Clinical Drug Development

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Slide 2

Clinical Drug Development

Discovery

Development

General Use

Slide 3

Long and Costly

• 10 years from Discovery to Market

• NZ$3,000,000,000 per drug (at least)

• 9 out of 10 that are tested in humans do not reach market

• Patent Protection Very Important to Drug Developers
Increased Cost in Phases II and III

Investment required for one successful drug launch (discovery through launch)

$1.18 Billion
Launch
Phase III/II
Phase I
Preclinical
Discovery

$1.70 Billion
Launch
Phase III/II
Phase I
Preclinical
Discovery


World Wide Sales 2018

Indication | Mechanism | Medicine | Brand | Company | US$ Billion
--- | --- | --- | --- | --- | ---
Rheumatoid arthritis, psoriatic | TNF inhibitor | adalimumab (NZF) | Humira | Abbie | $ 19.90
Multiple myeloma | IL-6 receptor antibodys | lenalidomide (NZF) | Revlimid | Celgene | $ 9.70
Metastatic melanoma | anti-PD-1 checkpoint inhibitor | pembrolizumab (NZF) | Keytruda | Merck & Co | $ 7.20
Breast cancer | HER2 antagonist | trastuzumab (NZF) | Herceptin | Roche | $ 7.10
Colorectal cancer | VEGF inhibitor | bevacizumab (NZF) | Avastin | Roche | $ 7.00
Lymphomas | CD 20 B cell antibody | rituximab (NZF) | Rituxan | Roche | $ 6.90
Metastatic melanoma | anti-PD-1 checkpoint inhibitor | nivolumab (NZF) | Opdivo | BMS | $ 6.70
Anti-coagulant | factor Xa inhibitor | apixaban (NZF) | Eliquis | BMS | $ 6.40
Pneumococcal vaccination | pneumococcal vaccine | conjugate vaccine | Prevenar 13 | Pfizer | $ 6.00
Influenza | IL-12 & IL-23 inhibitor | ustekinumab (NZF) | Stelara | J&J | $ 5.20
World Wide Sales 2019
Leading pharmaceutical products by sales worldwide in 2019
( in billion U.S. dollars)

Phases of Drug Development

- Phase 0
  » Predictions for Humans
- Phase 1
  » Tolerability
- Phase 2
  » Effectiveness
- Phase 3
  » Safety
- Phase 4
  » Post Marketing

Biomarker/Surrogate/Outcome

- Biomarker
  » Readily measurable marker of response
    e.g. EEG response to anaesthetic induction agent
- Surrogate
  » Biomarker used for Regulatory Approval
    e.g. Reduction in HIV viral load
- Outcome
  » How the patient functions/feels/survives
    e.g. sex/pain/death
Learn and Confirm

- Learn
  » Exploration of the unknown
  » Develop hypothesis/model

- Confirm
  » Develop confidence
  » Test hypothesis/model

Phase 0 [Non-Clinical]
Predictions for Humans

- Data from non-human animals
- Probable mechanism of action
- Likely effective concentrations
- Major routes of elimination
- Oral Absorption properties

Phase 1
Tolerability

- Start with very small doses
- Slow increase
- Stop when adverse effects noted
- Learn
  » Single and multiple dose PK
  » Adverse effect PD?

CFR - Code of Federal Regulations Title 21
FDA regulations
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=312.21
state:

(a) Phase 1. (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and
patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80. (2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

However, a more widely used objective is to determine the maximum tolerated dose ("side effects associated with increasing doses").

Phase 2
Effectiveness

- Phase 2A
  » "Proof of Concept"
  » YES/NO decision point
- Phase 2B
  » Learn Dose response curve
  » Learn effective doses
  » Learn target concentration

Phase III
Safety

- "Safety"
  » Learn Adverse effects in target population
- Confirm effective dose(s)
  » "Method Effectiveness"?
- Learn PD of Surrogate/Outcome
- Learn PK and PD covariates
  » Age, Sex, Other Drugs…

The common belief by drug developers and clinical researchers is that the major objective is to determine "Efficacy of an experimental therapy". This confuses
“efficacy” (a pharmacological term equivalent to Emax) and “effectiveness” which determines if the treatment has a useful therapeutic benefit. The word “efficacy” is not used in FDA regulations.

This information for patients misuses the word “efficacy”

http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm#Clinical_Research_Phase_Studies

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### Phase 4
**Post-Marketing**

- Confirm effective dose(s)
- Confirm common adverse events
- Learn uncommon adverse events
- Learn “Use Effectiveness”
- Learn Pharmacoeconomics

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### Alternative Medicines

- **Herbal/Traditional Medicines**
  - Digoxin, morphine, aspirin, quinine
  - Gossipol, artemisin, taxol
- **Patent Protection Unlikely**
  - Uneconomic for full Drug Development
- **Health Foods/Nutraceuticals**
  - No Claims  No Testing  No Good?
  - St John’s Wort -> Cardiac transplant rejection
  - Black Cohosh -> Liver failure requiring transplant
  - Bracken fern -> Carcinogenic
  - ‘Natural treatment’ contains sildenafil et al.

