The new paradigm for R&D

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definition

- “push”
  - Direct or indirect grants or subsidies that are given to entities who undertake R&D. Money is not linked to specific outcomes.
    - NIH budget, most of PDP funding, etc.
- “pull”
  - Rewards for successful R&D projects.
    - IPR marketing monopolies, APC/AMC, transferable patent extensions, Prizes

Old Paradigm

- Primary “pull” incentives are marketing monopolies for successful products

- Primary global instruments are those dealing with IPR and drug prices
  - WTO/TRIPS
  - US/EU/ bilateral/regional IPR agreement
  - US/EU agreements on drug prices (Korea, Turkey, Australia, Germany, etc)

New Paradigm

- Prizes replace marketing monopolies as primary “pull” mechanism
- R&D Agreement/Treaty to address “free rider” issue

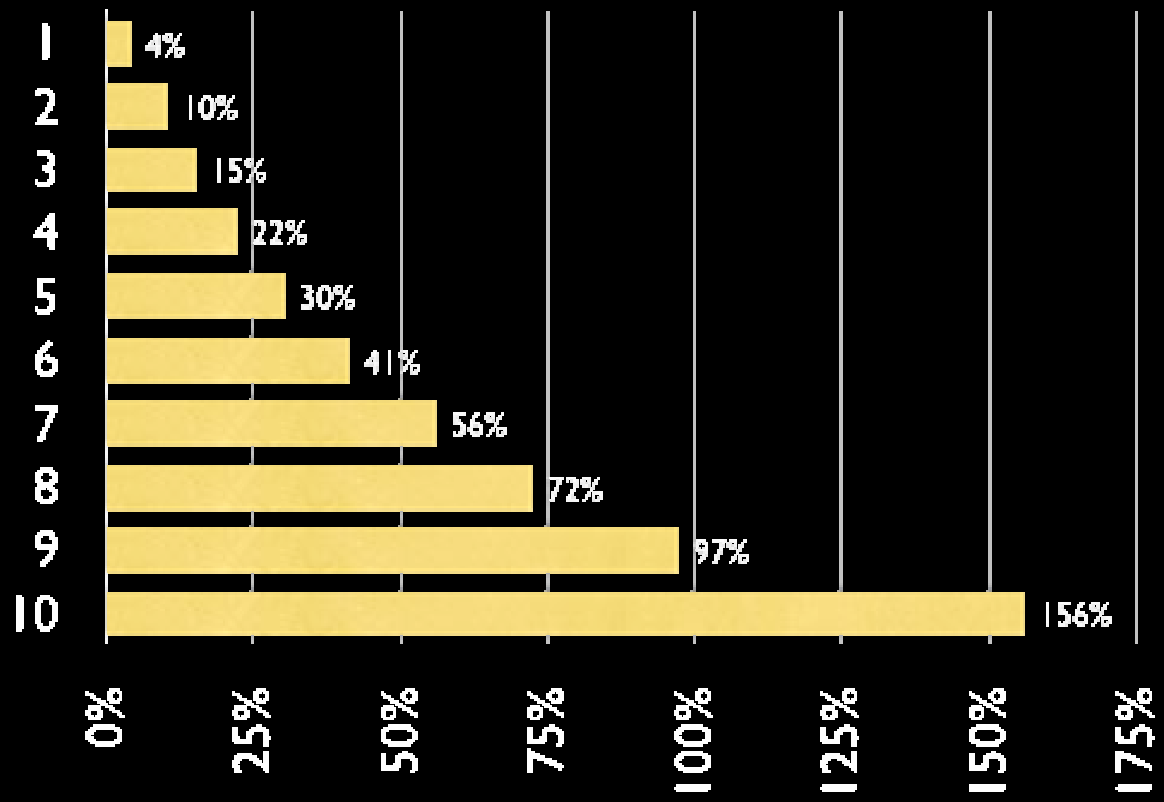
Aventis exercise

- Extensive academic literature on prizes
- September 2002, meeting organized by Aventis in Ottrott-le-Haut, France on "Pharma Scenarios for Sustainable Healthcare
- 2003/4/5 Hubbard Love papers on R&D treaties, innovation prizes and “competitive” intermediaries”

Main idea:
Separate market for innovation from market for product

Consequences of exclusive marketing rights to finance R&D on Access

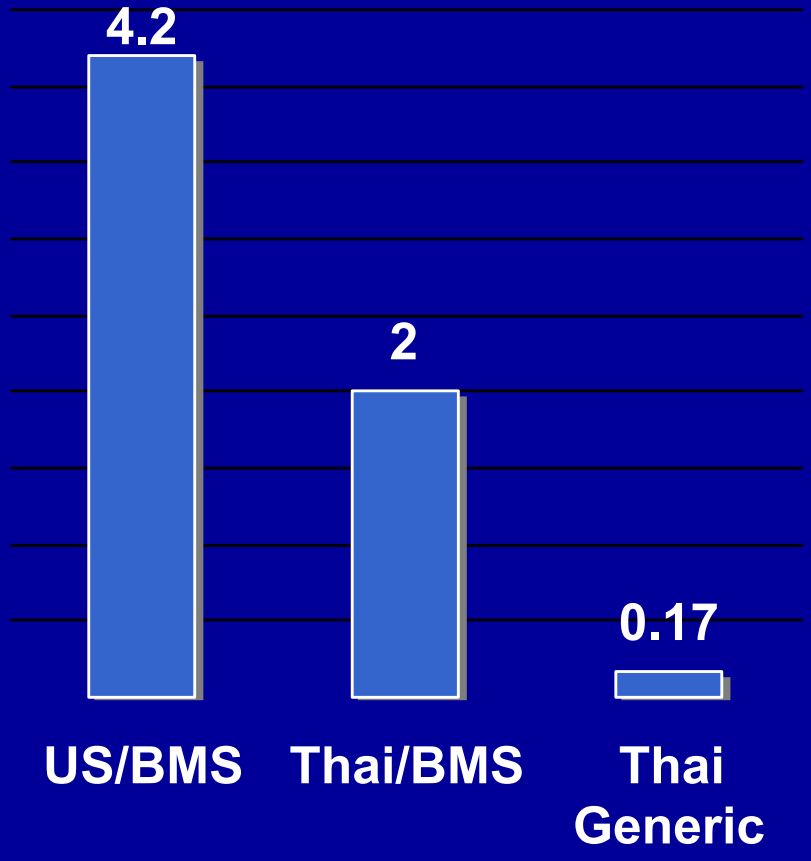
Price of Singulair as a share of per capita income in South Africa



