Ethics Forum: Thalidomide

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Background
• 1957 - 1961
• Grunenthal: German drug company
• World wide impact
• Developed to treat morning sickness
Chemical Structure
People Involved

- Heinrich Muckler: CEO of Grunenthal
- Frances Oldham Kelsey: U.S. Pharmacologist
- (BGA) British-German Association
- Drug Companies
- Pregnant Women
- Children
Ethical Issues and Values
What are the ethical issues?

- Insufficient knowledge of drug
- Illegal distribution of drugs
- Scientific communication
- Doctor/Patient relationship
The biggest form of evidence of this ethical violation are the deformities seen in the children born to women taking Thalidomide during pregnancy.
Why?

- Insufficient testing
  - Inconclusive animal testing
  - Not enough human testing
- Lack of drug regulation
- Early evidence of peripheral neuritis and the teratogenic potential of thalidomide was ignored \(^1\)

At the time of Thalidomide’s development, it was a common belief among scientists that medication was incapable of passing through the placenta. ²

Consequences and Outcomes
Number of Cases

- Estimated 15,000 to 20,000 cases
- Germany - 10,000 babies (3,000 alive today)
- 17 cases in America
- Less than 6,000 total are currently alive
Outcomes

- Frances Kelsey received the first President’s Award for Distinguished Federal Civilian Service
- 1962 Congress enacted laws requiring tests for safety during pregnancy before a drug can receive approval for sale in the U.S.
- In 1970 $100 million was paid by Grunenthal and $320 million by the Federal Government of Germany to the Foundation for Disabled People
Ethical Consequences

- **Utilitarianism**
  - Do the ends justify the means?
  - Prevent future tragedy
  - Treatment for various other diseases

- **Deontology**
  - Is ignorance an excuse?
  - Categorical Imperative
Current use of Thalidomide
Method of Action

- Exact method of Thalidomide are currently unknown
- Known that drug is strong immunomodulator
- Weakens inflammatory cytokines
- Degrades endotoxin TNF-\(\alpha\), preventing its inhibitory effects on white blood cells \(^3\)

Discovery of other Thalidomide Uses

- In 1965, found to be beneficial in treating complications of leprosy
  - 99% of leprosy patients responded positively to treatment with Thalidomide within 48 hours
- Thalidomide has been found to be an effective drug for many other illnesses

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Treatment of Multiple Myeloma

• Approved for treatment of Multiple Myeloma in 2006
• Has become a standard of care for Multiple Myeloma ⁶
• Negative side effects are still present, with 17% of patients in one study developing deep vein thrombosis ⁷
• Effective in malignant and non-malignant diseases ⁸

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HIV

- Treatment of HIV patients with Thalidomide can help stabilize their disease
- Thalidomide can improve ulcers associated with HIV
- Treatment helped patients gain weight

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• High doses of Thalidomide has been shown to induce substantial reductions in prostate specific androgen
• In one study, administration of Thalidomide is believed to extend survival by an average of 14 months \(^\text{10}\)

Thalidomide has been used in trials to treat a variety of diseases, including:

- Crohn’s Disease
- Rheumatoid Arthritis
- Renal-Cell Carcinoma
- Glioma
- Melanoma

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Aside from teratogenic effects, clinical trials have shown side effects like:

- Neuropathy
- Rashes
- Constipation
- Fatigue
- Nausea
- Tremors
- Leukopenia \(^{12}\)

The Future of its Clinical Use

- Because of its efficacy in the treatment of various diseases, Thalidomide is still being administered.
- Despite known side effects, it has the potential to become more effective and widely used drug.\textsuperscript{13}

Recommendations
Recommendations

- What should have been done?
- What have we learned from this that is worth knowing about today?
- What can we do to prevent similar situations?
What should have been done?

- Tighter regulation by the monitoring authorities
- More extensive animal testing
- Proper procedure for reporting postmarket safety concerns

-W. G. McBride’s Letter \(^{14}\)

What have we learned from this tragedy?

- Drug developers and mothers or potential mothers should be especially attentive to the effects of taking said drug while pregnant
- Failure to properly safety test new drugs can lead to widespread crippling birth defects
- Health of human beings $>\$\$\$\$\$
What have we learned from this tragedy?

### The Drug Discovery, Development and Approval Process

It takes 12-15 years on average for an experimental drug to travel from the lab to U.S. patients. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.

<table>
<thead>
<tr>
<th>Discovery/Preclinical Testing</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>FDA</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years</strong></td>
<td>6.5</td>
<td>1.5</td>
<td>2</td>
<td>3.5</td>
<td>15 Total</td>
</tr>
<tr>
<td><strong>Test Population</strong></td>
<td>Laboratory and animal studies</td>
<td>20 to 100 healthy volunteers</td>
<td>100 to 500 patient volunteers</td>
<td>1000 to 5000 patient volunteers</td>
<td>Review and approval process</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>Assess safety, biological activity and formulations</td>
<td>Determine safety and dosage</td>
<td>Evaluate effectiveness look for side effects</td>
<td>Confirm effectiveness, monitor adverse reactions from long-term use</td>
<td>Additional post marketing testing required by FDA</td>
</tr>
<tr>
<td><strong>Success Rate</strong></td>
<td>5,000 compounds evaluated</td>
<td>5 enter trials</td>
<td>1 approved</td>
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</tbody>
</table>

Source: Pharmaceutical Research and Manufacturers of America, www.phrma.org
What can we do to prevent similar situations?

- Continue our endeavors to understand model organisms
- Do not hastily draw conclusions about efficacy without considering all side effects
- As Thalidomide has been shown to be effective in the treatments of inflammatory and malignant disorders, continued use in these treatments necessitates extreme caution in administering to those who may become pregnant
Questions?