Governance of Pharmaceuticals Policy
Workshop:
Corruption of the Canadian Drug Regulatory System

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Learning Objectives

• Understand the relationship between Health Canada and the pharmaceutical industry

• Be able to explain weaknesses in the way that Health Canada regulates the pharmaceutical industry

• Discuss the differences between risk management and the precautionary principle when it comes to drug regulation
Points to Cover

- Regulatory philosophy & user fees
- How quickly are drugs approved
- Drug safety
- Risk management versus precautionary principle
- Transparency in drug regulation
- Notice of compliance with conditions
- Data quality in drug regulation
Regulation - Who Benefits?

Public health

Vs.

Private Profit
Views on Regulation

• Service to public
• Medications are an essential element of health care

Vs.

• Service to industry
• Medications as commodities
Consultations on Regulatory Modernization

- Officials from Health Canada sitting at one long table
- Industry officials sitting at another long table opposite Health Canada
- Public sitting off to the side as the audience
- Health Canada put forward proposals, then industry would respond and finally people in the audience would get to ask questions
User Fees

• Up until 1994 all of the revenue for the drug regulatory system came from parliamentary appropriations
• At present user fees make up about 40% of the drug regulatory system operating budget
• Health Canada would like to see this rise to 70%
The Golden Rule?

“Those who have the gold make the rules”
Who is the Client?

“The client is the direct recipient of your services. In many cases this is the person or company who pays for the service.”

Dann Michols, Director General TPD (1997)
Business Transformation Strategy

- Introduced early 2003
- “builds on the commitments made by the Government of Canada to ‘speed up the regulatory process for drug approvals’, to move forward with a smart regulations strategy to accelerate reforms in key areas to promote health and sustainability, to contribute to innovation and economic growth, and to reduce the administrative burden on business”
New Drug Approvals in Canada

• 1997-2014
  – 356 drugs approved that have also had therapeutic value assessed by the Patented Medicine Prices Review Board
  – 36 (10.1%) rated as either major therapeutic advance or breakthrough
User Fees and Review Performance

• 1998 Health Canada document about user fees:
  – “A formal link between fees and review performance, recommended at the July 1995 workshop, was not included in the approved fee regulations ... However, it was agreed that the fee regulations would be amended to make this link as soon as possible after the government determines the best way to proceed”
Standard vs. Priority Review

Drugs

Standard Review

Priority Review
## User Fees and Drug Safety

### Table 1. Safety-Related Events for Drugs Approved Just before the Review Deadline and for Drugs Approved at Any Other Time in the Review Process, 1993–2004.*

<table>
<thead>
<tr>
<th>Safety-Related Event</th>
<th>Just-before-Deadline Approvals (N = 97)</th>
<th>All Other Approvals (N = 216)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety-based withdrawal</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>No</td>
<td>90 (93)</td>
<td>212 (98.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (7)</td>
<td>4 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Black-box warning</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>No</td>
<td>87 (90)</td>
<td>212 (98.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (10)</td>
<td>4 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Withdrawal, black-box warning, or both</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Neither</td>
<td>83 (86)</td>
<td>209 (96.8)</td>
<td></td>
</tr>
<tr>
<td>Either or both</td>
<td>14 (14)</td>
<td>7 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Dosage-form discontinuation</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>None</td>
<td>72 (80)</td>
<td>187 (91.2)</td>
<td></td>
</tr>
<tr>
<td>At least one</td>
<td>18 (20)</td>
<td>18 (8.8)</td>
<td></td>
</tr>
</tbody>
</table>

Carpenter et al. NEJM 2008;358:1354-61
User Fees in Canada

• Revision to user fees in drug regulation
  – If the actual performance in a given fiscal year is more than 110% of the target for a particular fee category, penalties apply for the amount in excess
  – Fees reduced for the next reporting year by a percentage equivalent to the performance not achieved, up to a maximum of 50%; so if approvals are 20% overtime fees will drop by 20%
  – How will this effect the quality of reviews?

• Health Canada suffered a loss of $1.9 million in 2013-2014 and $2.7 million in 2014-2015
Withdrawals and Questions

• Valdecoxisb and Sitaxentam
  – 20 days from NOC to first safety warning
• Cerivastatin, Lumiracoixib, Efalizumab
  – 23 to 62 days from safety warning to withdrawal
• Calcitonin, Ceftobiprole, Drotrecogin alpha, Grepafloxacin, Idebenone, Pergolide, Remoxipride, Tegaserod, Tolcapone, Troglitazone, Trovafloxacin,
  – All withdrawn without any prior safety warning
  – Were there prior concerns about safety
# Resource Distribution: Drug Approvals vs Drug Safety

<table>
<thead>
<tr>
<th></th>
<th>Annual operating cost base</th>
<th>Number of full time equivalent employees</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year ending March 31, 2010</td>
<td>Year ending May 25, 2017</td>
</tr>
<tr>
<td>Therapeutic Products Directorate</td>
<td>44,900,000</td>
<td>53,171,014</td>
</tr>
<tr>
<td>Biologics and Genetic Therapies Directorate</td>
<td>29,700,000</td>
<td>31,336,308</td>
</tr>
<tr>
<td>Marketed Health Products Directorate</td>
<td>23,600,000</td>
<td>23,414,897</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>98,200,000</td>
<td><strong>107,922,219</strong></td>
</tr>
</tbody>
</table>

