New approaches to funding drug R&D for neglected diseases

Pharmaceutical R&D Policy Project
Wellcome Trust/London School of Economics
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The current perception…

• Only 13 new drugs for neglected diseases since 1975
  – despite “push” incentives for over 20 years

• PPPs have started but they are inexperienced, unproven and may yet fail:
  – alone, they are not capable of delivering what is needed

• Therefore we need an additional large “pull” incentive to commercialise neglected disease markets and bring large pharma companies back into the field
The reality

Drugs developed 1975 - 2000*

20

Drugs registered or in development since 2000

55**

- TDR 11
- GATB 7
- DNDI 5
- MMV 22

Number of drugs/projects

PPP: Pure industry

* Some with TDR collaboration
** Further SME in-house activity and IOWH projects (3) are yet to be included
The reality (2)

• There has been a boom in neglected disease R&D since 2000*

• This boom is being driven by PPPs
  – 75% of current projects

• Pure “in-house” industry R&D is becoming less popular - companies are moving towards PPPs as their preferred R&D approach
The reality (3)

• The 55 drug development projects since 2000, as included in our analysis to date, have been catalysed and progressed despite the lack of additional incentives

• They include registration of several valuable new drugs for neglected diseases:
  – Miltefosine for leishmaniasis (SME in PPP)
  – Lapdap for malaria (Multinational pharma company [MNC] in PPP)
  – CoArtem for malaria (MNC, subsequent MNC/PPP for paediatric label extension)

• Some projects have exceeded industry R&D metrics
  – Synthetic peroxide for malaria: 4 years from exploratory to clinical trials (PPP with developing country pharma partner)
  – 4(1H)-pyridones: 1.5 years from lead identification to preclinical (PPP with MNC)
In the absence of new industry incentives, what is driving this R&D?
The R&D landscape
Drug development for ND from 2000 up to now

With PPPs

Model 1
Small-scale commercial
- DB 289 (Immtech)
- Novel Tetracyclines (Paratek)
- Synthetic Peroxides
- PA 824

Model 2
Big Pharma non-commercial
- CDA (GSK)
- Moxidectin (Wyeth)

Model 3
Big Pharma Commercial
- Zythromycin + chloroquine (Pfizer)
- Sitamaquine (GSK)

- PPPs subcontracted
- MNC within PPPs
- MNC alone

- SMEs & DC PPP partners
PPPs as driver/ co-funder

The MMV example

- MMV
  - Total R&D budget: $70m

- 30% Academics
- 27% SMEs
- 40% Big pharma

Translation of basic research

67% to industry

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At a policy crossroads

• Current R&D activity is under models 1 and 2
  – Main area of current industry interest (in word and deed) with 55 projects total (SME research not finished)
  – PPP framework is the preferred approach
  – Could build a thriving “niche” market for small EU firms and support MNC goals
  – Neglected by public policy: PPPs are in a funding crisis
  – Much smaller scale of funding required (10s to 100s of millions)

• Current policy focus is on model 3
  – Approach is to commercialise neglected disease markets to bring large pharma companies back into the field
  – Has not yet been used to develop a drug
  – All new incentive proposals are targeted here (Advance Purchase Commitments, Tradeable Patent Extensions)
  – Funds needed: Billions to match MNC commercial model

• If policymakers prioritise funds for model 3, industry will go this way*

*We are reviewing model 3 incentives in the coming months
Cautionary words…

• **We need to know which model is most effective**
  – Each approach has merits and drawbacks
  – The PRPP are currently analysing these to allow policy makers to match incentives to approaches depending on their priorities (industrial, health, SME support, political etc)

• **This analysis if for drug R&D only**
  – Vaccines have very different cost-structures, markets and types of industry participation and may well need a different incentive approach

• **Next step …**
  – Outline new funding and incentive approaches for models 1 and 2
  – These models are currently the least well supported but most active source of new drugs for neglected diseases
Model 1
Small-scale commercial

- Immtech
- Novel Tetracyclines
- Paratek
- Synthetic Peroxides
- PA 824
- CDA
- GSK Moxidectin
- Wyeth Zythromicin+
- chloroquine
- Pfizer Sitamaquine
- GSK

20% 27.5% 27.5% 18%

With PPPs

Model 1
Small-scale commercial

- SMEs & DC PPP partners
- PPPs subcontracted
- MNC within PPPs
- MNC alone
Model 1: Small scale commercial (1)

This represents around half of the 55 projects now underway, including*:

- PPP partnerships with SMEs/ biotechs/ DC firms
  - 20% of projects
  - We have defined “partnerships” as involving some in-kind contribution from the company, or where the company holds the Intellectual Property (IP) being developed
  - Examples are DB-289 (new malaria drug with Immtech/MMV) and miltefosine (new leishmania drug with Zentaris/WHO-TDR)

- PPP subcontracted projects, with R&D outsourced to small firms and/or academics
  - 27% of projects
  - We have defined “PPP subcontracted” as being projects that are fully managed by the PPP or where the PPP holds the IP, with R&D tasks being contracted out by the PPP to industry or academic partner who are paid for their services*
  - Examples are the TB Alliance’s new TB drug (PA-824) and WHO’s rectal artesunate

* (Some academics and companies may provide a charitable discount, or omit to charge for overheads, management time etc)
Model 1: Small scale commercial (2)
What is the driver?

