



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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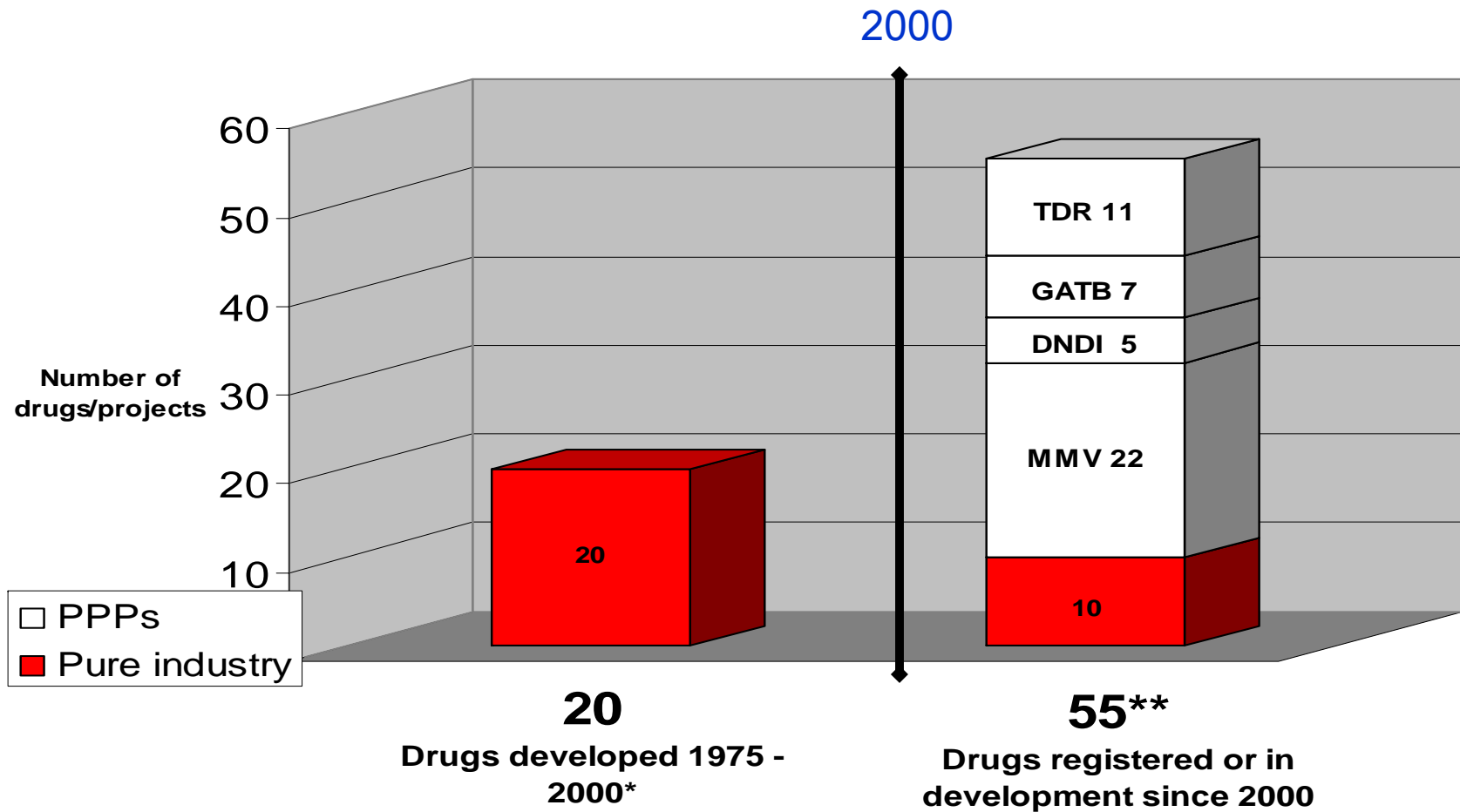
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The current perception...

