May 30th: THEME A

What are the current trends in terms of the global burden of disease and how should they inform R&D and financing priorities?

RESULTS
The size and nature of the problem

- Innovative interventions aren't just about pharmaceuticals
- **Health research has three major drivers:**
  - the problems that need solving,
  - the state of the science (what is known about the problems to be solved and about the tools to solve them), and
  - external incentives/rewards (market, regulatory & social)
- We began with the first but also had to take account of the other two
- "Need" could be understood in terms of the global burden of disease—but must go beyond
The size and nature of the problem

- Given the incentives (potential profit; responsiveness to interests of societies that fund basic research), we assume that the diseases that afflict large numbers of people in the most developed 10% of the world will be addressed, to the extent that science permits
  - Even publicly funded basic research is largely concerned with problems that afflict the developed world
  - This has important consequences regarding the appropriateness of tools to address the health problems of lower income groups/countries
  - Result is unavailability/inaccessibility of drugs for many health problems of low and middle income countries
The size and nature of the problem

Therefore, the focus of our attention was on middle- and low-income countries

- Another way of examining would be to look at situation of low-income portion of the population in all countries

- Distinctions among "High"/"Middle"/"Low" income countries can be useful but can also mask some problems (Africa v. S. America v. India & China)

- Commission may need to disaggregate data

31 May 2005
Commission on Intellectual Property, Innovation and Public Health, WHO
The size and nature of the problem

- Ill-health issues arise in context of social, economic and political determinants
  - Importance of looking both "upstream" (what causes ill health) and "downstream" (how new products will—or won't—be picked up by health systems and be made accessible)
- This puts focus on "neglected diseases," but this term can mean different things to different people
  - Diseases of the poor or of countries with low development
  - Diseases which pharmaceutical companies don't address
  - The diseases where interventions are either unavailable (don't exist) or inaccessible (exist somewhere but not for particular population) or unaffordable
- Complex and changing picture of epidemiological profiles
  - Triple burden: Noncommunicable, infectious diseases, injuries
  - Reproductive health
Major causes of burden of disease, 2002 and 2015
low and middle income countries

Total population 6.1 billion, total DALYs 1.4 billion

2002

- Injuries 13%
- HIV/AIDS 9%
- TB & malaria 5%
- Vaccine-preventable 2%
- Respiratory infections 5%
- Other infectious 8%
- Other noncommunicable 15%

2015

- Cardiovascular 10%
- Cancers 5%
- Perinatal causes 2%
- Maternal 2%
- Nutritional deficiencies 5%
- Neuropsychiatric 13%
- Sense organs 6%

31 May 2005
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Matching Priorities and Incentives

- **Need for continual incentives**

- **One key decision is whether to focus on target drug profiles, or on rewards in terms of improving health outcomes**
  - *Push policies pay for research*
  - *Pull policies pay for performance, i.e. reward specific outcomes*
    - Could harness power of the market with the goal for reduction in DALYs (but whose DALYs?)
    - No particular design for a product, no predetermined outcome / disease target
  - *Need not be "either/or" scenario: "Push" from PPP point of view is in fact a mixture of push and pull for very specific deliverable*
  - There are advantages to defining the goal/setting product profile, and then leaving innovators free to decide how to get there

- **Input factors for decision making are multifaceted (e.g. DALYs, unmet medical need, tractability)**
  - Higher order decision: which diseases to attack
    - Have starting point (1998/9 IFPMA/WHO document on R&D priorities)
  - Who will make this decision?
Look beyond single issues
Managing Interfaces
Research and Development Continuum

- Knowledge gaps still exist, such as regarding the extent of unmet need

- Need to consider the sustainability of the overall drug research effort
  - Identify elements that can be transferred to developing countries

- Major challenges exist for translational/implimentational research
Some Remaining Questions

- What about prevention? How might we provide rewards for research in this area?

- Are DALYs an appropriate benchmark for determining priorities?
  - Hard to quantify DALYs saved due to prevention, diagnosis

- Does the U.S. Orphan Drug Act provide a model for diseases that "neglected diseases" for developing countries?