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“If its an alternative medicine then its not a medicine that is known to be safe and effective”

http://thinking-is-dangerous.blogspot.com/2008/01/complementary-and-alternative-medicine.html (alternative medicine humbug)

http://pharmacy.otago.ac.nz/rongoa/pages/rahurahu.htm/ (carcinogenic bracken)

http://www.msnbc.msn.com/id/31088175/ (contaminants in ‘natural’ products)

World Wide Sales 2010

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug (brand name) use</th>
<th>2010</th>
<th>1-year growth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hydrocodone/acetaminophen (Vicodin) pain</td>
<td>131.2</td>
<td>2.34%</td>
</tr>
<tr>
<td>2</td>
<td>simvastatin (Zocor) high cholesterol</td>
<td>94.1</td>
<td>12.29%</td>
</tr>
<tr>
<td>3</td>
<td>levothyroxine sodium (Synthroid) hypothyroid</td>
<td>70.5</td>
<td>6.82%</td>
</tr>
<tr>
<td>4</td>
<td>amiodipine besylate (Norvasc) high blood pressure</td>
<td>57.2</td>
<td>11.50%</td>
</tr>
<tr>
<td>5</td>
<td>omeprazole (Prilosec) acid reflux</td>
<td>53.4</td>
<td>17.62%</td>
</tr>
<tr>
<td>6</td>
<td>atorvastatin (Lipitor) high cholesterol</td>
<td>52.6</td>
<td>-2.23%</td>
</tr>
<tr>
<td>7</td>
<td>valsartan (Brilinta) high blood pressure</td>
<td>48.3</td>
<td>9.03%</td>
</tr>
<tr>
<td>8</td>
<td>hydrocodone/acetaminophen (Vicodin) pain</td>
<td>47.8</td>
<td>-0.21%</td>
</tr>
<tr>
<td>9</td>
<td>alprazolam (Xanax) anxiety</td>
<td>46.3</td>
<td>5.47%</td>
</tr>
<tr>
<td>10</td>
<td>amlodipine besylate (Norvasc) high blood pressure</td>
<td>45.3</td>
<td>-12.38%</td>
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<tr>
<td>11</td>
<td>metoprolol tartrate (Lopressor) high blood pressure</td>
<td>43.4</td>
<td>-0.23%</td>
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<tr>
<td>12</td>
<td>hydrochlorothiazide high blood pressure</td>
<td>42.9</td>
<td>-7.63%</td>
</tr>
<tr>
<td>13</td>
<td>metformin HCL (Glucophage) diabetes</td>
<td>41.9</td>
<td>-0.21%</td>
</tr>
<tr>
<td>14</td>
<td>gabapentin (Neurontin)</td>
<td>41.9</td>
<td>5.47%</td>
</tr>
<tr>
<td>15</td>
<td>morphine sulfate (MS Contin) pain</td>
<td>41.9</td>
<td>-7.63%</td>
</tr>
<tr>
<td>16</td>
<td>warfarin sodium (Coumadin) blood thinner</td>
<td>41.9</td>
<td>5.47%</td>
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<tr>
<td>17</td>
<td>zolpidem tartrate (Ambien) insomnia</td>
<td>41.9</td>
<td>-7.63%</td>
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<tr>
<td>18</td>
<td>furosemide high blood pressure</td>
<td>41.9</td>
<td>-7.63%</td>
</tr>
<tr>
<td>19</td>
<td>celecoxib (Celebrex) high blood pressure</td>
<td>41.9</td>
<td>-7.63%</td>
</tr>
<tr>
<td>20</td>
<td>ibuprofen pain</td>
<td>41.9</td>
<td>-7.63%</td>
</tr>
<tr>
<td>21</td>
<td>azithromycin (Zithromax) antibiotic</td>
<td>41.9</td>
<td>-7.63%</td>
</tr>
<tr>
<td>22</td>
<td>amoxicillin antibiotic</td>
<td>41.9</td>
<td>-7.63%</td>
</tr>
<tr>
<td>23</td>
<td>metoprolol succinate (Toprol) blood pressure</td>
<td>41.9</td>
<td>-7.63%</td>
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<tr>
<td>24</td>
<td>citalopram (Celexa) depression</td>
<td>41.9</td>
<td>-7.63%</td>
</tr>
<tr>
<td>25</td>
<td>ibuprofen pain</td>
<td>41.9</td>
<td>-7.63%</td>
</tr>
</tbody>
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World Wide Sales 2011

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Indication</th>
<th>Company</th>
<th>Sales ($Billion/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Lipitor</td>
<td>hypercholesterolemia</td>
<td>Pfizer</td>
<td>12.5</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Plavix</td>
<td>thrombosis</td>
<td>Bristol-Myers Squibb</td>
<td>9.1</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Cerivastatin</td>
<td>hypercholesterolemia</td>
<td>Sanofi</td>
<td>8.7</td>
</tr>
<tr>
<td>Gastroproic</td>
<td>Nexium</td>
<td>acid reflux disease</td>
<td>AstraZeneca</td>
<td>8.5</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Crestor</td>
<td>hypercholesterolemia</td>
<td>AstraZeneca</td>
<td>7.4</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Capoten</td>
<td>hypertension</td>
<td>AstraZeneca</td>
<td>7.2</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Livalo</td>
<td>hypercholesterolemia</td>
<td>Abbott</td>
<td>6.6</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Exel</td>
<td>hypertension</td>
<td>AstraZeneca</td>
<td>6.5</td>
</tr>
<tr>
<td>Losartan</td>
<td>Hyzaar</td>
<td>hypertension</td>
<td>AstraZeneca</td>
<td>6.4</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Zolec</td>
<td>gastritis</td>
<td>Zydus</td>
<td>6.2</td>
</tr>
</tbody>
</table>