- 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



* Some with TDR collaboration

** Further SME in-house activity and IOWH projects (3) are yet to be included

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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)



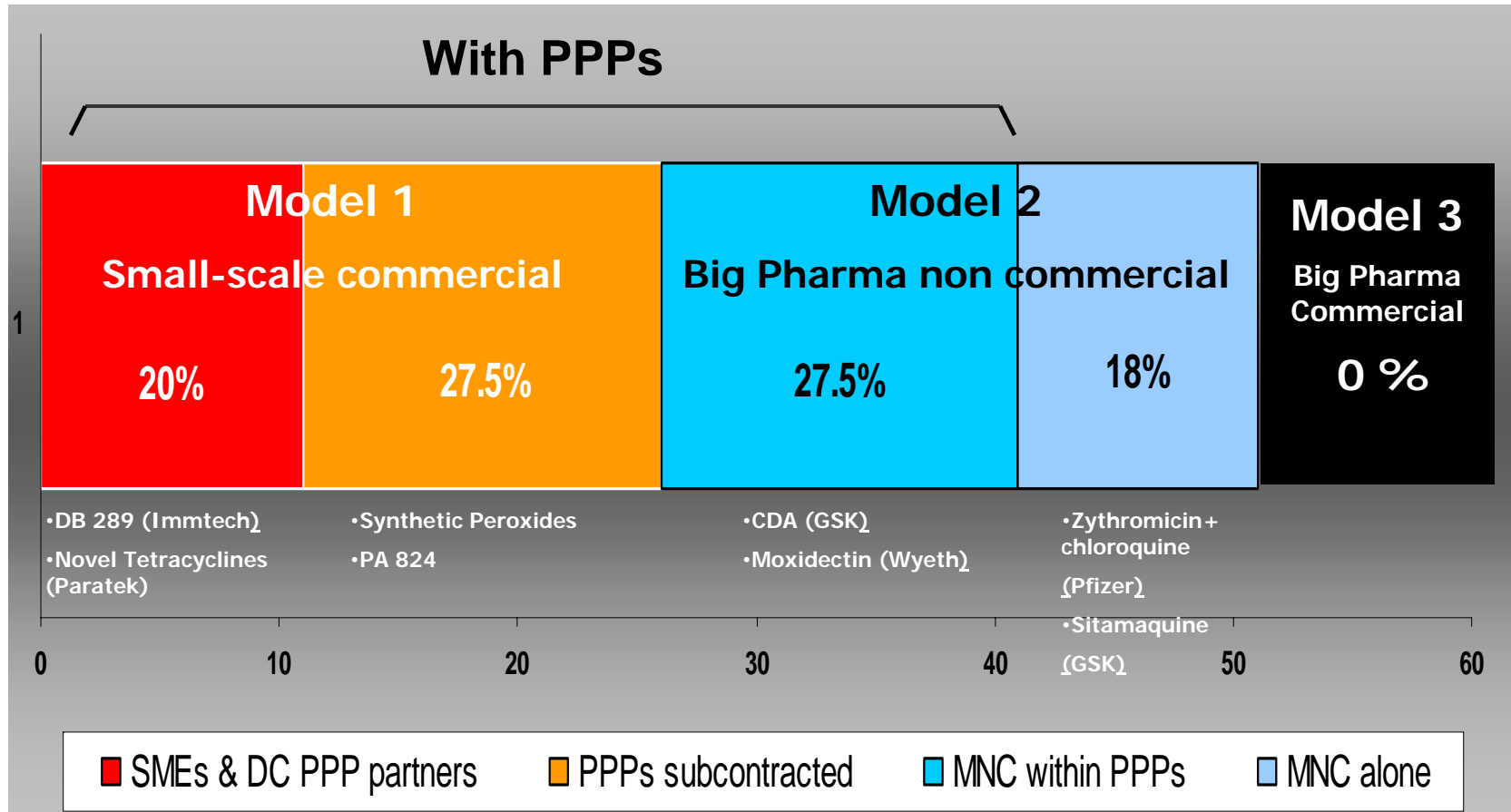
In the absence of new industry incentives,
what is driving this R&D?