- How do we address disease burden in a way that takes account of equity issues?
Role of Government

- Defining priorities (with WHO support)
- Creating frameworks to support access to scientific knowledge
- Creating enabling environments, e.g. through "push" and "pull" mechanisms

Developed Countries can play a key role in:

- Regulation, research environment, transfer of technology and know-how
- Legislation (e.g. Orphan Drug Act) to stimulate innovation, depending on opportunities
- Funding basic research
- Securing markets, e.g. Advance purchase commitments
Role of Government

- Developing Countries can a play key role in:
  - Fostering functioning health system
  - Building innovation systems
  - Encouraging role of private sector in developing countries (in innovative developing countries)
  - Building product development infrastructure / clinical trials where the disease population exists

- Regulation
  - Value in using existing mechanisms like EMEA, FDA & encouraging consistent tools/analytic methods
  - But need for regulatory capacity in countries / regions (for approvals, specific risk-benefit ratios, pharmacovigilance)
  - Trends towards the harmonization of standards, but need flexibility in determining risk-benefit on country-by-country basis
Other Actors

- Pharmaceutical companies have a package of key competencies combined with infrastructure
  - Stages in innovation process have seen major changes
  - Pharma works with academics, biotech & other partners
  - How to better leverage "good corporate citizenship" movement

- Need to broaden the field of players and scope of potential partners (beyond pharma) to address neglected diseases
  - This capacity can be built, e.g. FIOCRUZ, CONCEPT Foundation (but opportunity costs are substantial)
Other Actors

- **Biotech companies can be innovative but are limited by resources**
  - Cost per compound can be higher for them so have incentives to partner with pharmaceutical companies
  - New knowledge today, e.g. functional genomics, but will not see payoff for 10-12 years

- **PPPs**
  - More than 10 existing with product development focused
  - Still gaps, diseases unaddressed

- **The public sector can:**
  - In some cases, do product development, e.g. FIOCRUZ
  - Do studies on *acceptability* of interventions
  - Tackle sensitive areas (e.g., RHR on reproductive health)
Cross-Cutting Issues

- Strengthening of innovation systems /local capacity in low- and middle-income countries (Theme D)

  - Importance of regulatory reform in assuring access to appropriate products (Theme D)

  - Need to further develop the concept and role of PPPs (Theme C)
Conclusions/"Proposals"

- Integrate thinking downstream from the creation of new products about how they will be picked up by health systems and be made available to people.

- Refine distinctions (e.g. "High income" / "Middle- and Low-countries") to allow more nuanced approach to needs-based research.

- Input factors for decision making should take account of broad set of factors:
  - BOD/DALYs + unmet medical need + technological opportunity.

- Improve translational/implementation research, which is key to ensuring:
  - More efficient / product R&D process
  - Products better tailored to needs of end-users.
Conclusions/"Proposals"

- Establish a "mediated industry collaboration" with a TDR-like group as clearinghouse for promising compounds
  - In absence of market, need means to find common perspectives about target profiles
- Support must be adequate & sustainable
  - Innovation continues after first products
- Focus on need, must take account of social, economic environment of use
CIPIH WORKSHOP

MAY 30^{th}: THEME B:
How does the IP system affect R&D and access and how might national patent systems need to change

RESULTS
Session 1:
The Patent System:
Making it better

- Are research tools a problem?

- Are one or more of the following an answer: patent pools, arbitration, research exemptions and humanitarian use exceptions?
Session 1: Major Issues

- Research use exemption: Differentiation: experimenting on → exemption / experimenting with → licensing
- Differentiation between up-stream / down-stream R&D
- Problem: Academia has a growing interest in commercial results of its research.
- Strong research exemption (although no total agreement)
- Humanitarian licensing → broad public sector support
- IP pooling / cost of licensing/
Session 1: Major Issues (2)

- Protection v. innovation: optimal protection level?

- Main problem with gene patents:
  - dependency on previous patents
  - Difficulty to enter technological field because of too many patents;...

- Patenting of gene sequences
  limitation to functions disclosed? claims limited to the part of the gene sequence relevant for the function disclosed?
Session 1: recommendations

- Data gets patented and protected for the wrong reasons. Suggest for non-patented material, wide use of licenses such as scientific creative commons, to allow immediate access without transaction costs while ensuring creativity credited and creator protected from being blocked for future use. For patented material, define legally binding maximum royalties, to provide confidence in later access, and improve information flow.
- Recommendations around the scope of patentability and evergreening and second use of new formulations
- Standardized agreements adopted by public sector institutes that research tools can be used for neglected disease research by any entity anywhere in the world
- Encourage greater public sector collective action to test various models of a technology trust (pooling of IP plus normative leverage) (SARS, PPP)
- Explore innovation model with early public venture capital purchase of the value chain of production and subsequent generic production at close to marginal cost
- Develop a more strategic role for reagent repositories in encouraging a research commons (transparency of reagents)
- Broad research exemption
- Express support for the sector neutral patent system as an engine for innovation and economic development
- Create a special system for incentives for research into neglected diseases
- Promote PPPs
- Explore mechanisms to new medicines including patent pools, automatic lic provision, proposals for equitable lic agreements when products are developed with public financing
Session 2:  
IP implications for access to new treatments  
legal and economic aspects