2004 study

BMS/Sanofi prices for clopidogrel bisulfate (Plavix)

- According to the Thai Ministry of Health, BMS/Sanofi prices for the heart drug Plavix were unaffordable for 80 percent of patients
- The BMS/Sanofi price was more than eleven times the price of an imported generic



Novartis at the World Bank in 2004

- We consider India to be a market of 50 million

The World Health Organization's "essential medicines list" (EML) is limited to products that are "cost-effective."

- The most recent version of the list included only 14-patented products
  - 11 of which were for the treatment of AIDS, and
  - only 3 for all other diseases.
- AIDS drugs were only added to the list after activists launched a campaign for compulsory licenses on patents for AIDS drugs, and lobbied wealthy governments to fund the cost of treatment.

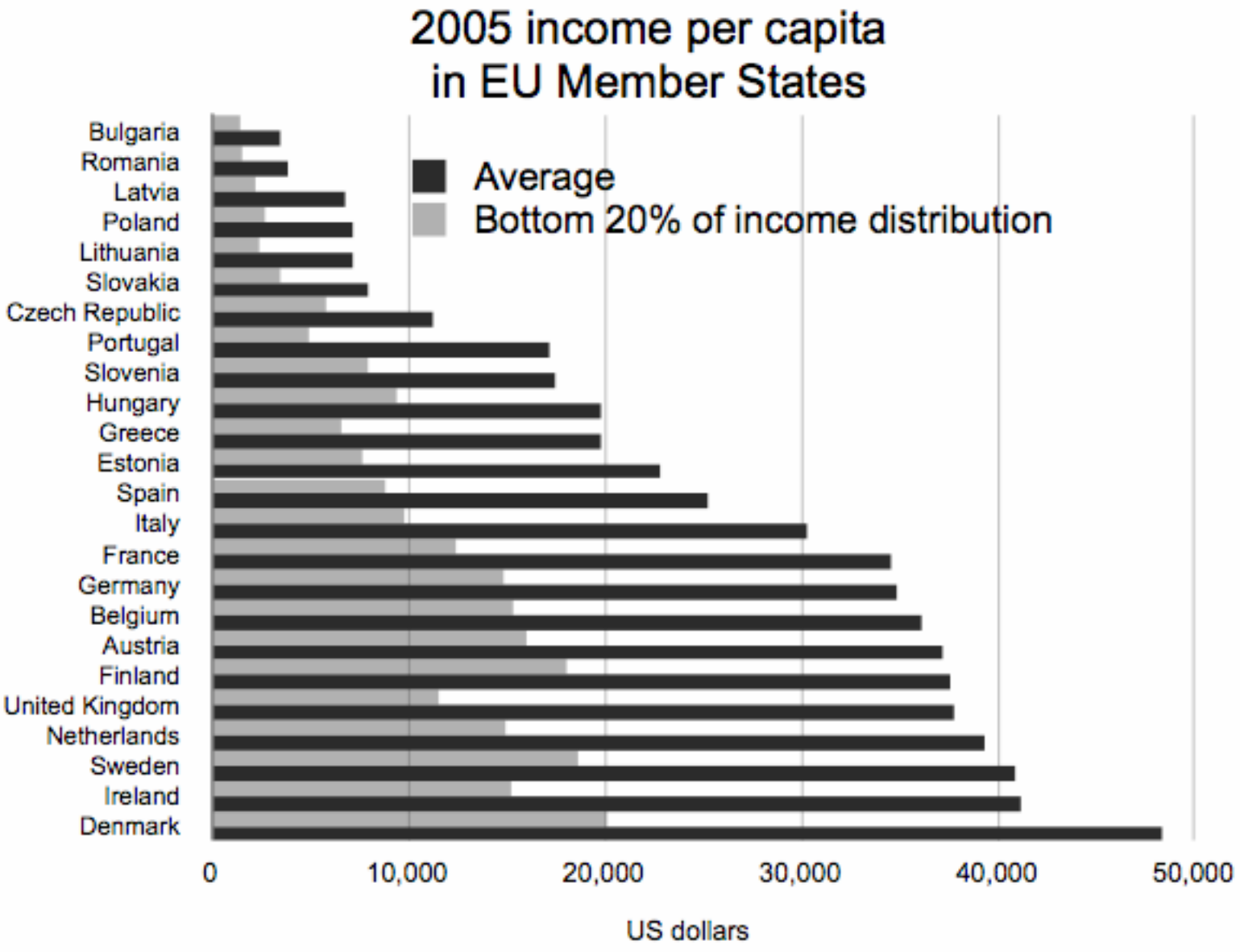
US: Cancer Weapons, Out of Reach

Robert Wittes, June 15, 2004, Washington Post

Third-party payers will not react passively to pricing that increasingly threatens their balance sheets, especially as more drugs like these are commercialized over the next few years. They will carefully scrutinize all proposed uses of expensive new drugs. Historically, an FDA judgment of "safe and effective" -- the statutory criterion for drug approval -- has almost