Incentivising innovation in the biopharmaceutical sector

Presentation to the RPI Conference

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Agenda

- Objective of today's presentation
- Types of regulation and the cost of R&D
- More efficient price/utilisation regulation
- Use of "push" and "pull" incentives
- Can we get there?

Objective of today's presentation

- Look at moves away from traditional drug price regulation in HICs and at incentives for R&D for vaccines (and drugs) in LICs
- More efficient price/utilisation through indirect price control
  - Need to restrict reference pricing and parallel trade
- Use of "push" and "pull" incentives to incentivise R&D:
  - neglected diseases in LICs
  - Orphan Drugs in HICs
  - Drugs to tackle AMR resistance in HICs
- Can we get there?

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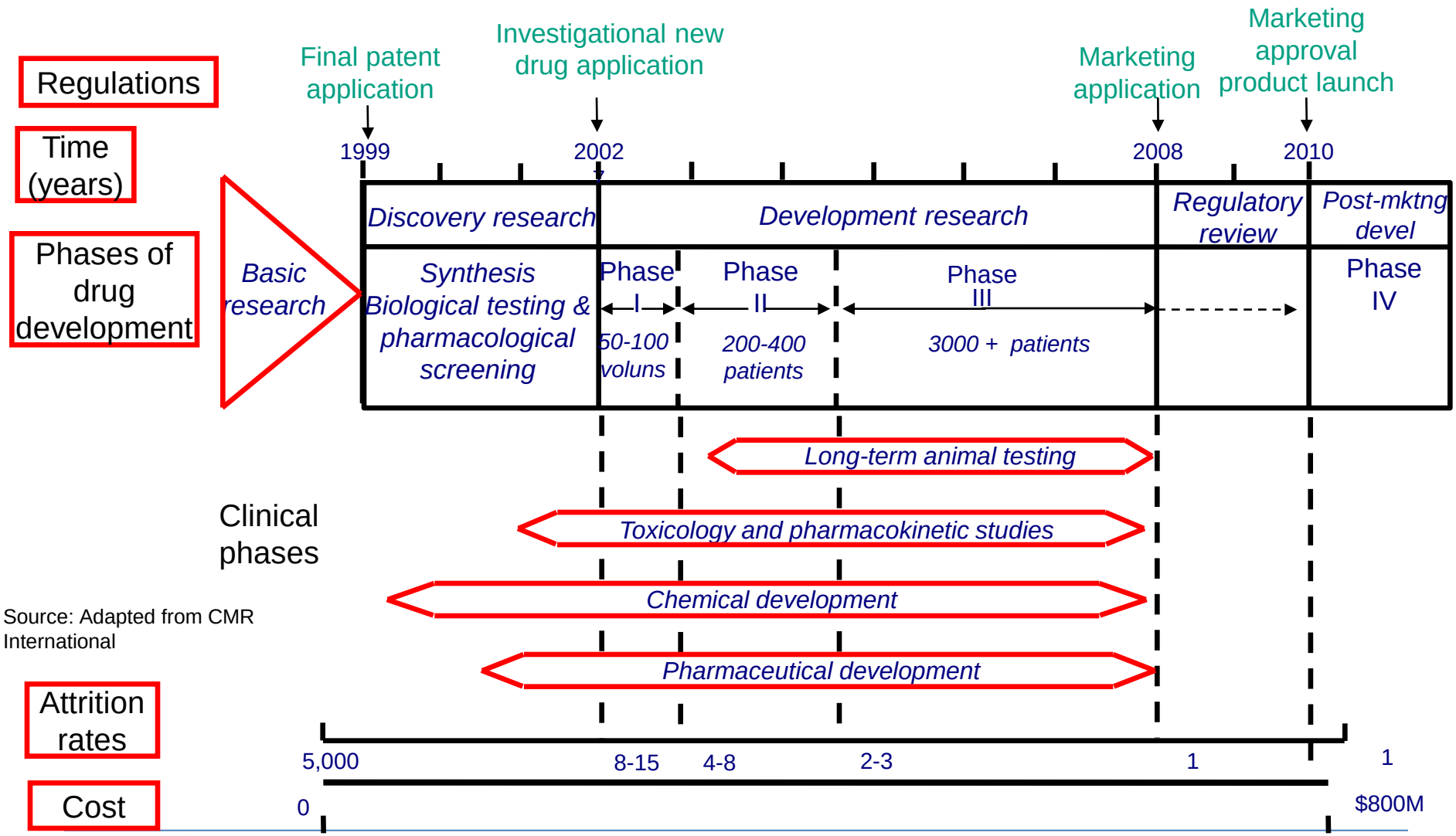
R&D and regulation

