

BIOVISION PRE-CONFERENCE REPORT FORMAT

INTRODUCTION

BioVision introduces a NEW ARCHITECTURE by adding 9 Pre-conferences in 2006 and a web Forum hosted by BioVision NXT. and will take place between March and October 2006.

The Pre-conferences will ensure continuity, between the two successive forums by enlarging the circle of participants in order to better meet the needs of the key BioVision participants: Science, Society and Industry.

OBJECTIVE

The OBJECTIVE of Pre-conferences is to explore and develop the topics for debate and discussion at BioVision Forum.

The WORK PRODUCT of a pre-conference will consist of an EXECUTIVE SUMMARY of the discussion, RECOMMENDATIONS FOR ACTION and CONCLUSIONS recorded in table format specifically spotting the key issues in the field and the viewpoints of the communities: Science, Society and Industry.

METHODOLOGY

Pre-conferences will consist of small meeting of up to 10 participants to develop the key issues for the BioVision Parallel Conferences in three sectors: Health, Agriculture and Environment.

Each Pre-conference will have Host Partners. The Host Partners with BioVision support will organize the meeting, choose the participants.

The topic recommendations of the Pre-Conferences will be honed and refined for the BioVision Forum. Due to time limitations of the Forum, not all identified topics and issues may be covered in the Forum.

PRE-CONFERENCE TITLE: DISEASES OF POVERTY: Disease Burden, the MDG's and Child Survival

TOPIC DESCRIPTION: Diseases of Poverty

Disease burden and regulatory and legal issues with R&D for drugs for neglected diseases

LOCATION: Geneva, Switzerland

DATE: September 11, 2006

HOST PARTNER: DNDI

BIOVISION PARTICIPANTS:

Jean Michel Roy
ENS-LSH / BioVision Human Sciences Advisor

Dianna Derhak
Programme Director

Marc Girard
CEA/ Biovision advisor for health

MODERATOR:

Peter Fold, Medical Research Council

Yves Champey, Chair of DNDI

PARTICIPANTS:

- ▶ **Dr. Precious MATSOSO**, WHO
- ▶ **Patrice TROUILLER**, CHU Grenoble
- ▶ **Dr. Andrew Y. KITUA**, Director General, National Institute for Medical Research, Tanzania
- ▶ **Gianni TOGNONI**, Director, Mario Negri Sud, istituto ricerche farmacologiche mario negri
- ▶ **Dr. Clive ONDARI**, WHO HQ Medicines Policy and Standard Department
- ▶ **Prof. Peter I. FOLB**, Chief Specialist Scientist, Medical Research Council, South Africa
- ▶ **Dr. Krisantha WEERESURYA**, Regional Adviser, Essential Drugs & Medicines Policy, who
- ▶ **Philippe KOURILSKY**, Collège de France / Institut Veolia Environnement, Paris
- ▶ **Ginny BARBOUR**, Managing Editor, PLoS Medicine
- ▶ **Paul MODEL**, ESQ, IPM International Partnership from Microbicides, Silver Spring, USA
- ▶ **Dr. Mary SINGER**, Medical Officer, FDA Food & Drug Administration, Division of Special Pathogens and Transplant Products
- ▶ **Suresh JADHAV**, Executive Director, Serum Institute of India LTD
- ▶ **Dr. Sergio NISHIOKA**, ANVISA, Nacional Health Surveillance Agency, Brazil
- ▶ **Dra. Analia PEREZ**, Directora, Direccion de Evaluacion de Medicamentos, ANMAT, Administration Nacional de Medicamentos, Alimentos y Tecnologia Medica, Argentina
- ▶ **Mr. Jean-François ALESANDRINI**, Fundraising & Advocacy Director, DNDi
- ▶ **Bernard PECOUL**, Executive Director DNDi
- ▶ **Prof. Simon CROFT**, Scientific Director, DNDi
- ▶ **Dr. Viswewaran NAVARATNAM**, University Sains, MALAYSIA Centre for Drug Research
- ▶ **Nicoletta DENTICO**, Policy & Advocacy Advisor and Research Coordinator, DNDi
- ▶ **Els TORREELE**, Project Manager, DNDi
- ▶ **Rob DON**, Project Manager, DNDi
- ▶ **Jean-René KIECHEL**, Project Manager, DNDi
- ▶ **Dr. Catherine ROYCE**, Project Manager, DNDi
- ▶ **Anita PEIL**, Regulatory Consultant, DNDi