*Sales are for the 12 months preceding June 30, 2011.
World Wide Sales 2012

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active Ingredient</th>
<th>Main Indications</th>
<th>Company</th>
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<tbody>
<tr>
<td>Lantus</td>
<td>Insulin glargine</td>
<td>Diabetes</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Humira</td>
<td>Adalimumab</td>
<td>Immunology</td>
<td>AbbVie Inc.</td>
</tr>
<tr>
<td>SynthaTran</td>
<td>Aprepitant</td>
<td>Oncology</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>Zyvox</td>
<td>Linezolid</td>
<td>Infectious</td>
<td>Pfizer Inc.</td>
</tr>
<tr>
<td>Nexium</td>
<td>Amlodipine</td>
<td>Hypertension</td>
<td>Pfizer Inc.</td>
</tr>
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<td>Amlodipine</td>
<td>Hypertension</td>
<td>Pfizer Inc.</td>
</tr>
<tr>
<td>Regacept</td>
<td>Etanercept</td>
<td>Immunology</td>
<td>Pfizer Inc.</td>
</tr>
<tr>
<td>Remicade</td>
<td>Infliximab</td>
<td>Immunology</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>Adalimumab</td>
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<td>Immunology</td>
<td>AbbVie Inc.</td>
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<tr>
<td>Innoxa</td>
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<td>Hypertension</td>
<td>Pfizer Inc.</td>
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<td>Pfizer Inc.</td>
</tr>
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<td>Regacept</td>
<td>Etanercept</td>
<td>Immunology</td>
<td>Pfizer Inc.</td>
</tr>
<tr>
<td>Remicade</td>
<td>Infliximab</td>
<td>Immunology</td>
<td>Johnson &amp; Johnson</td>
</tr>
</tbody>
</table>

Blockbusters

- Zoloft=sertraline (selective serotonin reuptake inhibitor)
- Norvasc=amlodipine (calcium channel blocker)
- Lipitor=atorvastatin (HMG CoA reductase inhibitor)
- Nexium=esomeprazole (S-enantiomer of omeprazole; proton pump inhibitor)
- Singulair=montelukast (leukotriene antagonist)
- Zocor=simvastatin (HMG CoA reductase inhibitor)
- Advair=fluticasone (anti-inflammatory steroid) and salmeterol (beta2-agonist) (Diskus is blister pack)
- Plavix=clopidogrel (platelet aggregation inhibitor)
- Effexor=venlafaxine (selective noradrenaline reuptake inhibitor) (XR=extended release)

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World Wide Sales 2016

<table>
<thead>
<tr>
<th>Rank</th>
<th>Product</th>
<th>Active Ingredient</th>
<th>Main Indications</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Humira</td>
<td>Adalimumab</td>
<td>Immunology</td>
<td>AbbVie Inc.</td>
</tr>
<tr>
<td>2</td>
<td>Harvoni</td>
<td>Ledipasvir/sofosbuvir</td>
<td>Hepatitis B</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>3</td>
<td>Entrel</td>
<td>Etanercept</td>
<td>Immunology</td>
<td>Amgen/Pfizer</td>
</tr>
<tr>
<td>4</td>
<td>Remicade</td>
<td>Infliximab</td>
<td>Immunology</td>
<td>Johnson &amp; Johnson/Merck &amp; Co.</td>
</tr>
<tr>
<td>5</td>
<td>MabtheraRituxan</td>
<td>Rituximab</td>
<td>Oncology</td>
<td>Roche</td>
</tr>
<tr>
<td>6</td>
<td>Revlimid</td>
<td>Lenalidomide</td>
<td>Myeloma</td>
<td>Celgene</td>
</tr>
<tr>
<td>7</td>
<td>Avastin</td>
<td>Bevacizumab</td>
<td>Oncology</td>
<td>Roche</td>
</tr>
<tr>
<td>8</td>
<td>Herceptin</td>
<td>Trastuzumab</td>
<td>Oncology</td>
<td>Roche</td>
</tr>
<tr>
<td>9</td>
<td>Lantus</td>
<td>Insulin glargine</td>
<td>Diabetes</td>
<td>Sanofi</td>
</tr>
<tr>
<td>10</td>
<td>PrevnarPrevenar 13</td>
<td>Pneumococcal 7-Valent Conjugate</td>
<td>Anti-bacterial</td>
<td>Pfizer Inc.</td>
</tr>
</tbody>
</table>

Sales of Blockbuster Drugs in 2005 as a portion of the Total Revenues of Pharmaceutical Companies.