- Intellectual property protection
- Animal testing
- Regulation of clinical trials
- Marketing Authorisation (approval to launch the product – quality, efficacy and safety)
- Payer price/utilisation regulation
- Competition and merger law

Understanding the R&D Process

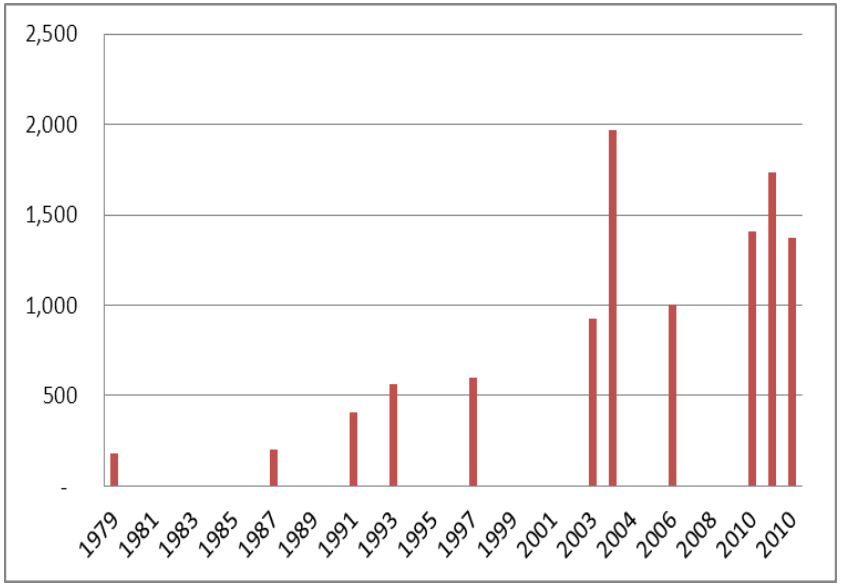


Source: CMR International

The Cost of an NME is Rising

Estimates of the full cost of bringing a new molecular entity to market
(US$ million, 2009 prices)

	2009
Hansen, 1979	179
Wiggins, 1987	204
DiMasi et al., 1991	406
OTA, 1993	562
Myers and Howe, 1997	598
DiMasi et al., 2003	928
Gilbert et al., 2003	1,967 (2000-02)
	1,273 (1995-2000)
Adams and Branter, 2006	1,004
Adams and Branter, 2010	1,404
Paul et al., 2010	1,735
Mestre-Ferrandiz et al., 2011	1,369



Each bar represents one study, plotted at the year of study publication.

Source: Mestre-Ferrandiz J, Sussex J and Towse A. (2011) *Updating the cost of a new medicine*. Office of Health Economics – forthcoming

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We are done USAID-supported nutrition research over the past 30 years. REB currently receives funding from USAID for maternal and neonatal health research.

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A flexible blueprint for the future of drug development

The current model for developing new drugs is becoming unaffordable. Costs to research and develop new drugs are steadily increasing,[1] resulting in higher prices and mounting concerns among payers about affordability and cost-effectiveness. Ultimately this spiral in costs threatens new and effective drugs reaching patients. The problem is global and urgent.

Recent years have seen various initiatives to streamline development processes[2–4] but, without a coherent and agreed blueprint into which they fit, progress has been insufficient to stem the rising tide of delays and costs. After discussions with an expert group of regulators, drug developers, patients' representatives, and value-assessment agencies, I set out such a basic blueprint, as a basis for discussion, refinement, and more concerted action (figure).

