HOW DOES THE REGULATORY FRAMEWORK AFFECT INCENTIVES FOR RESEARCH AND DEVELOPMENT?

A proposal for a regulatory framework to improve regulatory capacity and introduce incentives for research and development in areas of public health importance

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<th>Definition</th>
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<tr>
<td>AFRO</td>
<td>African Regional Office (WHO)</td>
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<tr>
<td>AI</td>
<td>Active ingredient</td>
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<td>ALADI</td>
<td>Latin American Association for Integration</td>
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<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
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<td>ARV</td>
<td>Antiretrovirals</td>
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<tr>
<td>ASEAN</td>
<td>Association of South-East Asian Nations</td>
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<td>BU</td>
<td>Buruli cancer</td>
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<tr>
<td>CAC</td>
<td>Central African Community</td>
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<td>CADREAC</td>
<td>Collaboration Agreement of Drug Regulatory Authorities in European Union</td>
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<td>CARICOM</td>
<td>Caribbean Common Market</td>
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<tr>
<td>CMR International</td>
<td>Centre for Medicines Research International</td>
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<tr>
<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<td>COMESA</td>
<td>Common Markets for Eastern and Southern Africa</td>
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<td>CPMP</td>
<td>Committee for Proprietary Medicinal Products</td>
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<td>CRO</td>
<td>Contract Research Organization</td>
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<tr>
<td>DCVR</td>
<td>Developing Countries Vaccine Regulators</td>
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<td>DDDC</td>
<td>Diseases that Disproportionately affect Developing Countries</td>
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<td>DRA</td>
<td>Drug Regulatory Authority</td>
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<tr>
<td>EAC</td>
<td>Eastern African Community</td>
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<tr>
<td>EC</td>
<td>European Commission</td>
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<tr>
<td>ECOWAS</td>
<td>Economic Community of West African States</td>
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<td>EDCTP</td>
<td>European and Developing Countries Clinical Trial Partnership</td>
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<td>EDL</td>
<td>Essential Drugs List</td>
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<tr>
<td>EEC</td>
<td>European Economic Community</td>
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<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries Association</td>
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<tr>
<td>EFTA</td>
<td>European Free Trade Association</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Evaluation Agency (now called European Medicines Agency)</td>
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<tr>
<td>EMRO</td>
<td>Eastern Mediterranean Regional Office</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>EURO</td>
<td>European regional Office</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FDC</td>
<td>Fixed Dose Combinations</td>
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<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccines Immunation</td>
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<tr>
<td>GCC</td>
<td>Gulf Cooperation Council</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practices</td>
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<td>GDP</td>
<td>Good Distribution Practices</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>HAT</td>
<td>Human African Trypanosomiasis</td>
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<tr>
<td>HIC</td>
<td>High Income Countries</td>
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<tr>
<td>ICDRA</td>
<td>International Conference of Drug Regulatory Authorities</td>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>ICH-CTD</td>
<td>International Conference on Harmonization Common Technical Document</td>
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<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers Association</td>
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<td>IMMP</td>
<td>Intensive Medicines Monitoring Programme</td>
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<tr>
<td>IND</td>
<td>Investigational New Drugs</td>
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<td>IRB</td>
<td>Institutional Ethical Review Board</td>
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<tr>
<td>IVR</td>
<td>(WHO) Initiative for Vaccine Research</td>
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<tr>
<td>LDC</td>
<td>Least Developed Country</td>
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<tr>
<td>MCA</td>
<td>Medicines Control Agency</td>
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<td>MCANZ</td>
<td>Medicines Control Agency of Zimbabwe</td>
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<tr>
<td>MCC</td>
<td>Medicines Control Council</td>
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<tr>
<td>MERCOSUR</td>
<td>Mercado Comun Suramericano (South American Common Markets)</td>
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<tr>
<td>MNC</td>
<td>Multinational Corporations</td>
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<tr>
<td>MRA</td>
<td>Medicines Regulatory Authorities</td>
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<tr>
<td>MS</td>
<td>Member State</td>
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<td>MSF</td>
<td>Médicins sans Frontières</td>
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<td>MSM</td>
<td>Multi-Source Medicines</td>
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<tr>
<td>NACCAP</td>
<td>Netherlands African Partnership for Capacity Development and Clinical Trial</td>
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<td>NCE</td>
<td>New Chemical Entity</td>
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<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>NEBRA</td>
<td>Networking for Ethics on Biomedical Research in Africa</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-Governmental Organizations</td>
</tr>
<tr>
<td>OECD</td>
<td>Organization for Economic Co-operation and Development</td>
</tr>
<tr>
<td>PABIN</td>
<td>Pan-African Bioethics Initiative</td>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
</tr>
<tr>
<td>PANDRH</td>
<td>Pan American Network for Drug Regulatory Harmonization</td>
</tr>
<tr>
<td>PEM</td>
<td>Prescription Event Monitoring</td>
</tr>
<tr>
<td>PICS</td>
<td>Pharmaceutical Inspections Convention and Cooperation Scheme</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Reports</td>
</tr>
<tr>
<td>PSVM</td>
<td>Public Sector Vaccine Manufacturers</td>
</tr>
<tr>
<td>PTR</td>
<td>Patent Term Restoration</td>
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<tr>
<td>R &amp; D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>SADC</td>
<td>Southern African Development Community</td>
</tr>
<tr>
<td>SARS</td>
<td>Severe Acute Respiratory Syndrome</td>
</tr>
<tr>
<td>SEAMRAC</td>
<td>Southern and Eastern African Medicines Regulatory Authorities Conference</td>
</tr>
<tr>
<td>SIDCER</td>
<td>Strategic Initiative for Developing Capacity in Ethical Review</td>
</tr>
<tr>
<td>TFDA</td>
<td>Tanzanian Food and Drug Administration</td>
</tr>
<tr>
<td>TLCA</td>
<td>Trade in Latin American and Caribbean Countries</td>
</tr>
<tr>
<td>TRIPS</td>
<td>Trade and Related Aspects of Intellectual Property Rights</td>
</tr>
<tr>
<td>UEMOA</td>
<td>Economic and Monetary Union of West Africa</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USPTO</td>
<td>United States Patent and Trademark Office</td>
</tr>
<tr>
<td>VL</td>
<td>Visceral Leishmaniasis</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>WTO</td>
<td>World Trade Organization</td>
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## GLOSSARY