- Approves new drugs
- Monitors safety of drugs
Risk Management vs. Precautionary Principle

• Risk management:
  – Products can be marketed unless they are shown to be unsafe

• Precautionary principle:
  – If products cannot be shown to be safe then they should not be marketed
Current State of Transparency

Drug company submission
- Basic chemistry
- Laboratory data
- Animal studies
- Clinical trials
- Manufacturing information

TPD

Outcome
- Notice of compliance (NOC = marketing authorization)
- Product monograph (data sheet)
- Summary Basis of Decision
Accessibility of Information

• Confidential business information is not accessible without the consent of the company

• Confidential business information includes all safety and efficacy data submitted as part of the regulatory package
### Summary Basis of Decision document:
Scores of components and individual items

<table>
<thead>
<tr>
<th>Component characteristics</th>
<th>Individual item</th>
<th>0 – 20%</th>
<th>&gt; 20 – 40%</th>
<th>&gt; 40 – 60%</th>
<th>&gt; 60 – 80%</th>
<th>&gt; 80%</th>
<th>No. of SBDs* analyzed</th>
<th>Mean component score as a percent of maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td>Age</td>
<td>109</td>
<td>7</td>
<td>40</td>
<td>1</td>
<td>4</td>
<td>161</td>
<td>40.1</td>
</tr>
<tr>
<td></td>
<td>Gender in each trial arm</td>
<td>129</td>
<td>3</td>
<td>15</td>
<td>0</td>
<td>14</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In/outpatient</td>
<td>64</td>
<td>0</td>
<td>35</td>
<td>1</td>
<td>61</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eligibility criteria</td>
<td>13</td>
<td>5</td>
<td>22</td>
<td>5</td>
<td>116</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td><strong>Drug risks and benefits</strong></td>
<td>Length of study</td>
<td>21</td>
<td>5</td>
<td>33</td>
<td>12</td>
<td>90</td>
<td>161</td>
<td>53.2</td>
</tr>
<tr>
<td></td>
<td>Results</td>
<td>1</td>
<td>3</td>
<td>107</td>
<td>10</td>
<td>40</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mention of statistical significance of results</td>
<td>34</td>
<td>8</td>
<td>43</td>
<td>9</td>
<td>60</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparator (placebo or active)</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>9</td>
<td>140</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Withdrawal rate</td>
<td>70</td>
<td>8</td>
<td>79</td>
<td>2</td>
<td>2</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mention of statistical significance between withdrawal rates</td>
<td>153</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td><strong>Basic trial characteristics</strong></td>
<td>Pivotal status</td>
<td>2</td>
<td>0</td>
<td>34</td>
<td>3</td>
<td>122</td>
<td>161</td>
<td>70.7</td>
</tr>
<tr>
<td></td>
<td>Number of patients</td>
<td>11</td>
<td>6</td>
<td>79</td>
<td>8</td>
<td>57</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single or multisite</td>
<td>50</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>101</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study ID§</td>
<td>54</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>106</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td>1</td>
<td>14</td>
<td>85</td>
<td>60</td>
<td>1</td>
<td>161</td>
<td></td>
</tr>
</tbody>
</table>
Twenty Months of Waiting

JANSSEN PHARMACEUTICAL INC.
S/NDS FOR
IMODIUM* loperamide
CAPSULES AND LIQUID
Paediatric Use
# Table of Contents

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Change is Coming…Slowly

• Vanessa’s Law
  – Passed in November 2014

• Three years later
  – Health Canada is working on regulations for Vanessa’s Law that would mean proactively releasing safety and effectiveness data once a drug is approved
Notice of Compliance with Conditions

• Established in 1998

• Allows drugs to be marketed on the basis of surrogate markers for “patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs”

• In return companies commit to undertaking additional studies to confirm effectiveness of the product
## Status of Drugs with NOC/c*

<table>
<thead>
<tr>
<th>Conditions Fulfilled (years)</th>
<th>Conditions Not Fulfilled (years)</th>
<th>NOC/c revoked, suspended, not fulfilled, conditions removed, product removed from market</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-2</td>
<td>2-4</td>
</tr>
<tr>
<td>No. of indications</td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>

83 NOC/c for new products or new indications (64 separate products):
- 45 conditions fulfilled
- 30 conditions not fulfilled
- 8 revoked, suspended, not fulfilled, conditions removed, product removed from market before fulfilling conditions

*As of April 12, 2017*
Therapeutic Gain and Safety of NOC/c Drugs

• 27 new drugs approved under this policy between January 1998 and March 2013
  – 20 no major therapeutic advance
  – 5 major therapeutic advance
  – 2 no accessible rating about therapeutic advance

• NOC/c drugs much more likely to have safety problems than drugs approved through standard pathway
Data Quality in Drug Regulation

- Nearly half of drugs are approved based on surrogate outcomes
  - Oncology drugs – time to tumour progression, tumour response rate
  - Hypertension – decrease in blood pressure
  - Diabetes – decrease in blood sugar measures
- Men outnumber women in clinical trials
- Almost no trials have a median age >65
- Although most trials are randomized the majority are not blinded
Conclusions

• Governments are adopting an agenda that de-emphasizes state regulation in favour of business interests

• Private values - the right to earn a profit - are being prioritized over public values - openness, safety and provision of objective information about medicines