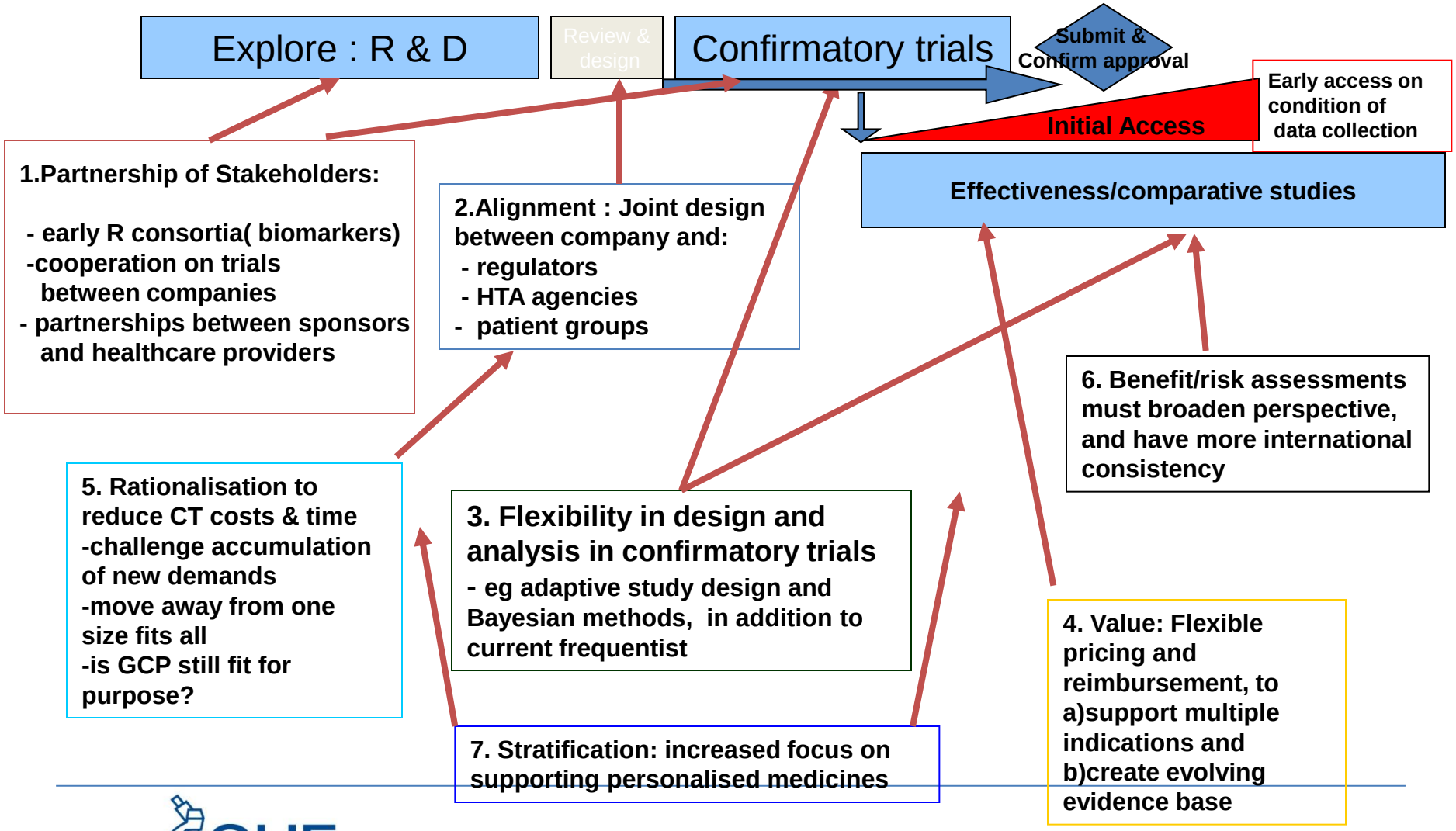
The current model, derived after decades of increasing regulatory requirements, has major limitations, including insufficient flexibility to handle different therapeutic challenges, a grafting on of the requirements of health-technology assessments (HTA) at the end of the process, and poor alignment between stakeholders. The result is a lengthy, complex, and overly rigid sequence of steps, involving trials in phases 1, 2 (sometimes divided into 2A, to determine dosing, and 2B, to assess efficacy), and 3 (again, often more than one trial), leading to regulatory approval. Often, phase 3 is followed by an HTA-oriented study, and results from all of these trials need to be assessed before any non-trial patients have access to the drug. The attrition rate is high, with substantial failure rates even after the expensive phase 3.