Driven by commercial considerations (Altruistic motives may co-exist, but are not the driver):

- Cash flow (grants from PPPs, Gates etc)
- Business contracts (eg. CROs)
- Cross-transfer of R&D findings to commercial programmes (e.g. Paratek - tetracyclines)
- The commercial scale of some ND markets matches the cost-structures of small companies
  - 17% of new drug applications in the US are under Orphan Drug, of which 70% come from small companies. Average orphan market is around $100 million peak sales compared to $500 million for non-orphan new drugs (Grabowski 2003)
  - The European SME who co-developed the new leishmaniasis drug (miltefosine) said:

    “While such a market would be negligible for a big pharmaceutical company, it has a good economic scale for us.” (Mathias Pietras, Zentaris, 2004)
Model 1 incentives: Small-scale commercial
(SMEs, biotechs, CROs..)

• We need financial incentives since these companies are financially motivated

• Ideal incentives should be:
  – Suitable scale for these actors (100s of millions, not billions)
  – Able to allocate funds efficiently across 50+ projects with different payments to different companies for multiple tasks with different PPPs
  – Require little or no government intervention (minimum choice/ minimum risk)
  – Require minimum new infrastructure

• Two proposals: Draw-down fund and Transferable Fast-Track (TFT)
  – These are also applicable to Model 2 (see later)
Currently SME participation in PPPs puts them at a commercial disadvantage

- Delays due to PPPs funding shortages, therefore NPVs deteriorate
- Companies pressured to offer “charitable” discounts
- Only direct R&D costs covered: infrastructure and overheads usually not included

A draw-down fund

- A cash fund of around $150 million/year (for example, funded from TFT)
- To “reimburse” companies for R&D contributions to PPP projects
  - The PPP would pay SMEs/CROs up-front for a service (tox, chemistry etc) and would subsequently be reimbursed from the draw-down fund
    - This is more administratively simple than reimbursing companies directly, which would increase SME paperwork
  - Can also help make MNC input under the “strategic/ethical” model cost-neutral
- Should cover full commercial rates for SMEs, and subsidise direct project costs for large companies
- Should include a PPP co-payment (?20%) to mitigate against over-use
$ Draw-down fund $

Packaging → Shipping → Trial → Data Management → PK studies → Toxicology

55 Drug Development Projects

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Draw-down fund (3)

- **Highly efficient**
  - Allows every R&D step across the 50+ projects to be funded as it needs to happen: no delays, no need for integration
  - Resource allocation is driven by those with the most information i.e. PPPs rather than government
  - Company services are contracted competitively in the existing market by the PPP
  - Funds are precisely targeted to the R&D gap, no more, no less

- **Cash flow to SMEs**
  - No delays in claiming/applying for funding (payment as per normal commercial practice, rather than grant-based)
  - Makes neglected disease R&D a more attractive business option
  - A form of social venture capital

- **No government choice/risk (automatic mechanism)**
  - No need to weigh up which PPP or which project is most deserving
  - All funds go entirely to industry
  - Essentially a low-risk, high efficiency industry subsidy
Transferable Fast-Track registration (TFT)

- **Mechanism to raise ~ $150 million/year for neglected disease drug R&D**
  - Could be used to finance the draw-down fund
  - But in practice, the cash could be applied to any model

- **TFT would auction off the right to “fast-track” a commercial drug, with the resulting funds used for ND drug development**
  - Built on the existing fast-track programme (currently restricted to drugs for serious and life-threatening diseases)
  - Regulatory efficiencies are used to cut R&D and registration times (no R&D shortcuts allowed!)
  - Delivers time-savings of 6 months to 2 years on time to market (revenues)
  - Revenue models (NPVs/risk-adjusted) show value to industry is hundreds of millions on a peak commercial drug
  - Auction off one, or at most two, TFTs per year (or could sell it?)
  - Depending on their drug portfolio and competitors’ position, companies would bid for the right to fast-track one of their commercial drugs to market
  - Funds raised could be matched 1:1 by governments if desired
FT: How it works

Fast Track increases patent productivity by decreasing drug development time.