AGENDA:

1. Welcome by host partner and introduction of participants
2. Presentation of DNDI
3. Presentation of concept paper
4. Presentation of 3 case studies and discussion
5. Brainstorming and debate

EXECUTIVE SUMMARY:

The preconference was a special meeting of DNDi, an organization dedicated to elaborating new models of research and development for drugs for neglected diseases. Twenty one experts from several countries had a one day gathering in Geneva for discussing how to improve the drug regulatory approval processes in order to facilitate the fast and safe delivery of treatments to populations in need of special health assistance.

Neglected diseases can be broadly defined as diseases not benefiting from sufficient efforts in drugs research and development, essentially because they fall outside of market mechanisms. They affect in priority developing areas of the world, and reducing their toll relates directly to several of the Millennium Development Goals. Examples of neglected diseases are leishmaniasis, sleeping sickness, Chagas disease, malaria. Existing treatments for such diseases offer strong limitations, such as lack of efficiency and flexibility, excessive toxicity and side effects, unsuitable complication, high cost, dependency on highly developed health care systems. For some of them, treatments are still non existent. Insufficiencies in drug research and development for these diseases can be located at various levels: lack of basic research, gap between basic research and preclinical development, or between preclinical and clinical development, for profit reasons, registration obstacles, production and delivery difficulties. Statistics are telling. Of the 1556 new drugs marketed between 1975 and 2004, only 1% were for tropical diseases and tuberculosis; and 90% of the 105 billions \$ spent annually on drug research and development are dedicated to diseases that affect no more than 10% of the world population.

Although the awareness of the problem is growing in the international community, as shown by the recent increase in press articles, appeals from dedicated organizations and the emergence of specific projects as well as innovative models in drug research and development, the situation is still worrisome.

The consensus among the experts present at the meeting is that there are patent inadequacies in the current drug development and drug approval processes that make them unfit to the respond to specific needs of patients, especially in the field of neglected diseases. These processes encourage risk-averse and other such defensive strategies in research and development that result in the production of redundant drugs for an overly limited number of diseases. The experts claim that public health needs, rather than competitive drug registration policies, should be the guiding criteria, with early involvement of communities as the essential condition for the outcome to be granted. The procedures for evaluating the safety and efficiency of drugs should therefore be restructured around the concept of "essential standards", i.e. the basic principle that drugs must be developed according to the needs of patients, the severity of the diseases and the availability and quality of existing treatments (risk/benefit assessment).

In their analysis of the sources of the inadequacy of the current regulatory system, the experts point to the question of cost. It is estimated that the average cost for developing a drug was in 2004 in the order of 800 millions \$. Although arguments have been made that this cost is inflated, investments of such magnitude require a large and low-risk market from a for-profit perspective. One very relevant issue refers to the economic impact of non essential procedures in the drug approval process. This has in turn led to a general lack of transparency as well as the existence of obvious conflicts of interest, which have produced

unsatisfactory regulatory evaluation of efficacy and safety of drugs. From a purely scientific point of view, the approval processes are criticized for being too formally and rigidly enforced to the detriment of scientific good sense, and even dissimulating at times serious scientific gaps, such as lack of serious clinical trials or use of fraudulent data. One very serious problem is, among others, the failure to complete the pharmacovigilance commitments after approval (phase 4), to confirm the drug's efficacy and safety. The multiplicity and isolation of national regulatory authorities is seen as an additional source of constraints, especially in developing countries: it makes it hard to determine which authority is the most appropriate for a certain research and development project and it often leads to multiple, time-consuming and expensive applications.