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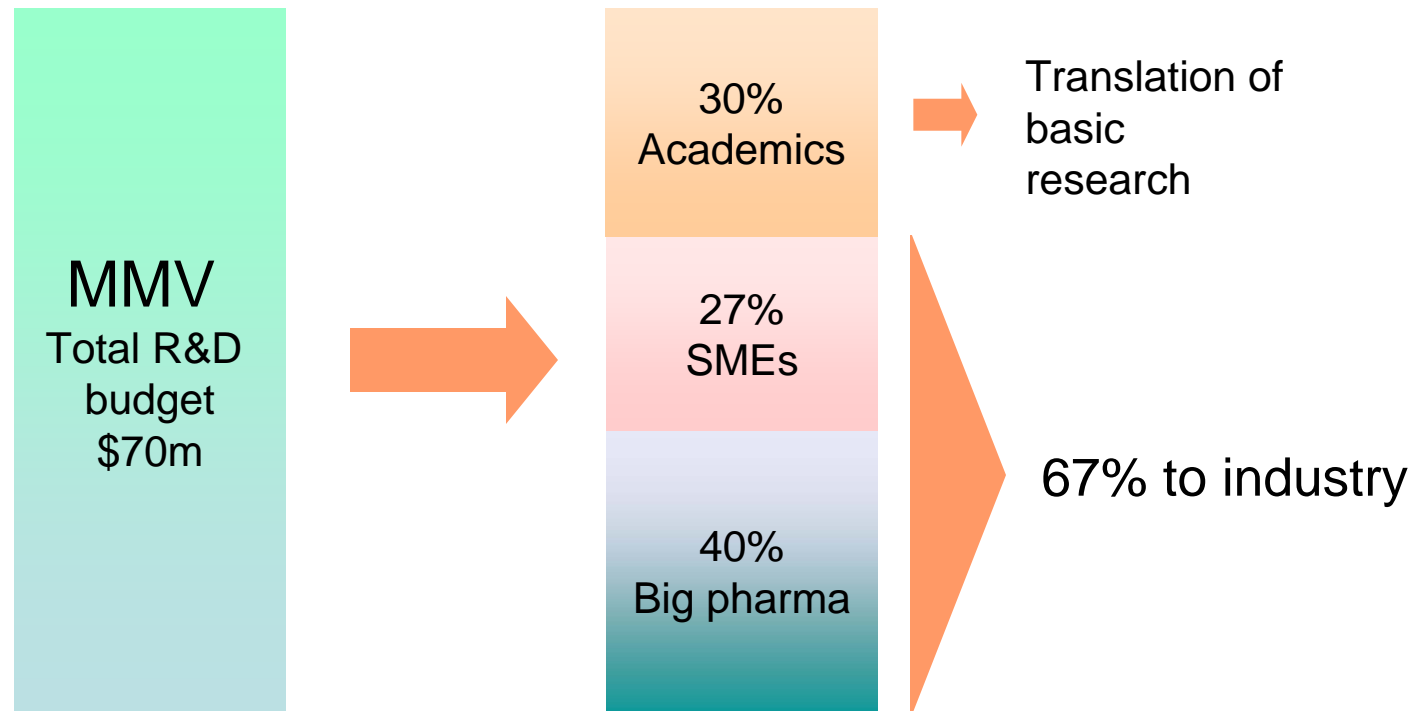
The R&D landscape