A new blueprint must embody simplicity and flexibility, reflect different therapeutic needs, and be designed to deliver the evidence needed for both regulatory approval and value assessment. In appropriate cases, early access by patients should be allowed while additional data is collected on comparative effectiveness, rare side-effects, or both.

To achieve the scale of reductions required in cost and time to access for patients, seven areas of new or increased initiative are required. First, partnerships between stakeholders are needed to share expertise

A flexible blueprint for the future of drug development
The Lancet, Volume 375, Issue 9712, 30 January 2010-5 February 2010, Pages 357-359. Richard Barker

Potential new flexible blueprint



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Use of pre-competitive collaboration

- Evidence of externalities from R&D “failures” due to disclosure associated with patenting
- Has been an interest in patent pools where others can “take out.” But mixed effects
- More important is the opportunity to “internalise” learning in Phases I and II to avoid the number of “dry holes” by sharing learning from trials as well as patenting
- Issue is how to structure to retain strong IP incentives

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Optimal Pricing of Pharmaceuticals

- High levels of R&D means that pricing drugs at marginal cost, to achieve static efficiency will not cover total costs
- Patents enable companies to price above marginal cost for the patent period and potentially recoup their R&D investment. This is “second best” foregoing some utilization efficiency.
- Universal insurance coverage protects consumers from financial risk and makes health services affordable. However, it makes patient demand highly price-inelastic.
- Public and private insurers use various strategies to control drug prices but these are generally not efficient.
- R&D is a global joint cost. Appropriate global pricing requires appropriate relative contributions from different countries to this joint cost.
- Economic models of price discrimination imply that price discrimination across countries is likely to be welfare superior to uniform pricing, if differential pricing increases utilization.

Optimal pricing of pharmaceuticals*

- Garber and Phelps (1997) show that an individual will spend on a health technology at the margin when opportunity cost equals incremental health benefit. We can measure health benefit in QALYs. This is the willingness to pay for health gain or the cost-per-QALY threshold.
- They state that this "is equivalent to determining optimal coverage for an actuarially fair insurance policy, under perfect information."
- Most countries operates a universal insurance system that covers drugs and other treatments for all citizens
- We might expect the system willingness to pay or the cost-per-QALY threshold to reflect that of a representative citizen
- *Danzon, Towse and Mulcahy, (2011).

Cost per QALY threshold as an indirect price control

- Several countries e.g. UK, Australia, Canada, Sweden, Netherlands, use cost-per-QALY assessments of value at or around launch
- In the UK there is an explicit threshold of £20K-£30K willingness-to-pay for a QALY on the part of the NHS as the third party payer
- If this threshold reflects societal willingness to pay for health gain and takes account of heterogeneity of preferences then it is efficient
- There are ways heterogeneity can be accommodated, even in universal systems: using different thresholds to address social preferences e.g. “end of life” or enabling patients deemed ineligible for a given product to pay out of pocket

Achieving Appropriate Price Differentials Across Countries

- If two countries have similar preferences for medical care, the optimal willingness to pay for medical care will be higher in the country with the higher income per capita.
- Manufacturers can set higher prices in these countries.
- There will not be exact proportionality of prices with income - other factors play a role, including preferences, disease burdens, and income distribution.
- These prices should differ appropriately across countries and in aggregate should add up to an appropriate incentive for manufacturers to invest in R&D.
- Increased use of external reference pricing undermines price discrimination across countries.
- Manufacturers rationally seek the same prices across linked markets, accepting launch delays and non-launch
- Parallel trade, legal in the EU, similarly undermines differential pricing