In order to remedy this situation, a number of propositions were suggested, calling for further discussion, in particular in the context of the 2007 Biovision session. Whereas there is a recognition among experts that the current regulatory processes emanating from the International Conference on the Harmonization of Technical Requirements of Pharmaceuticals for Human Use have been beneficial, there is a clear view that protocols and strategies for R&D should not be pre-defined by univocal standards. Scientific quality improves generally when research is adapted to the context of care, and the real conditions for implementation. Good science is what gives a response to specific needs with hard and transferable outcomes, and changes the history of the disease; on this definition consensus emerged among experts. In addition, there is also a fair amount of consensus regarding the fact that there is perhaps less room for maneuver from a strictly scientific point of view, and that most of the adjustments are to be sought in what might be called the process side of the regulatory process; however, it must be acknowledged that science, process and policy are closely linked. Indeed, all experts insist that they in no way advocate to lower the standards of safety and efficiency for neglected diseases. Finally, most of them also underline that the improvements will not be reached by a policy of exceptions to current rules, but only through an overall restructuring of these rules that build in them the appropriate mechanisms to meet the specificities of neglected diseases. The exceptional rules already enforced by agencies such as EMA or FDA, although helpful, have proven to be insufficient.

At the scientific level, such mechanisms could for instance include increased flexibility in the measurement of safety and efficiency in trials, faster transition from Phase 1 to Phase 2 trials, development of innovative protocols, and simplification of tools. Far from lowering the standards of safety and efficiency, the introduction of such mechanisms would go hand in hand with the enforcement of more stringent basic scientific and ethical principles, such as a rigorous identification of the needs, a mandatory complete follow up of all the patients involved in the trials, a clear endorsement of responsibility of the scientific teams and institutions conducting the trials and a full transparency of the data collected. The key problem is seen as that of reaching a satisfactory definition of the notion of *essential standards* in drug research and development. WHO has a key role to play in this respect.

At the process level, WHO pre-qualification scheme is increasingly perceived as a solution to the many obstacles in the drug regulatory approval. One additional recommendation is to work on possible cost reductions. Cutting on costs will boost drug research and development in the area of neglected diseases and will be an incentive for the industry to see it as viable option in their drug portfolios. In addition, it will make it more accessible to emerging pharmaceutical industries. Although the involvement of the profit driven private sector is considered to be crucial, it is also acknowledged that increasing governments' leadership at the national, regional and international level is indispensable to determine a more favorable environment to essential health R&D. New models of partnerships with non profit institutions and organizations are proving that change is possible. However, to ensure a long-term and sustainable response, WHO needs to recapture its central role in health, and exercise it fully. Efforts should also be made towards building stronger research and development capacities in developing areas where neglected diseases are prevalent, and towards facilitating the necessary technology transfers. Better coordination, even a possible centralization, of national regulatory authorities is also recommended. The

establishment of a dialogue with national agencies early on in the process of research and development would also facilitate the later registration phase. A stronger reliance on local communities (for instance when seeking patients' approval in trials) is also seen as an important factor for reaching faster and more efficient results, and as leading in addition to better acceptance of the product once approved and marketed.

KEY QUESTIONS:

- ▶ How to best define the notion of neglected disease?
- ▶ What are the main inadequacies of the current approval regulations?
- ▶ How much room is there for a reformulation of these rules? At what level? To what extent can the simplified in order to fasten the development of new drugs and vaccines?
- ▶ How to bridge innovation with access?
- ▶ How to define essential standards of drug research and development?
- ▶ What role for WHO in a needs-focused regulatory system?
- ▶ How to help building stronger drug research and development capacities in developing countries?

RECOMMENDATIONS FOR ACTIONS:

- ▶ elaborating further a DND/platform for reforming of the regulatory system
- ▶ circulating this platform
- ▶ publishing additional studies analyzing the defects of the current regulatory system and the benefits to be expected from a reform
- ▶ continue calling attention of governments and international institutions on the importance of the neglected disease problem