Drug development for ND from 2000 up to now



PPPs as driver/ co-funder

The MMV example



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*

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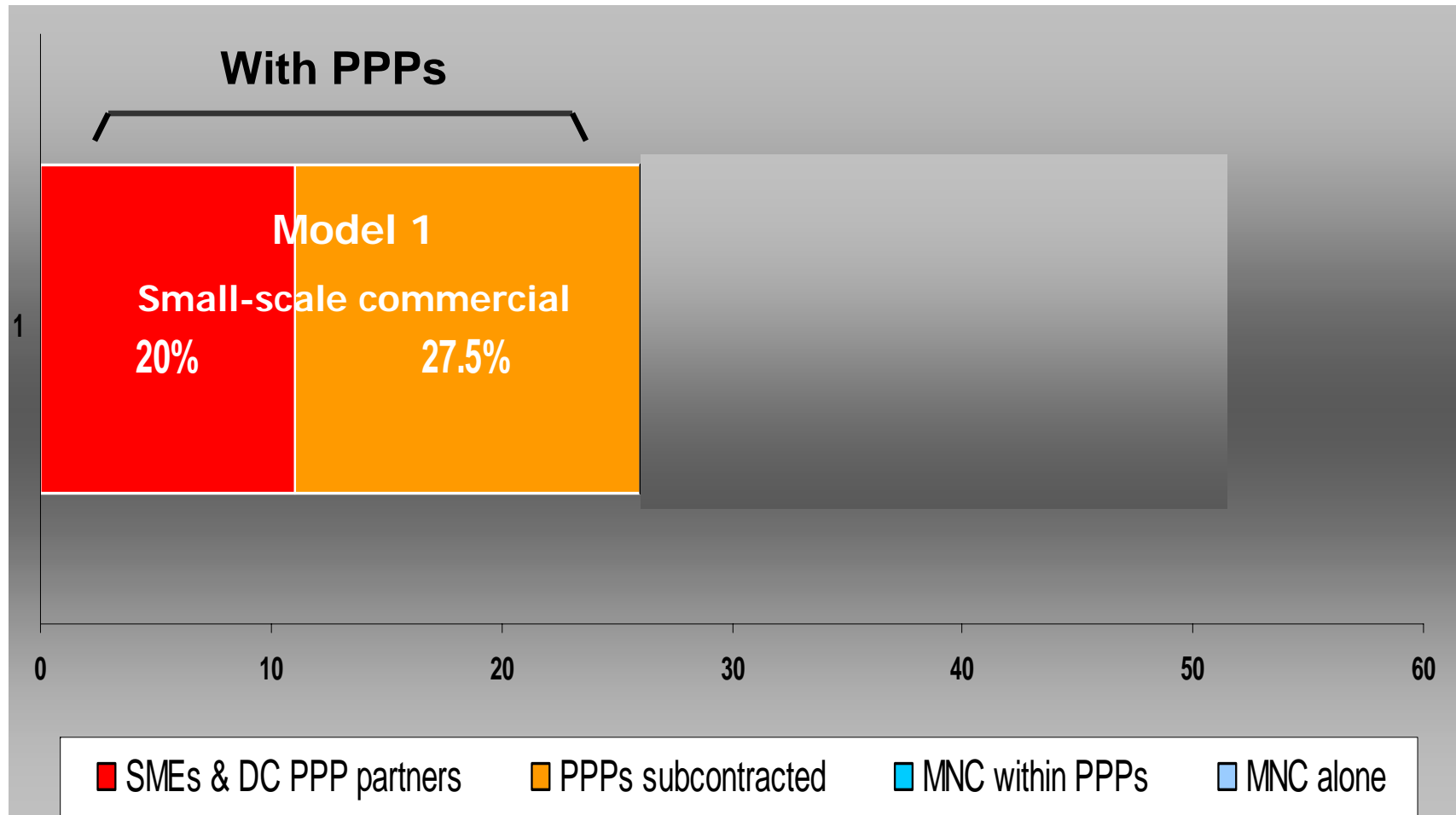


Cautionary words...