automatically triggered an agreement by payers to reimburse, which is the real gateway to widespread use and market success. We may now see payers deciding, for the first time, that certain novel "safe and effective" medicines are simply not worth paying for. In addition, payers will surely try to limit "off-label" uses of these drugs -- that is, uses other than the FDA-approved ones. Unlike other areas of medicine, physicians have commonly prescribed cancer drugs for a broader array of indications than specifically approved by the FDA, as clinical research routinely reveals additional uses after market introduction. A very high bar to new uses by payers is a virtual certainty.

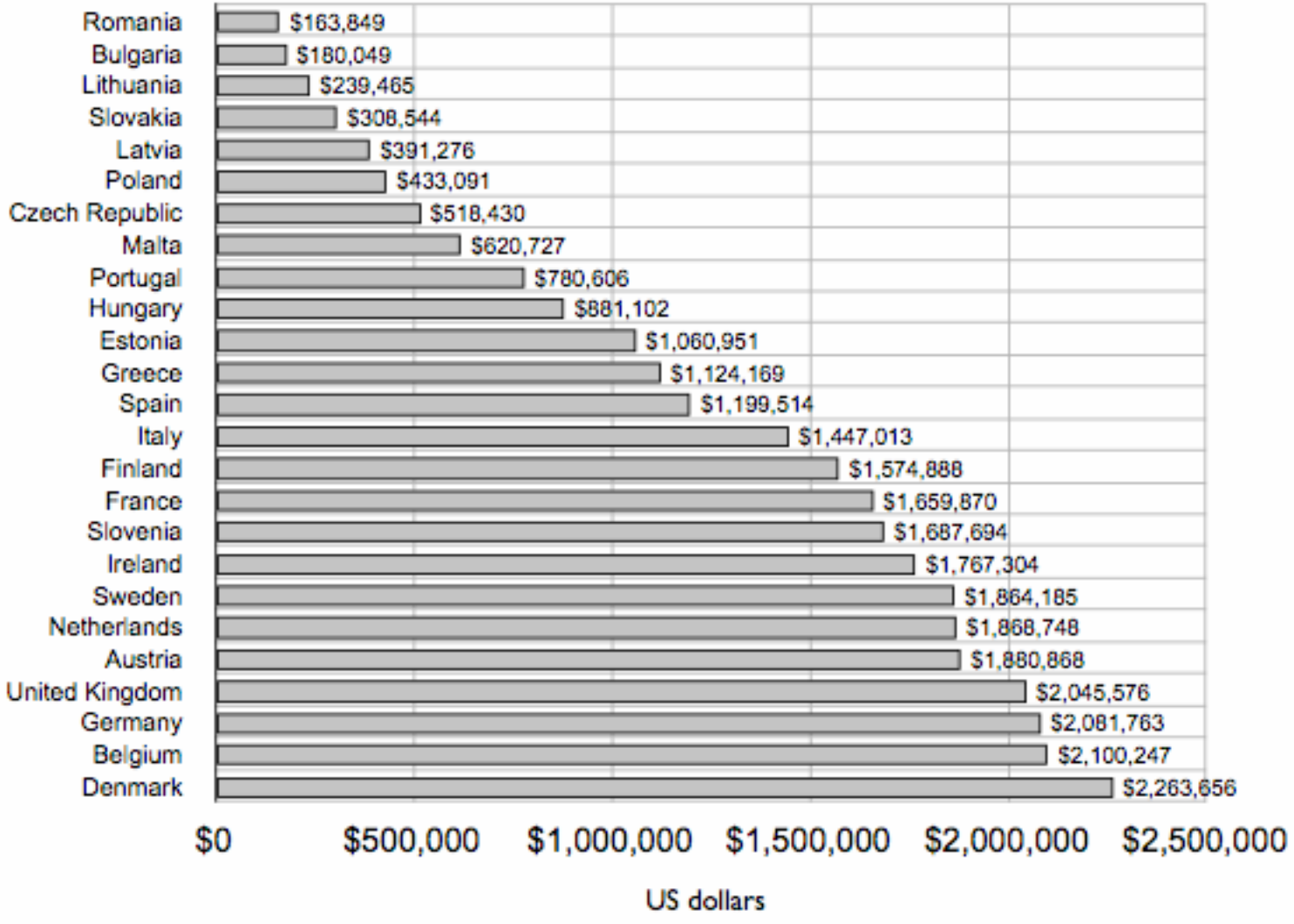
Table 3

EU Member State	Population in millions	2004 GDP/POP
Bulgaria	7.8	$ 3,090
Romania	21.8	3,358
Latvia	2.3	5,913
Poland	38.6	6,277
Lithuania	3.4	6,559
Slovakia	5.4	7,611
Estonia	1.3	8,615
Hungary	10.1	9,970
Czech Republic	10.2	10,490
Malta	0.4	13,250
Slovenia	2.0	16,100
Portugal	10.4	16,125
Greece	11.1	18,486
Cyprus	0.8	19,250
Spain	42.6	24,411
Italy	58.0	28,928
Germany	82.6	33,179
Belgium	10.4	33,875
France	60.3	33,940
Austria	8.2	35,646
United Kingdom	59.5	35,704
Netherlands	16.2	35,741
Finland	5.2	35,750
Sweden	9.0	38,489
Ireland	4.1	44,293
Denmark	5.4	44,704
Luxembourg	0.5	63,800