- Can the flexibilities in the TRIPS agreement be used effectively to promote access to medicines?
- What will be the economic consequences for access to medicines post-2005?
Session 2: Major Issues

- Flexibilities: gen. at least one implemented
- Discussion on IP-related policies of Ind countries (USA, EU)
- FTAs (no objectives; non-violation; test data protection). Risk for flexibilities?
- **Effect of introduction of TRIPS compliance** (Big, medium, small firms). Protection in India (eco study: effect on R&D; less export to LDCs; more to regulated markets. Difficulty of access to new technologies)
- Little research into local diseases
- Importance of art 7-8 TRIPS: benefit to society as a whole.
- Market v. public health interest.
- Flexibilities difficult to apply.
- High costs ⇔ access issue
Session 2: Major Issues II

- Applicability of TRIPS flexibilities?

- On the other hand:
  - Other factors important too (e.g. infrastructure);
  - prevention of price discrimination through // imports;
  - Effective enforcement of India’s new law only in 2008-2010

- CLs are not an instrument for fostering R&D

+ Effect of price regulations
Session 2: recommendations

- Implementation of flexibilities, + help (Exclude IP chapters from FTA in order to prevent TRIPS plus initiatives)
- It’s not all about patents, but the issue has to be addressed properly
- FTA: actual affect; focus on the effect of the rules that are going to be developed (“TRIPS +”)
- To advise countries on ways to promote comp lic. in the private sector in developing countries
- To advise countries on ways to promote public programs that utilize the strengths of the local industry to conduct R&D in neglected diseases
- Highlight no evidence that patents have done anything good for developing countries.
- Highlight para 7 of doha dec allows LDCs not implement patent protection for pharm products.
- Advise countries to adopt an integrated legislative framework to accelerate access to medicines dealing with medical regulatory authorities and competition authorities.
Session 3:  
IP: Implications for R&D

- How will the introduction of TRIPS-compliant IP systems in developing countries affect incentives for research on diseases that disproportionately affect developing countries?

- How do other policies, such as pricing, affect R&D and access?
Session 3: Major Issues I

- **TRIPS: incentive to R&D? ex. of India (1972)**
  - Shrinking of R&D (*but: possible other reasons*)
  - No interest in neglected diseases
  - New molecules developed are licensed to multinat. companies
  - Other incentives: “push” (by reducing costs)
  - Other solutions: cross subsidies, 1% to neglected diseases?

- Q: Are drugs launched in DC’s at all? Time/Launching of drugs: depends on policies. Distinction between poor, middle income and high income countries. Surprising results (Prof Lanjouw)
Session 3: Major Issues II

- Drugs for R&D for specific needs of poor countries: Increasing trend in patenting for diseases without treatment
- For the industry: patents are a fundamental premise (but is not the only thing, in particular for neglected diseases)
- Recall of fundamental importance of IP protection for the biotech industry
- If no market, patents have no importance
- Clear lack of R&D in neglected diseases, but patent system is probably not the answer, as no market.
- Patents for PPPs: interested in IP rights not for returns, but to make sure things are done. Maybe need for alternative to patents, but with some property rights.
Session 3: Recommendations

- Cannot say that patent system is the big obstacle for access to medicine; patent system does not really acting as a strong incentive for R&D for neglected diseases
- To expand the capacities of national patent offices to effectively and efficiently process patents for the benefit of local and foreign innovators
- Test data: The importance of test data protection
- Consider or analyze the incentive effect of patentability of secondary use on collaboration between corporations with chemical libraries and public interest research
- To address the 10/90 gap, the access to medicines gap and the market failures regarding access and affordability of new pharm products in developing countries
- To take into account the current patent protection rationale must apply differently in developed and developing countries.
- Explore all the possible alternative ways for the R&D of new drugs.
- Don’t undermine future innovation: don't limit or eliminate IP protection in certain areas
Theme C Tasks

- What new ideas are there to stimulate innovation and to promote access? Can we improve the R&D process for medicinal products?
  - Is there a role for new-IP and non-IP forms of rights and policies to spur innovation?
  - How can we make the R&D process more efficient?
  - Is there proper complementarity between the public sector, private sector and PPPs?
  - What needs to be done to make the PPP model effective?
  - What needs to be done to make it sustainable?
OVERARCHING POINTS

- Time of increased interest in innovation for ‘neglected diseases (ND) and great opportunity for real change
  - MDGs, Aid pledges
  - Upcoming G7/8

- Important to define our goals, expectations and time frames, and to communicate realistic expectations

- Period of change in approaches to pharmaceutical innovation and capabilities
  - Major pharma, emerging biotech, advanced developing countries

- Very strong consensus across many areas (!!!!!)
  - Some disagreements on (potentially significant) details, which probably can be clarified but might remain policy ‘choices’

Session 1: Innovation for neglected diseases (1)

- Solving all problems in the Research-Development-‘Access’ (R-D-A) continuum through a single solution is not realistic

- Need a mix of interventions/instruments that can be matched to the gaps we identify in R-D-A
  - ‘Push’, ‘pull’, PPPs, , enhanced efficiencies, capacity strengthening...