- **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 is 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



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)*

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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)

Draw-down fund (1)

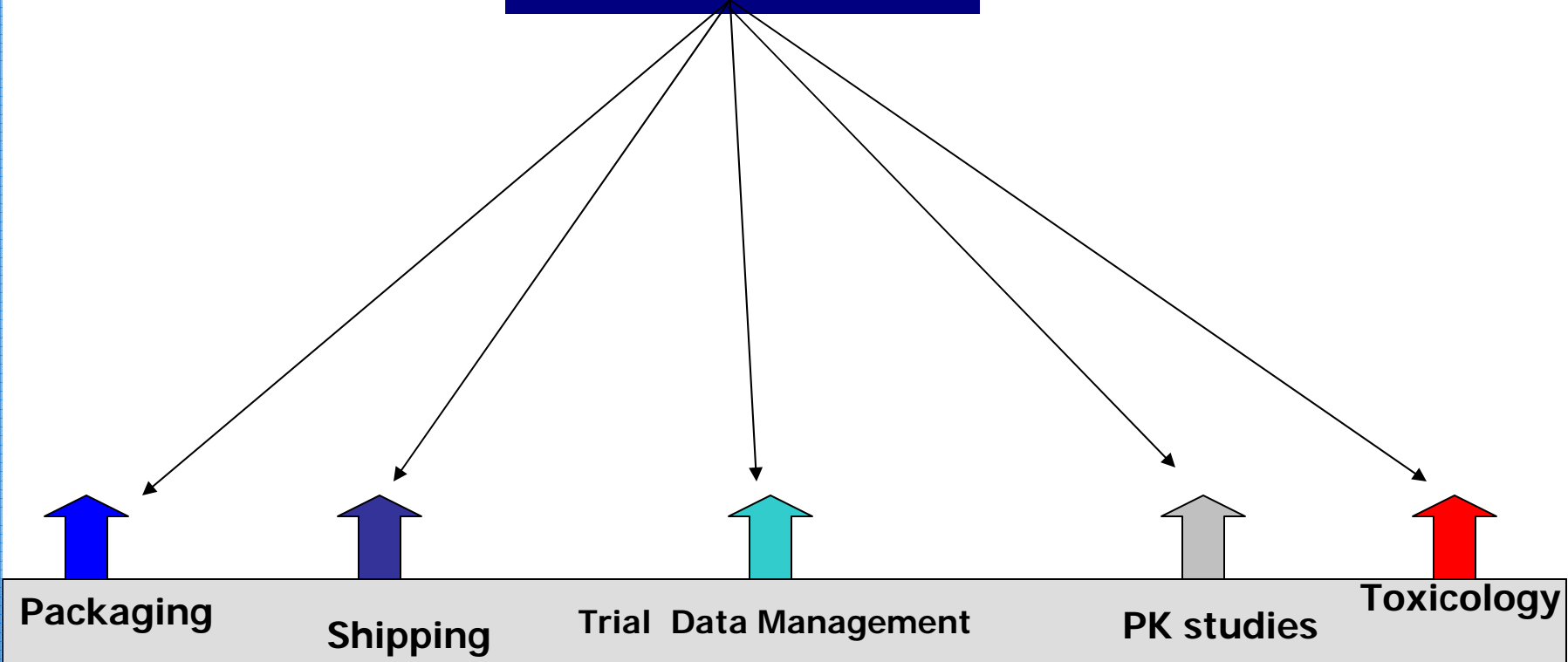
Currently SME participation in PPPs puts them at a commercial disadvantage