2005 income per capita
in EU Member States
Average
Bottom 20% of income distribution
Bulgaria
Romania
Latvia
Poland
Lithuania
Slovakia
Czech Republic
Portugal
Slovenia
Hungary
Greece
Estonia
Spain
Italy
France
Germany
Belgium
Austria
Finland
United Kingdom
Netherlands
Sweden
Ireland
Denmark
0
10,000
20,000
30,000
40,000
50,000
US dollars

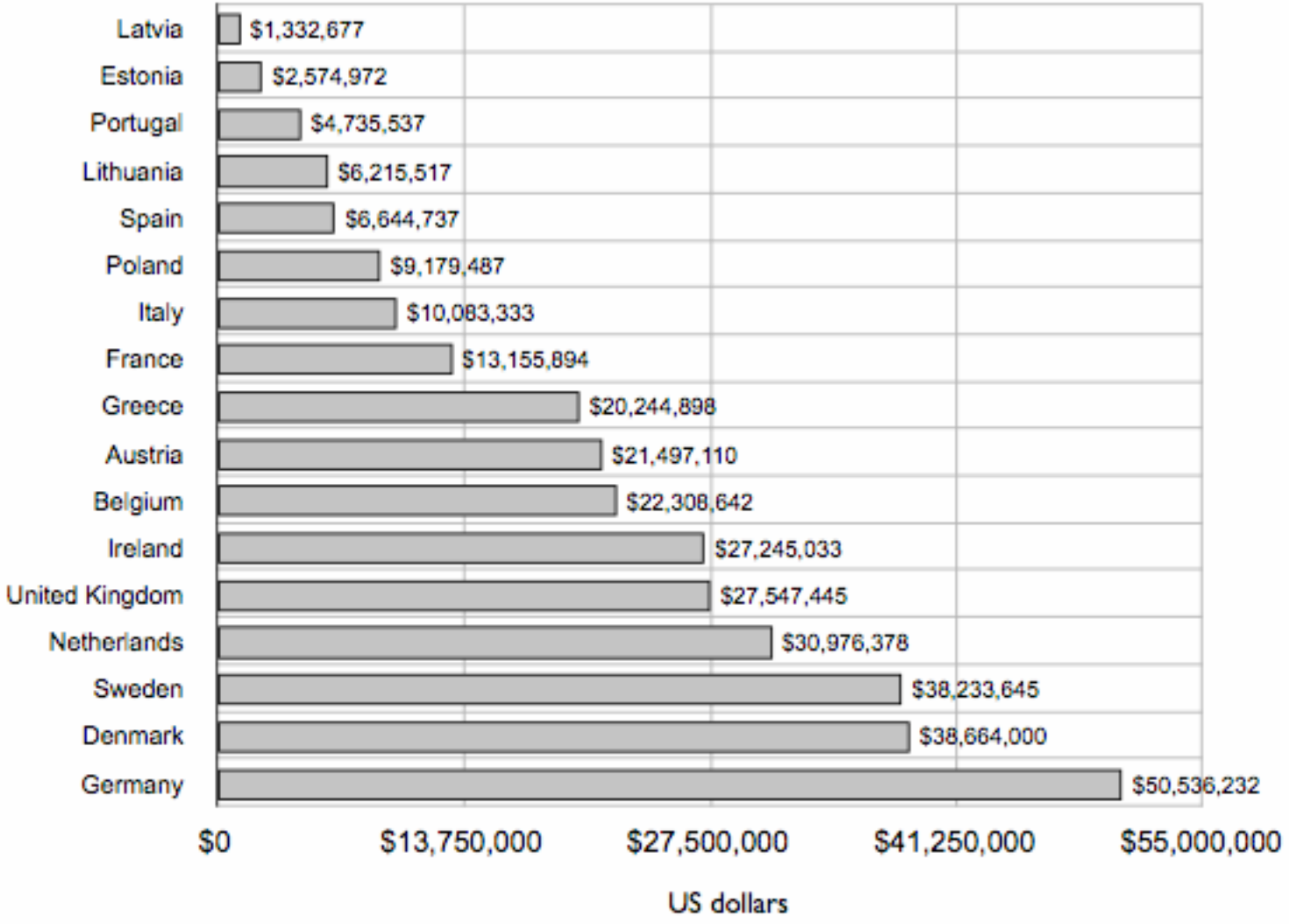
Capacity to pay for cancer treatment in EU Member States