- Interventions (or other mechanisms) must link up components of the R-D-A continuum so as to ensure research feeds product development, which leads to uptake/rational use and access
  - Otherwise no timely improvement in health

- Must assess the potential for competition/’crowding out’ between different mechanisms in the “toolkit”
Session 1: Innovation for neglected diseases (2)

- In choosing the components of the ‘mix’ of instruments we should strictly apply economic criteria in a transparent manner:
  - Should be selective about what is in the ‘toolkit’ initially – based on clearly specified goals
  - Any interventions that do not seem to ‘work’ should be dropped

- Push mechanisms essential part of the ‘mix’
  - various inc funding R&D
  - Some overlap with productivity/efficiency interventions
    - Fast track regulatory process over development process

- Pull mechanisms
  - Those involving creating markets directly seemed most favoured
Session 1: Innovation for neglected diseases (3)

- Commercially motivated firms can make a significant contribution to R&D on neglected diseases (NDs)
  - Incentive mechanisms should be available to any competent company irrespective of size/
  - Practicable incentives will most likely retain or encourage further those already interested in neglected diseases

- Ensuring money will be there for purchases (‘APCs’) and work on long-term, sustainable financing is critical
  - “Value’ products for NDs appropriately and grow a sustainable, reliable market for them, from development aid and DEC resources (Advocacy role for WHO)

- Remuneration for innovation, should be related to social benefit, should not reduce ‘access’
  - Some thought separation of reward for innovation could/should be separated from reward for manufacturing
Session 2: Improving R&D productivity, efficiency and lowering costs (1)

Improving productivity/lowering attrition rates

• Learning from ‘history’ i.e., better sharing of information on what has failed
• Mechanisms for communicating between those involved in Research-Development-Access at different points in the continuum (‘Bird’s eye view’ needs to be laid out)
• Early engagement in the product development process with ‘ICH grade’ regulatory agencies reduces ultimate problems and approval times, i.e., enhances success
• Using new scientific tools should facilitate regulatory compliance processes

■ Improving efficiency/lowering costs and time
  • As above
  • ‘Partnership’ with competent developing country companies
Session 2: Improving R&D productivity, efficiency and lowering costs (2)

- Quality/safety cannot be compromised, i.e., no lower standard for products for developing countries

- FDA, EMEA and other industrialized country national regulatory agencies (NRAs) already working on ND products and strengthening regulatory capacity in developing countries
  - These expenditures culled from their general budgets which are constrained anyway

- Given the importance of regulatory interaction on products to combat NDs and capacity in disease endemic countries, possibility of additional, specified funding to these (NRAs) and similar bodies could be recommended
  - (Possible int’l center on regulatory advice, with an NRA)
Session 3: Interaction of PPPs, public sector and private sector

(Global) Product development PPPs are a key addition to the ND scene

- But they cannot replace/do everything

- There are common features, but also variety
  - which is good for ‘competition’ among non-profit approaches

- The rationale for PPPs is synergy, from complementarity of the different contributions that various collaborators bring
Session 3: Interaction of PPPs, public sector and private sector

- Major issues for PPPs are
  - Funding shortfalls for product development itself, requiring
    - Donor coordination and/or novel funding mechanisms
    - Regular funder re-education, given the long timeframes
    - New funder identification
      - Possibly including non-health sector business and research agencies
  - More engagement with developing country players (in some cases)
  - Identification of potential ‘downstream’ constraints including regulatory issues and
  - Funding for uptake
  - Metrics for demonstrating progress and ‘good practices’
Cross-Cutting Ideas

- Disease burden information is a key tool for PPPs and other partners/players seeking funding and/or other resources
  - WHO comparative advantage
- Need to gather information on R&D costs and other factors needed for economic analysis
  - Possible Commission/WHO role
- IP management must support product innovation for NDs while ensuring access
  - Developing countries need capacity strengthening
- Capacity building of Southern regulators is a key element in getting products for NDs into the market without delays
Session 1: Strategies for Developing Innovative Capacity in Developing Countries