FT does NOT increase patent term.
Model 2
Big Pharma non-commercial

With PPPs

Model 2
Big Pharma non-commercial

27.5% 18%

SMEs & DC PPP partners
PPP subcontracted
MNC within PPPs
MNC alone

[Graph showing the distribution of different models with and without PPPs, including Model 2 for Big Pharma non-commercial with approximately 27.5% involving PPPs and 18% without.]
Model 2: MNC non-commercial

This represents around half of the 55 projects since 2000, including:

- Multinational pharmaceutical companies (MNCs) working alone
  - 18% of projects
  - Driven by NON-financial motives (ethical/CSR; PR; reputational risk; strategic)
  - This approach has become less common as PPPs have become more established

- Multinational pharmaceutical companies (MNCs) working in PPPs
  - 27% of projects
  - Also driven by non-financial motives (ethical, PR etc)
  - Strong stated industry preference for this approach. Practice bears this out: in-house projects increasingly moving to PPP partnerships
  - Why is this approach preferred? Because in the ND area, companies often need public input
    - Scientific/technical skills/facilities that don't exist in-house
    - Subsidises direct R&D costs – projects need to be "cost neutral" to the company
    - Shares the risk
    - “Guarantees” use
    - Increases the PR value to the company
Model 2 incentives: MNC non-commercial (1)

Multinational companies (MNCs) fall into two different groups needing two quite different approaches

• **MNCs who actively conduct ND R&D**
  – 3-4 companies with a dedicated R&D programme
  – 4 companies with ad-hoc activity (e.g. developing a serendipitous in-house drug)

• **MNCs with limited in-house expertise/interest in neglected disease (ND) R&D but who nevertheless want to contribute in some way**
  – The remainder of the top 20 companies
Incentives for MNCs who are “R&D active”

• All the MNCs with dedicated ND R&D programmes are EU-based
  – GSK, AstraZeneca, Novartis +/- Sanofi

• Match the incentive to the companies’ motives (strategic, reputational etc)
  – Unwise to offer a financial incentive for an activity someone would do anyway (crowding out)
  – Offering an additional profit motive will shift company behaviour

• Match the incentive to the companies’ needs
  – If seek a PR/reputational gain
    → Provide a very prestigious prize (e.g. GSK’s contributions to R&D activity are insufficiently recognised)
  – If need their R&D role in a PPP to be cost-neutral or subsidised
    → Use the drawdown fund to reimburse company contributions, as with SMEs
  – If need lower complexity/costs/risks of getting involved in PPPs
    → Provide a clear partnering route (companies may have to set up new partnerships each time)
    → Provide a more reliable partnering route: Even when a clear route exists, companies cite lack of funding, with the consequent threat of PPP failure, as a strong deterrent.
Alternatives for MNCs who are “R&D inactive”

• Ad-hoc in-kind contributions are less useful
  • Economically inefficient, lead to delays
  • Highly counter-productive as removes cash from the SME sector, for example CROs, who would happily subcontract these services

• Provide these MNCs with structured alternatives to doing in-house R&D
  – Capture their expertise
    • FTEs: sabbaticals, company retirees, scientific secondments, part-time
    • Medicinal chemists: optimise academic leads; optimise public compound libraries
    • Generic platform skills: data management/ regulatory services
  
  – Capture skills/compounds/technologies of companies leaving the ID and/or vet fields
    • E.g. Roche’s malaria skills and technologies were captured and applied to support development of MMV’s new malaria drug
    • But most collect dust

  – TFT auction (cash out their role)
Informal thoughts …

The thoughts below have NOT been fully investigated by us, but are included to show that there are many more possibilities. Fuller analysis (industrial, economic, health, IP, political) would show if these are worth pursuing ….

- **Small APCs (or use for TFT funds?)**
  - For cheap adaptive work e.g. new developing country (DC) vaccine combinations; simplifying TB diagnostics for DC settings
  - To purchase SME leads, with social venture capital/PPPs acting as a buyer (playing a similar role to large pharma companies for commercial SME leads)

- **PPPs could share generic services via a common platform**
  - Data management, preparing regulatory submissions, legal
  - Industry expertise contributions would be very helpful here …
  - … and would lead to tech transfer over time ..

- **Amendments to Orphan Drug programmes to better match SME neglected disease markets (see separate paper)**
Overall

- Neglected disease R&D can be an active niche market for small EU companies (SMEs, including CROs) not a drain on resources:
  - This is industry policy, not just “DFID territory”
- SME activity in this area is tenuously supported by US philanthropists, instead of actively funded by EU governments
- PPPs are not a drain on resources, they are an efficient conduit for directing public funds to industry and academics
  - Efficient outsourcing to industry: pay for exactly what you need
  - Translation activities for academics: get better value out of your basic research
- PPPs are currently industry’s preferred approach but will collapse without public support
- Government financial incentives to support company contributions to PPPs are a win-win solution
  - Government funds are routed to industry with very little effort or risk
  - Cost to governments is modest ($150 million/year or less if TFT auctions are used)
  - Governments do not need to “pick winners”
  - The PPP approach has already been thoroughly piloted, using largely philanthropic funds
  - This approach underwrites industry’s preferred method of drug development (PPPs)
  - Good public health outcomes can be more easily safeguarded
The current models are working and are a low-cost effective way of targeting government funds ...

...but lack of funding will lead to their collapse, leaving both the public and companies with restricted and expensive alternatives