National income divided by loss of year of life from cancer, measured in DALYs



Capacity to pay for AIDS treatment in EU Member States

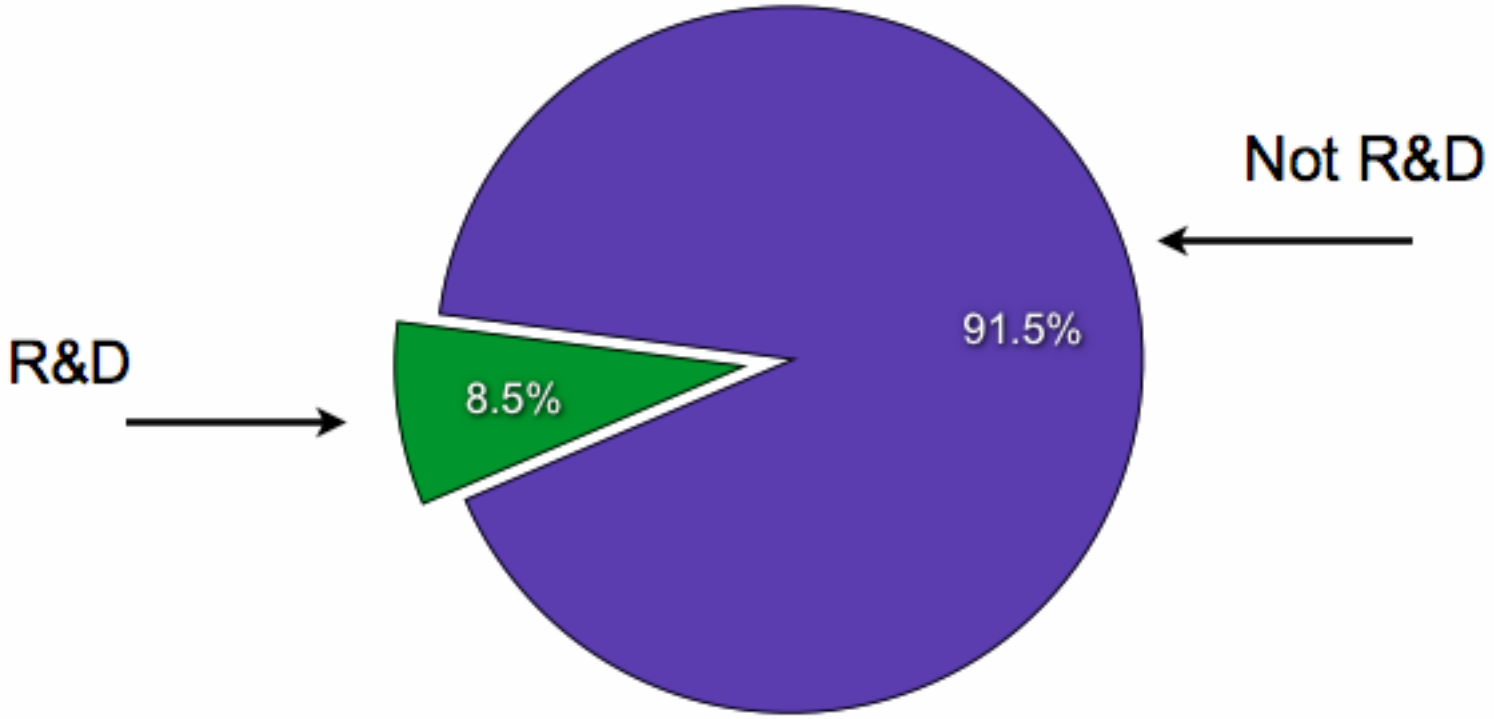
National income divided by number of HIV+ persons



Economics

- According to the market research firm IMS, global sales for pharmaceutical products were $602 billion in 2005, or 1.35 percent of global GDP.
- The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) claims global private sector investments in R&D were about $51 billion -- less than 9 percent of global sales.

Global R&D as Percent of Global Sales, 2005



- Some experts believe the current system of market monopolies for drug sales increased 2006 drug prices by $400 to $480 billion

Targets of R&D

US FDA Center for Drug Evaluation and Research (CDER) new drug approvals (NDAs) approved from 1990 to 2004

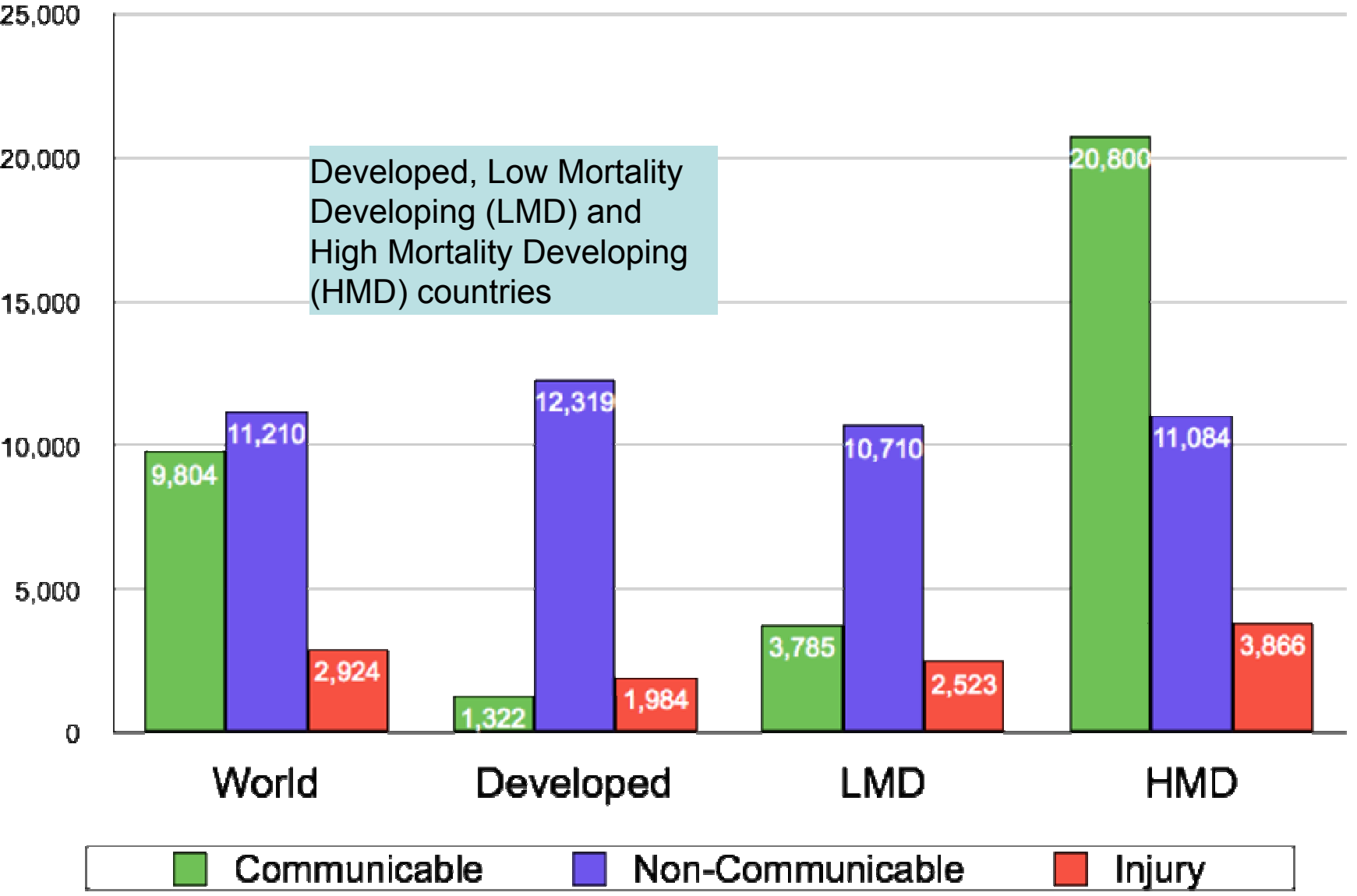
- Of the 1,284 new drug approvals (NDAs) approved from 1990 to 2004, only 289, or 22.5%, were for "priority" reviews, defined as a product that has "Significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease."

