200 Phase I
- ~40 to Ph II, 8 approval
Challenges Facing Pharma Companies

- Fragmented Healthcare industry
- Increasingly More Stringent Regulatory Compliance requirements
- Pressure from Payers to Reduce Cost
- Investors Want Higher Return on Investment

Appropriate Decision Making Process

Problems Facing the Drug Industry

Approaches to Resolve Problems

- Optimize M&A Strategy
- Optimize Outsource Strategy
- Contain Cost
- Improve Sale and Market Share
- Improve R&D Output
- Extend and Improve/Utilize Patents More Efficiently
- Improve Supply Chain

Drug Company

Optimize Supply Chain

Improve Sale and Market Share

Optimize Outsource Strategy

Contain Cost

Improve R&D Output

Extend and Improve/Utilize Patents More Efficiently

Improve Supply Chain

Optimize M&A Strategy

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Improve Supply Chain
Trend Changes in Pharma Industry

♦ Late 1990s and early 2000s: Blockbuster business model (Pharma 1.0)
  – Focus on one or two products with massive sales

♦ 2000s and continuing: Patent cliff: diversification of product portfolios (Pharma 2.0)
  – Innovative partnerships
  – Lower manufacturing and marketing costs – plant closings/layoffs

♦ 2010s-: a shift from being product-centric to being customer-centric and payer-insightful (Pharma 3.0)

♦ New trends in research and development: collaborate with academia?!
Problems in Decision Making

- Indecisive on killing projects
- Silo decision making
- Losses of focus of core competences
- Blockbuster mania and shift of decision to marketing solely
- Separation of research from development
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Strategic Decision Making Process

- Institutional and Historical
  - Current Practices
- Organization
  - Structural Design
- Organization
  - Strategies
- Human Resource Systems
- Change Processs
- External Environment
  - Dynamic for Change

External Environment
  - Dynamic for Change
Organizational Structure/Culture for Go/No-Go Decision

- Executive Committee (EC)
- Development Project Review Committee (DPRC)
- Research Project Review Committee (RPRC)
- Corporate Product/Project Portfolio
- Corporate Strategy

**Request for Development (RFD)**

- Development Projects
- Research Projects
- Dynamic and Open Communication
- Long-term vision: Regulatory, Commercial Strategy, Portfolio Management
- Significant overlap: Process Development Chemists and Medicinal Chemists
- Life-long responsibility: Pharmacokinetics, Toxicology, Drug Product Formulation/Delivery
External Environment

- **Current SOC:** What is the availability of the current standard of care in the market place; what is the mechanism of actions and treatment regimens of the existing drugs; what are the effectiveness, benefit and side effects of the current therapies;

- **Pipelines:** How many and what kind of products are present in the development pipelines by different companies and at which stage each development product is under trials; what kind of treatment regimens these products are being tried with;

- **Desired Regimens:** What will be the desired treatment regimens;

- **Cost and Market:** How much the current standard of care costs per patient per day, per treatment or per year; what is the patient population, demographic and geographic distribution; what will be the overall market sales and what will be the potential market share of a product under development;

- **Regulatory Landscape:** What is/will be the regulatory landscape for the therapeutic area; what is/will be the reimbursement and pricing regulations; what will be the government policy;

- **IP:** What is the intellectual property landscape, and so on.
Decision Gates and Trees

- Is the drug developable
- Is the drug safe
- Is the drug efficacious and effective
- Is the drug marketable
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Gilead Sciences: Who We Are

- Global bio-pharmaceutical company.
- Focused on areas of high unmet medical need.
  - HIV/AIDS, Liver Disease (Hepatitis B & C), respiratory, cardiovascular disease, and more recently - cancer and inflammation
- Founded in 1987, headquarters in Foster City, California.
- Edmonton (Raylo) site purchased by Gilead in 2006
  - Current Clover Bar site purchased/opened in 1995/97 and after purchase by Gilead in 2006 research and manufacturing activities were consolidated to the site.
- Expansion of R&D, QC, Warehousing and Plant since joining Gilead
- Continual expanding!
15 Products Contributing to Revenue Stream Through Direct Sales or Partner Promotion

- **Vistide**
  - CMV Retinitis/AIDS
  - Astellas (US and Canada)
  - Sumitomo (Japan)

- **Emtriva**
  - HIV/AIDS
  - Japan Tobacco (Japan)

- **Viread**
  - HIV/AIDS
  - Japan Tobacco (Japan)

- **Truvada**
  - HIV/AIDS
  - Japan Tobacco (Japan)

- **ATRIPLA**
  - HIV/AIDS
  - Bristol-Myers Squibb (US) and (EU)
  - Merck (Developing Countries)

- **Viread**
  - HIV/AIDS
  - GSK (Asia)

- **MACUGEN**
  - Age-related Macular Degeneration
  - OSI (US) / Pfizer (OUS)

- **Letairis**
  - Pulmonary Arterial Hypertension
  - GSK (EU)

- **Hepsera**
  - Chronic Hepatitis B
  - GSK (Asia, Latin America)

- **Lexiscan**
  - Myocardial Perfusion Imaging
  - Astellas (US and Canada)

- **Tamiflu**
  - Influenza A & B
  - Roche (Worldwide)

- **Ranexa**
  - Chronic Angina
  - Menarini (EU)

- **Cayston**
  - Cystic Fibrosis

- **Myocardial Perfusion Imaging**
Daily Pill Burden Then and Now

1996 (up to 35)
- Atripla® - first in the class, new golden standard
- Complera® launched 2011

Since 2006

Since 2006

GILEAD
Focus at Gilead Alberta

**MISSION:**
- To develop chemistry & produce API for clinical use.
- Prepare registration batches and launch material.
- Transfer technical packages to contract manufacturers.
- Optimization of commercial processes.

