Clinical Drug Development

Nick Holford
Dept Pharmacology & Clinical Pharmacology
University of Auckland
New Zealand

Clinical Drug Development

Discovery

Development

General Use

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


World Wide Sales 2018

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism</th>
<th>Medicine</th>
<th>Brand</th>
<th>Company</th>
<th>US$ Billion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis, psoriasis</td>
<td>TNF inhibitor</td>
<td>adalimumab (NZF)</td>
<td>Humira</td>
<td>Abbvie</td>
<td>$19.60</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Intracellular factors</td>
<td>lenalidomide (NZF)</td>
<td>Revlimid</td>
<td>Celgene</td>
<td>$9.70</td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td>PD-1 checkpoint inhibitor</td>
<td>pembrolizumab (NZF)</td>
<td>Keytruda</td>
<td>Merk &amp; Co</td>
<td>$7.80</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>HER2 antagonist</td>
<td>trastuzumab (NZF)</td>
<td>Herceptin</td>
<td>Roche</td>
<td>$7.10</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>VEGF inhibitor</td>
<td>bevacizumab (NZF)</td>
<td>Avastin</td>
<td>Roche</td>
<td>$7.00</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>CD-20 B cell antibody</td>
<td>rituximab (NZF)</td>
<td>Rituxin</td>
<td>Roche</td>
<td>$6.90</td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td>PD-1 checkpoint inhibitor</td>
<td>nivolumab (NZF)</td>
<td>Opdivo</td>
<td>BMS</td>
<td>$6.70</td>
</tr>
<tr>
<td>Anti-coagulant</td>
<td>Factor VIII inhibitor</td>
<td>apixaban (NZF)</td>
<td>Eliquis</td>
<td>BMS</td>
<td>$6.45</td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td>Pneumococcal conjugate vaccine</td>
<td>Prevnar 13</td>
<td>Pfizer</td>
<td>$6.60</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>IL-12 &amp; IL-23 antibody</td>
<td>ustekinumab (NZF)</td>
<td>Stelara</td>
<td>J&amp;J</td>
<td>$5.20</td>
</tr>
</tbody>
</table>
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/cfcfr/CFRSearch.cfm?fr=312.21

(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…

---

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

(b) Phase 2. Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

---

FCFR - Code of Federal Regulations Title 21
DA Regulations
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.21

(c) Phase 3. Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

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
Phase 4
Post-Marketing

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

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.

“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