- Only 183 (14.3 percent of the total) were new molecular entities (NMEs) classified as priority products.

- Very little investment in products that serve poor populations
  - WHO Type II and III diseases
  - Products designed for resource poor settings
- Poor incentives to develop products that are used as last resort or only in emergencies
- Excessive investment in R&D projects on little scientific value or limited medical importance

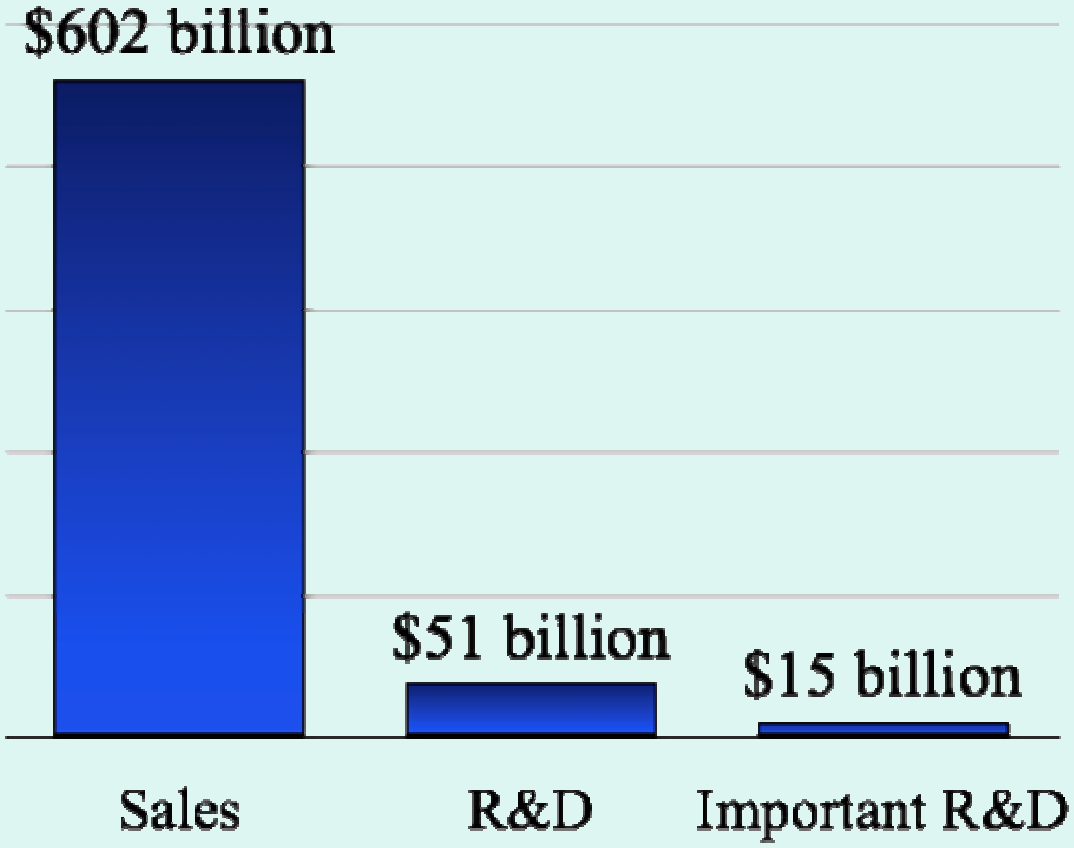
Burden of Disease by Cause and Level of Development

Disability Adjusted Life Year (DALY), per 100,000 persons.
Source: WHO GBD 2002



Marketing

Global market for pharmaceuticals 2006



Rewards (Prizes) based upon evidence of benefits

Prizes

Some recent prizes

- 2006 - Archon X Prize for Genomics. In 2006, the X Prize foundation announced the Archon X Prize for Genomics, offering $10 million for reaching targets for high speed and low cost in full genome sequencing.

- 2006 - Netflix Prize. In 2006, Netflix offered a prize of $1 million for a system to more accurately predict consumer preferences; specifically for a 10% improvement over Netflix's current accuracy in predicting whether a customer will like a movie given previous selections.

