The new world of neglected disease drug R&D

Dr M Moran
m.moran@lse.ac.uk
Pharmaceutical R&D Policy Project
Wellcome Trust
London School of Economics
CIPIH Conference
June 2005
The starting point

- Only 13 new drugs for neglected diseases since 1975 (seminal '99 article)
- Neglected disease R&D is non-commercial therefore companies aren’t interested
- PPPs have started but they are inexperienced, unproven and may yet fail:
  - alone, they are incapable of delivering what is needed
- Therefore we need to commercialise neglected disease markets to bring large pharma companies back into the field

Focus on big-ticket incentives aimed at big companies
Today’s landscape

- 61 ND drug projects (end 2004)
- 20 drugs in clinical (2005)
  - 10 in phase III
  - 1 in registration
  - Translates into 6-7 new drugs (at standard attrition rates) from Phase III alone
- 3 new ND drugs registered since 2000
- 3 new industry ND research centres
- Additional SME activity still to be captured
The drug R&D landscape

**With PPPs**

- **Small scale for cash**
  - SMEs, CROs, DC, Academics
  - 45.3%

- **Big Pharma non-commercial**
  - MNCs within PPPs
  - 25%

- MNCs alone
  - 25%

**Market pull incentive (billions?)**

**Number of Projects**

**Unable to verify details for 3 TDR projects**
SME commercial R&D
(Small and medium sized pharma)

- Around 60% of “for cash” projects involve Western SMEs and Contract Research Organisations (CROs) in PPPs
- Some additional activity from SME’s working alone eg. Sequella (being captured)
- All companies work on a purely commercial basis (“altruism at a profit”)
- Government incentives are poorly designed for SMEs
  - End pipeline incentives … but SMEs need cash up-front
  - Limited end-pipeline support where SMEs are weak
  - Incentives are well beyond the scale needed for small companies (10’s of millions not billions)
SME motivations: “It’s commercial”

- **SMEs with a US/EU focus:** PPP ND input supports their commercial business
  - Cash (social venture capital)
  - Data
  - Develop a core commercial technology
  - Extend into secondary DC markets (less important)

- **SMEs with a DC focus:** The commercial scale of some ND markets matches the cost-structure of small companies

  “While such a market would be negligible for a big pharmaceutical company, it has a good economic scale for us.” (Mathias Pieters, Zentaris, developer of new leishmaniasis drug

  - PPP input improves their “to market” cost and smooths the way
    - Cash
    - Skills (tropical disease and assistance in end-pipeline DC work
    - Access to DC markets

- **PPP subcontracted projects:** a rapidly growing niche sector
  - Over one-third of PPP projects now use full or partial CRO support
MNC non-commercial

Multinational drug companies

Represents around half of the 61 projects

• MNCs working in PPPs (50%)
• MNCs working alone (50%)
  • Most “alone” companies say they will seek partnering for the clinical stages

All these projects are conducted on a non-commercial basis (“no cost-no profit”)
Motivation for MNC R&D models

• **Non-financial motives**
  – Ethical/Corporate Social Responsibility
  – Minimise reputational risk
  – Strategic e.g. Chinese joint-ventures; Asian R&D experience

• **MNCs use PPP’s because they need public input**
  – Subsidise direct R&D costs (“no loss-no profit” model)
  – Excellent reputational risk reduction with minimal R&D outlays
  – Scientific/technical skills/facilities
  – “Guarantee” use

• **Current gov’t industry incentives are poorly designed**
  – Financial incentives … but MNCs have non-financial motives (currently!)
  – Preferentially target in-house activity … but MNCs want/need partners for DC markets
  – If you offer large incentives, companies **will** change their approach: no-one refuses billions
Developing Country industry

- New role as end-pipeline partners, including for SMEs
- Now some up-stream R&D (tech transfer)