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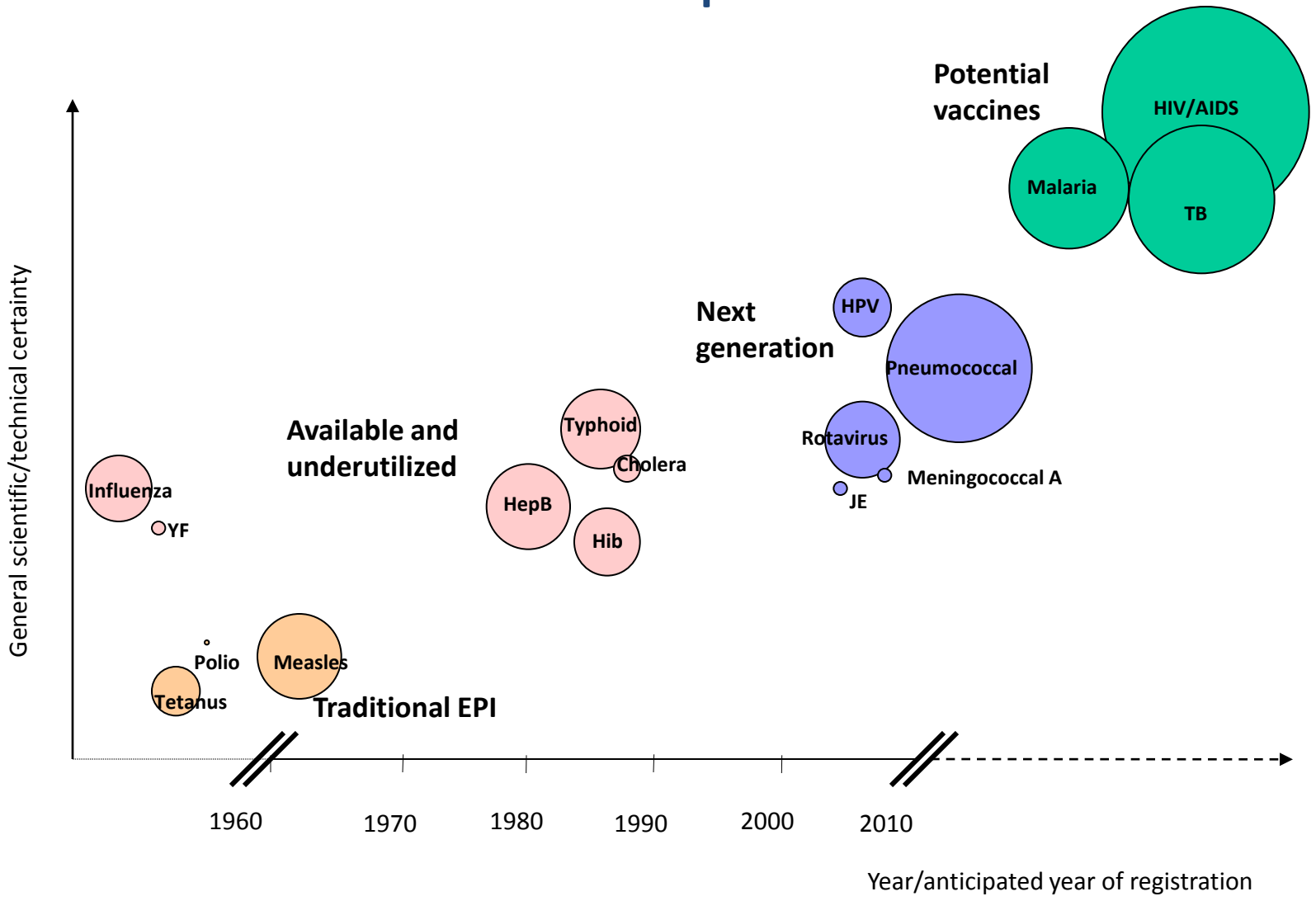
Use of “push” and “pull” incentives

- Incentives for neglected diseases
- Orphan Drug legislation
- Drugs to tackle Anti-microbial resistance

Towse, Keuffel, Kettler, and Ridley (2011).