- Promote Regional/Sub-regional approaches/arrangements in order to pool scarce resources (addresses multi-national needs, local disease burden, prioritize local R&D agenda)
  - Inter-country information sharing (Brazil- India)
- Quality of political leadership/ commitment for science and technology
- Entrepreneurship/Incubation
- Promote information linkages between institutions, organizations
- Promote a system-wide approach for innovation that involves multiple disciplines/agencies (Failure of Linear Approach)
Session 1: Strategies for Developing Innovative Capacity in Developing Countries

- Acknowledge differences in levels of capacity among developing countries to engage in R&D.
- Convert academic research into applied R&D and development of products.
- Countries with capacity (e.g. North) should invest beyond R&D to include investment on management of innovation, IP policies as they impact on health.
- Training in areas such as negotiation skills, IP systems, bioethical issues.
- Document what developed countries are doing vis-à-vis technology transfer and capacity building (TRIPS article 66.2)
Session 1: Strategies for Developing Innovative Capacity in Developing Countries

- While government needs to support more basic science, it needs to determine what part of the value-chain its investment will be placed in order to maximize economies of scale.
- Systematized process for sharing success/failure experiences with other countries.
- Tier 1 countries (e.g. India, Brazil, Mexico) should work stronger with Tier 2 countries (e.g. Nepal, Paraguay, Chad) to establish models of innovation.
- Need to develop new/revised processes for drug trials other than double blind placebo controlled studies.
- Risk/benefit analysis must be locally determined but not to comprise quality, safety and efficacy.
Session 2: The impact of regulatory and other policies on R&D and access

- Drug regulatory authorities (DRAs) need to pursue consumer/patient input. Importance of bringing DRAs and consumers to be more engaged with one another in determining risk/benefit analysis.
- Increase staff and training in areas such as bio-ethics, informed consent, standard of care.
- Use the Singapore fast-track model to expedite approval and market entry in order to avoid duplication of efforts.
- DRAs should use other well-established DRAs' results as a foundation upon which they could develop other regulation for local circumstances.
- Developing country DRAs should rely on WHO guidelines/EC scientific opinion to avoid duplication of effort and maximize economies of scale.
Session 2: The impact of regulatory and other policies on R&D and access

- Data exclusivity could inhibit/ enhance innovation/ access and therefore the need to study this further.
- Sub-regional harmonization i.e. registration, ethical reviews, technical capacity building, training.
- Inter-DRA knowledge sharing (best practices, problem solving, early warning systems).
- Redefine the "science" of evaluation (Bayes approach, observational studies) in order to fast-track approval, however not compromising quality, safety and efficacy.
- Public confidence in DRAs is critical. Fees may or may not compromise the integrity of a DRA, public perception may understand it otherwise and therefore they need to be reviewed.
Session 3: How can traditional medicine (TM) be used more effectively to generate new products/ provide affordable treatments?

- Reverse pharmacology
- R&D agendas should reflect people's actual pattern of TM use.
- Co-investment strategies to promote learning between allopathic and TM systems (triangulation).
- Incorporate TM into mainstream education curriculum in order to secure knowledge for future generations.
- *Sui Generis* systems, trade secrets and other IP protection regimes need to be carefully explored for their potential benefit (or detriment) on access, safety and efficacy.
- R&D on traditional medicine will raise costs (extraction and developing for a market in new form).
Session 3: How can traditional medicine (TM) be used more effectively to generate new products/ provide affordable treatments?

- TM practitioners should be educated in IP systems.
- Rationale for TM must be clear before redirecting R&D resources.
- Need for appropriate remuneration mechanisms for traditional practitioners/ benefit sharing.
- Common guidelines are needed for TM, for quality, efficacy and safety.
- We need more studies to understand the relationship of TM in public health.
- Need for greater public investment in understanding the importance of traditional knowledge.
Key Questions

- Does investment in local innovation effectively address local health needs?
- How do we define innovation? What are its determinants?
- Why is success so difficult to evaluate?
- How can costs and time of clinical trials be reduced?
- How can performance and efficiency of DRAs be improved?
- What system do we base evaluation for safety in TM?
- Should regulators become data police?
- If we develop TM, what are the implications for access especially for the poor?
- How can HBT innovative capacity be better utilized in developing countries: Promote private sector development
- Can we learn from agricultural biotechnology experiences
Cross-Cutting Issues

- Sub-regional approaches
- Linkages with other institutions
- Intellectual property (TRIPS article 66.2)
- Data exclusivity
- Developing countries are not homogenous- need for clear categorization