<table>
<thead>
<tr>
<th>Project</th>
<th>Disease</th>
<th>DC partner in:</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miltefosine</td>
<td>Leishmaniasis</td>
<td>India</td>
<td>SME manufacturing partner</td>
</tr>
<tr>
<td>DB-289</td>
<td>Malaria</td>
<td>China</td>
<td>SME manufacturing partner *</td>
</tr>
<tr>
<td>Dicationic back-up compounds</td>
<td>Malaria</td>
<td>China</td>
<td>SME manufacturing partner *</td>
</tr>
<tr>
<td>Artekin</td>
<td>Malaria</td>
<td>China</td>
<td>SME manufacturing partner</td>
</tr>
<tr>
<td>Artemisinin-production technology</td>
<td>Malaria</td>
<td>—</td>
<td>SME manufacturing and distribution partner (not yet secured)</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>TB</td>
<td>India</td>
<td>PPP manufacturing partner Possible development partner</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>Malaria</td>
<td>India</td>
<td>PPP manufacturing partner</td>
</tr>
<tr>
<td>Synthetic Peroxide</td>
<td>Malaria</td>
<td>India</td>
<td>PPP main industry partner: Development, trial manufacture, and likely final manufacture and distribution</td>
</tr>
<tr>
<td>Pyronaridine-artesunate</td>
<td>Malaria</td>
<td>South Korea</td>
<td>PPP main industry partner: Development, manufacture and distribution</td>
</tr>
<tr>
<td>Artesunate-mefloquine</td>
<td>Malaria</td>
<td>Brazil</td>
<td>PPP main industry partner Development and manufacture</td>
</tr>
</tbody>
</table>

* Joint venture in progress
Public-Private Partnerships

- PPPs now conduct 75% of all ND R&D projects**
- There are 4 ND drug development PPPs (+ TDR)
- PPPs suit industry needs (cash, expertise...)
  - Make it possible for MNCs to participate on a “not loss-not profit” basis
  - Make it more commercial for SMEs/CROs

** Additional independent SME activity being logged
PPP: a resource allocator

- Allocation role – PPPs deliver public funds to the "right" projects
- Reduce government risk/ choice
- Fund targeted industry activity - improve academic translation - DC tech transfer

* Up to end of 2004
# Sample PPP project costs

<table>
<thead>
<tr>
<th>Project Name</th>
<th>Type of project</th>
<th>R&amp;D costed</th>
<th>Indication</th>
<th>Cost US$*</th>
<th>Unquantified pro bono input</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS II</td>
<td>NCE</td>
<td>Lead identification</td>
<td>Malaria</td>
<td>2.7</td>
<td>Nil</td>
</tr>
<tr>
<td>PFT inhibitors</td>
<td>NCE</td>
<td>Lead identification</td>
<td>Malaria</td>
<td>2.2</td>
<td>Some expert advice and data from BMS</td>
</tr>
<tr>
<td>Pyronaridine-Artesunate</td>
<td>FDC</td>
<td>Preclinical (+ 3 months Phase I)</td>
<td>Malaria</td>
<td>5.3</td>
<td>Shin Poong's input (formulation chemistry)</td>
</tr>
<tr>
<td>PA-824</td>
<td>NCE</td>
<td>Preclinical</td>
<td>Tuberculosis</td>
<td>6</td>
<td>Expert advice from ex-company employee</td>
</tr>
<tr>
<td>Synthetic Peroxide</td>
<td>NCE</td>
<td>Discovery Lead Identification Lead Optimization Preclinical (+ 6 months Phase I )</td>
<td>Malaria</td>
<td>11.5</td>
<td>Expert advice from Roche in early stages</td>
</tr>
</tbody>
</table>

**PROJECTED COSTS**

<table>
<thead>
<tr>
<th>Project Name</th>
<th>Type of project</th>
<th>R&amp;D costed</th>
<th>Indication</th>
<th>Cost US$*</th>
<th>Unquantified pro bono input</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyronaridine-Artesunate</td>
<td>FDC</td>
<td>From preclinical up to registration</td>
<td>Malaria</td>
<td>15-20</td>
<td>Shin Poong’s input (formulation chemistry, and also manufacturing and distribution in the future)</td>
</tr>
<tr>
<td>PA-824</td>
<td>NCE</td>
<td>From preclinical up to end of phase III</td>
<td>Tuberculosis</td>
<td>86</td>
<td>Expert advice from ex-company employee</td>
</tr>
</tbody>
</table>

* We have used internal budgets, and added pro-rata’d indirect scientific costs and quantified pro-bono
Funding constraints are choking off this rapid-growth sector

- Only 5 OECD countries contribute to drug development PPPs
  - US, UK, Netherlands, Switzerland
  - EC minimal (<1%)

- Total government contributions for all 48 PPP projects since 2000 is $43 million

- PPP shortfall for 2005 is around 30%

- PPPs respond by:
  - Slowing down R&D
  - Delaying industry contracts
  - Pressuring industry for discounts/in-kind

- There are NO industry incentives to support industry PPP involvement
  - Currently over 30 drug projects

* Up to 2005
Performance metrics

Including:

– Development timelines
– Cost and cost-efficiency
– Level of innovation
– Health value
– Accessibility for DC patients