Courtesy of PATH

Vaccines Pipeline



Size of circle indicates number of deaths (400,000 deaths, 2002 data)
Left side of circle aligned with expected introduction date

Defining “push” and “pull”

Key distinction

Whether or not the reward is conditional on having a successful product on the market

Push incentives fund or reward R&D effort ex ante, i.e. irrespective of the outcome, whilst pull provides rewards for R&D effort ex post *if* the outputs of R&D achieve health gain

Note that there are hybrid approaches:

Push funding can be part conditional on outcome as well as on effort

Pull funding may be staged and reward intermediate outcomes prior to delivery of a product

Examples of “push” and “pull”

Push initiatives: pay as you go	Pull initiatives: pay for final deliverable
1. **National Institutes of Health** Funding for specific trials or discovery programmes within broad portfolio objectives 2. **Product Development Partnerships** (PDPs) Funding for specific trials or development /discovery programmes within a portfolio to achieve licensed products.	1. **Advance Market Commitment** (AMC) Funding to purchase products not yet completed development. The funding includes a return on R&D. 2. **GAVI /GFATM Fund** Funding to purchase products already on the market through a supply contract. 3. **Priority Review Vouchers** (PRVs) Priority FDA Review as a reward for neglected disease product. 4. **Transferable intellectual property rights** Right to a patent extension on another product as a reward