- 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 \$



← 55 Drug Development Projects →

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

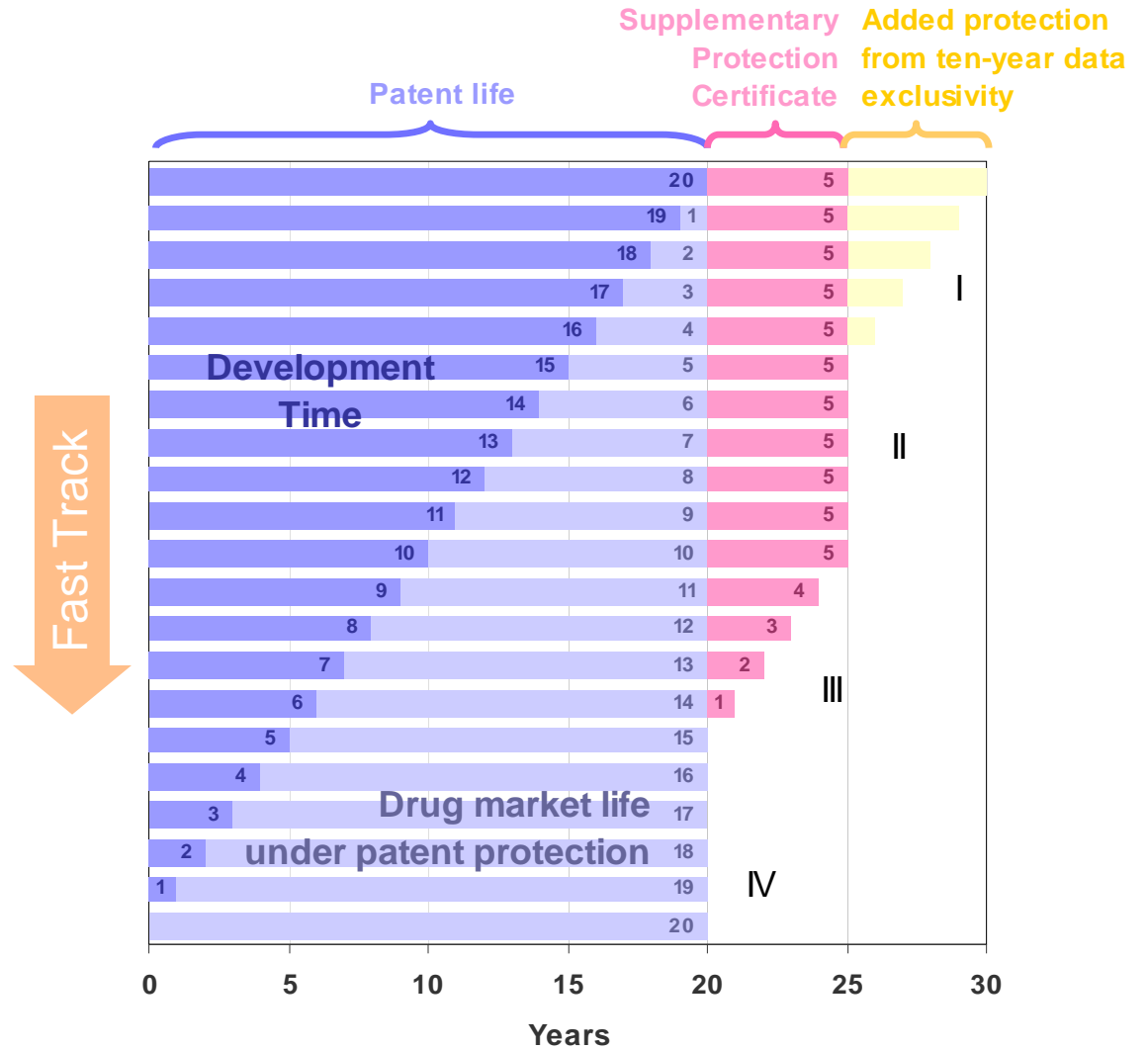
Transferable Fast-Track registration (TFT)