The terminology medicine and drug are used interchangeably throughout the report,

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<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>drug</td>
<td>Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.</td>
</tr>
<tr>
<td>drug regulatory authority</td>
<td>A national body that administers the full spectrum of drug regulatory activities, including at least all of the following functions: marketing authorization of new products and variation of existing products; quality control laboratory testing; adverse drug reaction monitoring; provision of drug information and promotion of rational drug use; good manufacturing practice (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels; enforcement operations; monitoring of drug utilization.</td>
</tr>
<tr>
<td>Innovator pharmaceutical product</td>
<td>The innovator pharmaceutical product is generally that which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to requirements at the time of the authorization). When a substance has been available for many years, it may not be possible to identify an innovator pharmaceutical product.</td>
</tr>
<tr>
<td>manufacture (manufacturing)</td>
<td>All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products and the related controls.</td>
</tr>
<tr>
<td>marketing authorization</td>
<td>An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products - the register - and is often said to be &quot;registered&quot; or to &quot;have registration&quot;. Market authorization may occasionally also be referred to as a licence or product licence.</td>
</tr>
<tr>
<td>Medicine</td>
<td>See drug</td>
</tr>
<tr>
<td>new chemical or biological (new APIs)</td>
<td>New chemical or biological APIs are those not previously authorized for marketing for any pharmaceutical use in the country in question. Those provisionally authorized at the time of the initial market inventory are not new pharmaceutical ingredients.</td>
</tr>
<tr>
<td>quality control</td>
<td>Quality control is concerned with sampling, specifications and testing, and with the organization, documentation and acceptance/rejection procedures which ensure that the necessary and relevant tests are actually carried out and that starting materials, intermediates and finished products are not accepted for use, sale or supply until their quality has been judged to be satisfactory.</td>
</tr>
<tr>
<td>scientific opinion of CPMP</td>
<td>Scientific opinion for the evaluation of medicinal products intended exclusively for the markets outside the community in the context of cooperation with WHO. It contains conclusions on quality, efficacy and safety and takes into account appropriate benefit/risk scenarios on the populations and conditions of use as documented with clinical data by the applicant.</td>
</tr>
<tr>
<td>transparency</td>
<td>The term transparency means (1) defining policies and procedures in writing and publishing the written documentation, and (2) giving reasons for decisions to the affected party. There is some overlap between transparency and accountability (see above).</td>
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EXECUTIVE SUMMARY

Terms of reference of the study
Review the ways in which the regulatory framework affects the incentives for, and costs of, R&D, and the effect on access, particularly in respect of medical products for developing countries,

- Review the issues involved in the growth of regulatory requirements for the approval of new products, in particular as these affect the cost of R&D, and the incentives for investment in R&D, particularly in respect of products of particular relevance to developing countries.

- Review the impact of international arrangements (e.g. ICH, the WHO prequalification project, WHO EDL) which have relevance for the approval of products, and access to them, in developing countries.

- Consider how the challenges posed by new medical technologies could be dealt with by regulatory authorities and the possible implications for developing countries.

- Make proposals for consideration by the Commission on possible changes in regulatory approaches, at both national and international levels, which could contribute to faster and more cost-effective regulatory procedures to facilitate the introduction of new medicines, vaccines and other products in developing countries consistent with ensuring the quality, efficacy and safety of medicines.

- Come up with practical proposals about how to strike an appropriate balance between risk and benefit in the construction and application of regulatory frameworks, recognizing that this balance may need to be different as between the developed and developing world.

- Finally, consider mechanisms to increase capacity for research (including ethical) review.