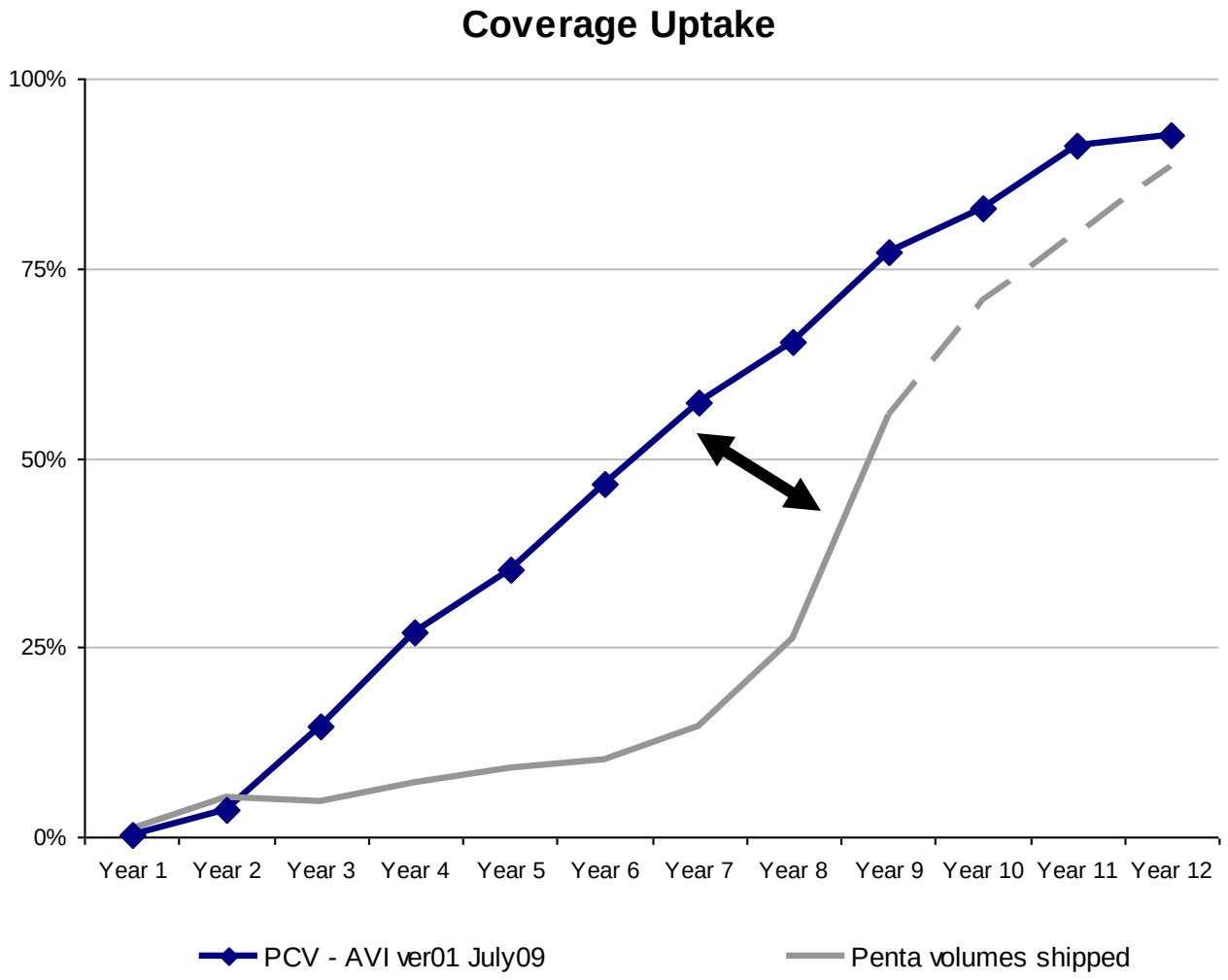
Use of “push” and “pull” incentives

- Incentives for neglected diseases
- Orphan Drug legislation
- Drugs to tackle Anti-microbial resistance

Advanced Market Commitment

- Offer a guaranteed price for up to a certain volume (or can be a guaranteed sum or prize)
- Offer has to be credible: pre-specified target, independent review group; secure financing
  - Needs to meet opportunity cost (over $3bn?)
  - Has to deal with follow-on products
  - Is a guaranteed “tail price” at manufacturing cost
- In 2010 AMC for Pneumococcal vaccine launched for $1.5bn, covering supply
- GSK and Pfizer have qualifying products and contracts

AMC should allow Pneumo to reach a faster uptake much earlier than Penta



Note - year 1 for Penta = 2001, for Pneumo = 2009

Orphan Drug legislation

- US ODA (1983), Japanese (1993) and EU (2003)
- Push/pull combination
  - Seven years of *market* exclusivity when launched
  - Higher prices to offset low volumes
  - Regulatory advice and fast track approval
  - Tax breaks in the US
- But resistance by payers in Europe to high cost-per-QALY prices

Drugs to tackle Anti-microbial resistance

- Anti-microbial resistance means that drugs become ineffective
- Estimates of 20,000 deaths per annum in the EU (cost of Euro 20bn)
- Pharmaceutical companies are exiting R&D for antibacterials
- Low returns in the market (Towse and Sharma, 2011)
  - Restrictions on antibacterial use
  - Low prices because of use of “old” generics
  - Scientific challenges
  - Regulatory challenges
- EU Commission has been tasked to come up with a package of R&D incentives by the end of 2011

Results

Incentive	Size of Incentive (€)	New NPV (€)
1 year AMC prize	980 million	154 million
*PRV	228 million	16 million
2 year transferable IP extension	850 million (425 million per year)	156 million
Market exclusivity	300% increase in antibacterial revenue in Europe	160 million

OHE Policy Recommendations for Europe

- Based on our results we recommend the following short list of incentives
  1. A hybrid policy (not dissimilar to Orphan Drug legislation) including both push and pull incentives with higher prices (but not volumes) to reflect social value. Volumes could be restricted using point-of-care tests
  2. An upfront payment for registration (rather than for volume) in the form of an AMC “prize” (advance market commitment) or a Transferable IP Extension
- These alternatives could both be on offer and the preferred one chosen by the company depending on expected use

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Can we get there?

- Use of cost-per-QALY indirect price control requires explicit willingness to pay; ability to assess costs and benefits; stopping use of reference pricing and parallel trade
- Push and pull incentives require money and long term credible commitment.
  - Orphan drug legislation shows success but also tensions with payers
  - There is resistance to “prizes”
  - EU Commission will not recommend AMR R&D incentives by end 2011
  - The portfolio approach to development through PDPs is working
  - Recent GAVI fund raising for rotavirus vaccine shows it can still be done, but a close run thing
  - The money is not there, however, to bring the neglected disease pipeline through the drug/vaccine licensing process and into use

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