- 2006 - Ibrahim African Leadership Prize . In 2006, businessman Mo Ibrahim announced a $5 million annual award for a former African head of state who has ceded power after significantly contributing to the welfare of his or her constituents. The prize is intended to reduce corruption as well as promote effective development strategies.

- 2007 - Virgin Earth Challenge. In 2007, Sir Richard Branson and former U.S. Vice President Al Gore announced the $25 million Virgin Earth Challenge for "a commercially viable design which results in the removal of anthropogenic, atmospheric greenhouse gases so as to contribute materially to the stability of Earth's climate." In announcing the prize, Branson cited inspiration from previous innovation prizes, including the Longitude Prize, French prizes for alkali and canning, and 20th century prizes for automobiles and aviation.

Other prizes

- 1994 - Rockefeller Prize. $1 million for developing a low-cost highly accurate diagnostic test for gonorrhea or chlamydia that could be easily administered in the developing world. The prize expired in 1999 without a winner, and has been critiqued for being too small, too inflexible, and offered for too short a period of time.

- 1995 - Ansari X Prize. The X Prize was modeled after the Orteig Prize won by Lindbergh, and offered $10 million for the first private team to build and launch a spacecraft capable of carrying three people to an altitude of 100km twice within two weeks. Mojave Aerospace Ventures won the prize in 2004 with a spacecraft designed by Burt Rutan.

- 2003 - Methuselah Mouse Prize. The Methuselah Mouse Foundation announced a prize for the development of long-lived genetically engineered mice in order to promote longevity research. The foundation solicits private donations to increase the prize amount, which now stands at more than $4 million.

More prizes

- Prize for life
- H-Prize
- Bright Tomorrow Lighting Prizes
- Climate Technology Challenge Program
- The Gotham Prize

Prizes to Replace Marketing Monopolies as the Mechanism to Stimulate Medical Innovation

The prize mechanisms should be thought of as part of a larger ecosystem of financing of medical R&D, and should be implemented in combination with other instruments, such direct or indirect government funding of basic research, non-profit product development partnerships (PDPs), clinical trials, and other traditional and non-traditional types of funding R&D. **What the prizes offer uniquely is an alternative to the marketing monopoly as an incentive for private investment**.

The elimination of marketing monopolies, the de-coupling of R&D incentives from prices, and the creation of an evidence based reward system linked to changes in health outcomes, will lead to significant reductions in expenditures to market products, the area of the largest waste in the current system.

Prizes

- Lots of different models

Main idea for prize

- De-couple incentive from *price* of product
- Reward successful inventions that improve health outcomes

Prizes and intellectual property rights

- Prizes could be thought of a substitute for IPR, compatible with IPR, or a new system of IPR
- IPR could be voluntary licensed in return for a prize, or prizes could be given without such licenses, or countries could decide that prizes would replace exclusive marketing rights

Prizes as an alternative reward system

- 2002, Aventis IPR scenario # 1 (Love, Hubbard)
- U.S. Sanders bill, 2005, 109th congress, HR 417

Optional approach for prizes

- Hollis, 2005
  - Rewards for priority R&D that improve health outcomes, with prizes proportional to QALY benefits
- Pogge 2005, Nathan 2007
  - Track II, for inventions rewarded through prizes for QALY/DALYs
- CPTech/KEI 2006
  - Eligibility of reward linked to licensing of patents to patent pool

How would a prize system work?

- It could work in a million different ways
- Consider this approach
  - Reward fund is fixed
  - Companies supply innovations
  - Over a ten year period, evidence is evaluated to evaluate and measure benefits of innovations, in terms of impacts on health care outcomes
  - Prizes funds are divided among firms on the basis of relative merits of inventions
  - Prizes completely replace marketing monopolies
  - Patents are used, after drug approval, but only to assign ownership in invention and hence claim on prize.

A simple model to value inventions

Size of Prize Payments

- $100 million

Supply of xQALYS

- Company A - 3,000
- Company B - 2,000
- Company C - 1,000

Total 6,000

$ per xQALY = $16,667

Divide Fund by Shares of QALYs

Company A - $50 million

Company B - $33 million

Company C - $16 million

Main idea

- Reward successful projects, with money directly, rather than through legal monopolies to charge high prices.
- Make every product available at generic prices.
- Argue over how large the prize rewards should be, who will pay for them

- Whilst additional detailed modeling will be required to improve reward structures and evaluation criteria, these efforts are feasible, and not materially different from efforts by governments or insurance companies to determine acceptable reimbursements for insured products.

- A significant shift to a new system of incentives that relies upon prizes rather than prices will also require a shift to a new global trade framework that focuses less on intellectual property rights and more on country contributions to mechanisms that support R&D, including but not limited to prize incentive mechanisms.