(Assessed across 80+ ND drug dev’t projects 1975 to 2004)
Industry timelines

- Marketing approval
- Registration
- Phase III
- Phase II
- Phase I
- Preclinical
- Lead Op
- Lead Id
- Discovery

Years

- Industry standard
- Industry - NCEs
- Industry - Label extensions (includes vet drugs)
Pure public timelines

- Discovery
- Lead Id
- Lead Op
- Preclinical
- Phase I
- Phase II
- Phase III
- Registration
- Marketing approval

Years
0.0 5.0 10.0 15.0 20.0 25.0

Industry standard
University projects
WRAIR projects
Correlates of success

• The same analysis across all metrics shows that several factors are associated with best outcomes (example: synthetic peroxide)
  1. A sole focus on ND drug development
  2. Management with an industrial mindset and experience (can be PPP or industry)
  3. Early public involvement
  4. Early industry involvement
  5. Adequate funding

• Metrics of ND drug dev’t show that industry does better with public health input & public groups do better with industry input
  ➢ They keep each other on track

• Not just a matter but of cash, but of getting the right skillset
  ➢ Drug development and neglected disease/DC knowledge

• Incentives promoting industry alone R&D or public alone R&D are likely be a less efficient use of public funds
Optimising outcomes

• The PPP framework best matches these correlates of success as well as political and industry needs

• But the PPP framework is only as good as its practice

• In the majority of cases, performance matches or sometimes exceeds industry standards - unsurprising given the large number of industry partners

• In some cases, practice falls short of this potential due to
  – Lack of sufficient industry input
    • Cost constraints
    • Cultural issues
  – Lack of cash
IRFF: A virtuous cycle

The IRFF is a public cash fund to subsidise industry input to PPPs

How it works:

1. PPPs contract industry deals as they do now.
   - Industry deals represent 2/3 of current PPP R&D spending…

2. The IRFF subsequently partially tops up PPPs for these industry payments (80%?)
IRFF: Advantages

Increased cash flow allows PPPs to
- Contract more industry deals
- … at commercially competitive prices and without delays (SMEs/CROs)
- On a no loss no profit basis with MNCs
- Be more viable long-term company partners

Greater industry input improves PPP outcomes (a correlate of success)

A stronger and more efficient R&D framework based on best practice
IRFF: Advantages

• Improved efficiency of funding:
  ➢ The best performers are the highest users
  ➢ Funds allocated in exactly the right amount at the right time across all 40+ industry projects
  ➢ Encourages increased R&D/ non-R&D spending ratios

• Public risk and “pick the winner” are reduced:
  ➢ Industry/health experts in PPPs select projects rather than governments
  ➢ Risk spread across total ND portfolio

• 10-year projected cost flattens out at $150 million/year to support all projects
  ➢ Current PPP portfolio (with no new projects) at standard attrition rates will deliver 6-7 drugs in this time

• Minimum new infrastructure is needed (VC host)

• Could easily be extended to cover academic translation activity
Fast Track registration: An efficiency gain

Fast Track increases patent productivity by decreasing drug development time

Fast track benefits derive from efficiency gains
  • Regulatory efficiencies
  • R&D shortcuts

FTO harnesses this efficiency gain to fund neglected disease R&D
Fast Track Option (FTO)

- FTO builds on the existing fast track mechanism
  - For treatments for serious and life-threatening diseases, and some commercial diseases (obesity, diabetes)
  - Currently 10% of drugs in the US

- We propose auctioning off the right to partially fast-track one additional commercial drug per year (admin efficiencies only; no R&D shortcuts allowed)
  - And using the revenue to fund neglected disease R&D

- Benefit to the company for partial FT on a top decile commercial drug:
  - 0.5-2 years faster to market
  - $0.5 billion - $0.75 billion additional revenues

- Auction mechanism “shares” this benefit with the public sector

- All resources to conduct the additional FT activity are covered from the auction fee (no diversion of priorities or resources)

- Auctioning one FTO per year could raise hundreds of millions per annum for ND R&D
  - 1:1 public sector matching an option
Next steps ..

- Analysis of data on timelines, health outcomes, innovation, cost-efficiency etc, which shows the strengths and weaknesses of each approach …

- And information on who, why and how R&D is now being done …

- Is giving us a better understanding of the new world of ND R&D …

- And allowing us to design improved R&D policies that
  - Match stakeholder needs and preferences
  - Support optimal approaches
  - Shift players towards best practice models
  - Put the right amounts of money in the right places

- There are many fruitful ideas and approaches worth further examination