- 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

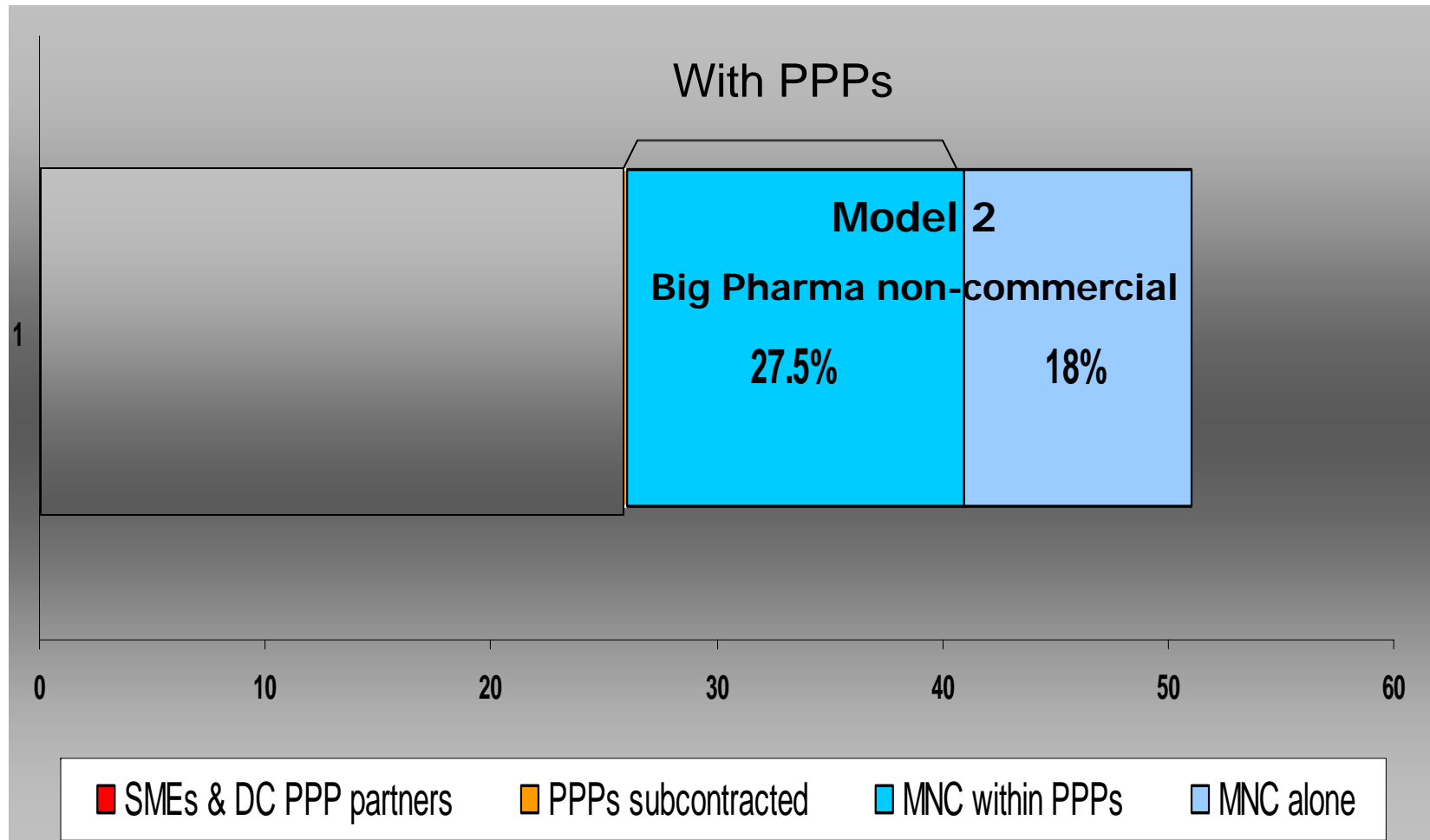
Fast Track increases patent productivity by decreasing drug development time.

FT does NOT increase patent term.



Model 2

Big Pharma non-commercial



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

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