Role of prizes in developing countries

- Ensure access to products at generic prices
- Preserve role for competitive manufacturing sector
- Tailor rewards to innovators to impact on improved health care outcomes, in the developing country
  - Companies chase improved outputs rather than incomes
- Possible set-asides or special implementation for neglected diseases

US proposal (Sanders bill)

1. Patent system intact through product development and market approval

2. No market exclusivity, generic companies can freely compete

3. Medical Innovation Prizes reward developers of new products

1. Prizes equal to.fraction of GDP.
   - .5 percent in 2005 bil. Maybe higher in new bill.

2. Payments to innovators over 10 year period are based upon incremental health care benefits

3. Organizations that develop new drugs compete against each other, on the basis of the incremental health care benefits their products deliver

Some of the fund is allocated to priority projects

- Global neglected diseases
  - 4 percent
- Orphan drugs
  - 10 percent
- Research on AIDS, including AIDS vaccines, global infectious diseases, and medicines to treat bio-terrorism
  - 4 percent

Other approaches

- Pogge, 2005
  - voluntary opt-in system,
  - Treaty with obligation to pay fixed reward per QALY
- Aidan Hollis, 2005
  - Voluntary system for neglected diseases
  - Fixed prize fund
  - Rewards determined by competition (HR 417 approach)

Global Fund for AIDS, TB and Malaria

- Donors make market for products
- Donors won't donate without cost effective outcomes
- High prices for new drugs threaten fund
- Set aside 10 percent of budget for drug purchases into prize fund
- Give prizes to drug developers who forgo patents or license patents to pool
- Benefits to drug developers
    - Makes donor market more sustainable
    - Eliminates conflict between drug developers and consumers
    - Sustainable business model for innovation

Neglected diseases

- Prizes linked to patent pool

More national prize systems

- Brazil story
  - Only for essential medicines
- Thailand story
  - Only for public sector
- India
  - Protect the poor, reward local innovators
- Kenya story
  - Only reward products for Type II, III diseases

Prizes v APC/AMC

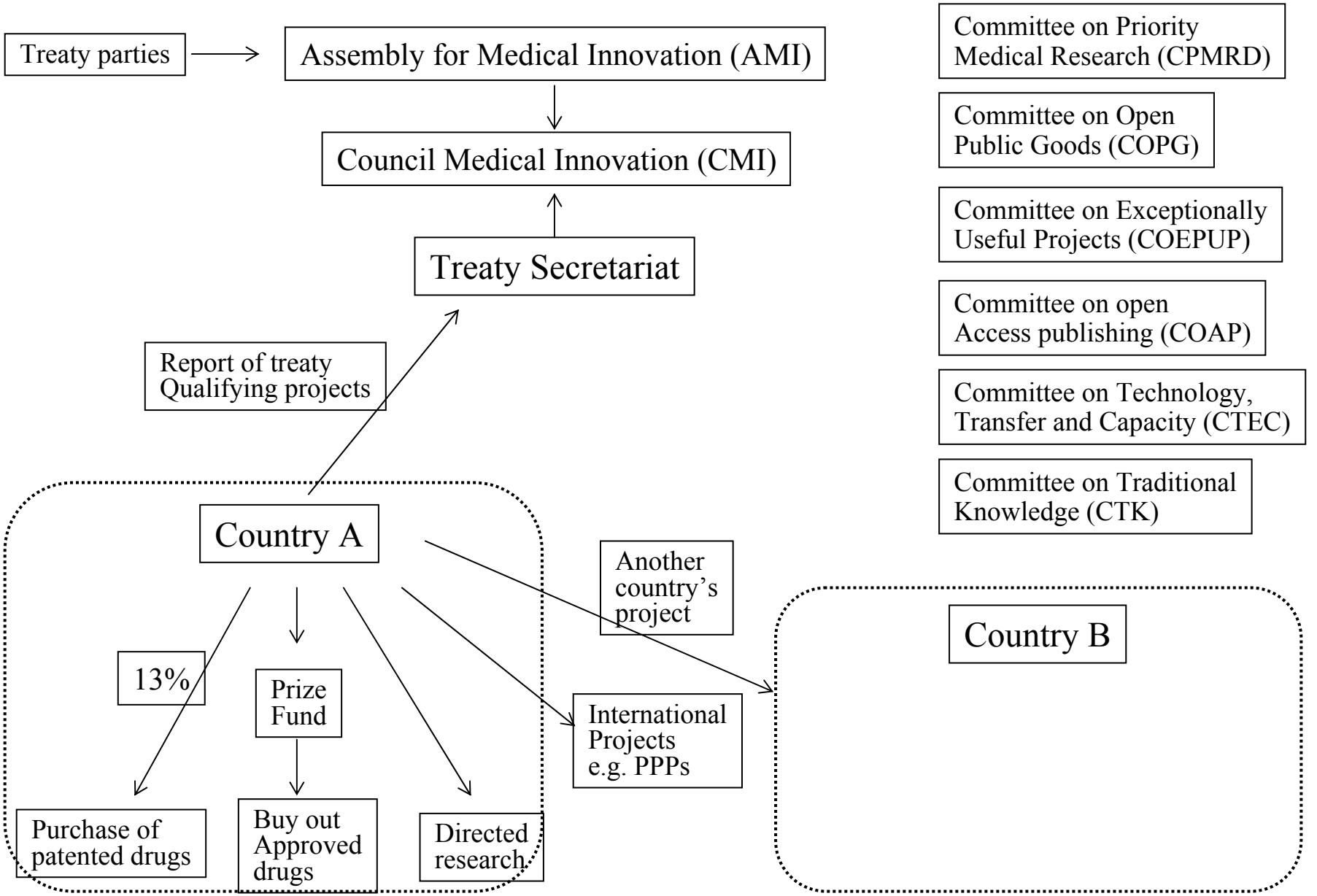
- APC/AMC
  - places greater reliance upon on specifying technologies
  - Maintains system where high prices stimulate R&D
  - Agreements are voluntary, and limited to goods under contract
  - Largely considered for “late stage” R&D projects that are not “fully cooked.”

Some key issues for prizes

- Relationship to patent system
- Treatment of Follow-on innovation
- Treatment of nearly simultaneous registration (R&D races)
- Proportional to QALY or more complex reward structure
- Term of evaluation

February 2005
R&D Treaty Proposal

Treaty mechanisms overview



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