**DEVELOPMENT**

**COMMERCIAL**

GILEAD
Gilead Alberta (Edmonton)

- NCE/API Discovery
  - API Manufacturing
  - Formulation (Tablet, Capsule, Suspension, ...)
  - Product Packaging
  - Marketing
  - Transportation

- Prescription (Drug Product)
  - Analytical Chemistry
  - Operations (MFG)
  - Quality Assurance
  - Engineering/maintenance
  - Material and Project Management
  - EH&S, G&A

- Chemical Process
  - R & D + MFG
  - Formulation Studies
  - Tox. Studies
  - Clinical Trials (Ph I, Ph II, Ph III)

- ~219 people
- R&D

- Development
- Commercial
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What Chemists Can Do?

Discovery and Preclinical Research and Development

- Discovery
- Preclinical

Clinical Trials

- Phase I
- Phase II
- Phase III

Surveillance

- NDA Review and Approval
- Phase IV

Drug Discovery/Medicinal Chemistry

- Lead generation Lead optimization
- Organic, Biology, Structure Chemistry, DMPK, Drug Safety

Drug Development and Commercialization

- Process R&D, Process Safety, Analytical Chemistry, Manufacturing
- Formulation/Drug Delivery, Packaging, DMPK, Commercial Strategy, Portfolio Management, Commercial/Marketing

Regulatory and Quality Assurance
Skill Requirements

♦ Technical Skills

♦ Soft Skills
  - Communications
  - Leadership
  - Project management
  - Team work
  - Dedication/work ethics
  - Versatility
Interview

- Be prepared
- Know yourself
- Be yourself
- Learn about the employer’s organization
- Be professional
- Remember – It is a mutual process
- Types of Interviews
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Process R&D/Process Chemistry

 Definition: In general, it is refers to the design, development and implementation of efficient synthetic routes and processes for the manufacturing of active pharmaceutical ingredients (API) (also referred as dug substances) at commercial scale (ultimately) in a timely manner.

- Elegant process development have also been done in fine chemical industry, which will not be our focus for this course.

 Criticality: Essential to the entire pharmaceutical development process, vital link, and part of the go/no-go decision making criteria.
Process R&D/Process Chemistry

♦ Dual goals (dictate constant balance and prioritization of process R&D activities, there is a set of norm)
  – APIs for preclinical and clinical trials
    • Grams to multi-kg – toxicological, formulation studies
    • Multi-kg to hundreds of kg – clinical trials
    • Hundreds kg to multi-metric tons - launch
  – Process knowledge for manufacturing (internal and suppliers) at scale
    • Synthetic routes evaluation and selection (multi-iterations)
    • Define and optimization of process parameters, operating ranges, proven acceptable ranges, design spaces…
    • Impurity identification and reduction/elimination
    • Development and validation of analytical methods (both in-process control and release tests)
    • Establishment of quality control strategies…
Process R&D/Process Chemistry

♦ Challenges
  – Time pressures (process development to keep up the pace of drug development)
    • High cost of pharmaceutical development (~ 2 billion/compound)
    • Patent life expectancy (~ 20 years)
    • Shorter time from active leads to approved and revenue-generating agents ($1-10 m/day)
  – Enhanced complexity of small molecular drugs
    • Molecular weight increases
    • Steps to make it increases
    • Delicacy increases (stability, stereo-centers, polymorphic etc)
  – Increased regulatory requirements
    • Impurity profile
    • Genotoxicity
Process Chemists’ Mind

- Organic/Inorganic Chemistry
- Chemical Engineering
- Analytical Chemistry
- Process Safety (Physical Chemistry)
- Formulation
- Product Quality (Specifications)
- Patient Safety
- Environmental Impact (Minimize Waste)
- Worker Safety
- Project Management
- COGS
- Process Efficiency
- Process Robustness & Durability

Science

Process Chemists

Business

Well-beings
Course Outline

- Handout: a combination principles and case studies (by different scientists)
- Evaluation: projects of interest
- Tour: sometime in the middle of the semester
- Feedback
References

- Rick Ng, Drugs: From Discovery to Approval, 2nd ed. John Wiley & Sons, New Jersey, 2009
- Nature Reviews, Drug Discovery
- Drug Discovery Today
- http://www.fda.gov/
- http://clinicaltrials.gov/
- A few other web sites from business consulting firms