In response to these terms of reference, a proposal was made, that the study will have three parts, each of which will be based on a review of existing literature combined with qualitative research.

Part one, identifies particular regulatory challenges that may exist in relation to specific areas of R&D of relevance to developing countries, including the development of new formulations and delivery systems. Many of the regulatory challenges related to new technologies are those presented by vaccines and biologicals. Therefore, in this study successful vaccine regulatory approaches have been used as the basis for proposed regulatory models.

Part two outlines regulation within the global landscape, including recent trends towards international and regional harmonization of regulatory requirements, and what it means for developing countries.

Finally part three investigates the specific question of clinical trials, considering the interplay of economic, ethical, safety and scientific concerns on the part of industry, government, and patients.

The linkages between the terms of reference (TOR), the proposal and the structure of this report are demonstrated diagrammatically:
The approach followed was through literature searches, design questionnaires and interviews with relevant people for specific areas. The questionnaires developed were targeted at manufacturers of generic medicines, innovator products, regulatory authorities, beneficiaries, civil society. The study was of an exploratory nature.
Brief summary of the chapters

Chapter 1 documents a brief overview of diseases that disproportionately affect developing countries and existing approaches to deal with these, and pharmaceutical gaps that exist. It also lists current debates about (R&D) costs and different opinions on how (R&D) from a clinical development perspective can be improved.

Chapter 2 outlines the medicines regulatory environment from both, a developing and a developed country perspective and some of the challenges, deficiencies as well as opinions of both regulators and industry through surveys recently conducted for this purpose. The data from these surveys have been self selected and do not represent a fully comprehensive global picture. Regulatory models are proposed for different regulatory capacities and settings. The experiences of regulatory authorities of large markets with capacity to conduct research and develop and/or produce medicines are documented to establish possible options. Approaches are considered for removal of possible barriers and creation of a conducive, precautionary regulatory environment, that is predictable and shortened regulatory approvals are suggested, without increased risks.

Chapter 3 documents the vaccine experiences and activities that can inform the drug development model based on some of the initiatives undertaken. It further shows how the scientific opportunities can be explored, market assessment can be enhanced, resources and capacities can be strengthened and medical needs can be met to address certain diseases. The general framework in the vaccine area shows promising results. The question that will be addressed is how this regulatory framework can apply in other areas taking into account the models proposed for developing countries, the subregional harmonization model, and the improved clinical trial environment. There challenges of biologicals and limitation of existing tools to prove bioequivalence, other approaches are considered.

Chapter 4 shows various harmonization initiatives to standardize regulatory requirements and streamline regulatory processes. There are regional and subregional approaches and global initiatives that are considered for pooling resources to deal with capacity challenges. None of these initiatives and harmonization models is a complete solution for resource constrained settings, and adaptation is suggested to help developing countries to deal with technical complexities and capacity challenges.

Chapter 5 documents the clinical research environment from a technical, ethical and operational context, barriers that exists, challenges to developing countries, and some of the initiatives to deal with these. Clinical research is a cornerstone of drug research. This chapter further highlights recent debates in the clinical research area, current scientific gaps and possible solutions and how these may be of benefit to developing countries to strengthen clinical research capacities, improve ethical concerns and incentives.

Chapter 6 lists some of the IPR issues as they relate to medicine regulation and possibilities that exit to improve access to medicines for treating diseases that disproportionately affect developing countries within the context of TRIPS Agreement.

Chapter 7 lists all the recommendations, models and strategies that can be applied in a sustainable way.
Study Outcome
This study points towards models and strategies that can be considered to create incentives for research and development for medicines that can be used to prevent or treat diseases that disproportionately affect developing countries. No single model or strategy will suit every country, disease or drug. In the present work, considerations for a model or strategy have been largely based on experiences from initiatives that have yielded positive results and that have been considered to be successful over a period.

The strategy proposed in this report addresses context within which the pharmaceutical industry makes decisions on Research and Development (R&D). The strategic decision making context of the pharmaceutical industry involves four interacting, but distinct strategic contexts including:

- Medical need,
- Scientific opportunity,
- Market assessment and regulatory environment, and finally
- Available resources.

The construct underlying these four strategic contexts is economic considerations rather than public health needs. Two of these strategic contexts (scientific opportunity, market assessment and regulatory environment) have greater direct relevance to the objectives of this study and play a central role in the proposed strategy. Scientific opportunities include innovative solutions (such as biogenerics or paediatric formulations) for developing countries public health problems as well as scientific methods of development and/or regulatory assessment of such innovations; i.e., clinical trials, post marketing studies, etc. Market assessment involves return-on-investment potentials, infrastructure, and other factors that would make a market attractive to a medicine manufacturer. An important factor in market assessment is the regulatory environment, practices and capabilities in a developing country market.

The other two contexts, are equally important, namely medical need and available resources of industry. They are however beyond the regulatory framework and are dealt with elsewhere.

The primary question of interest is, how to reconcile the economic-oriented interests and concerns of industry with the public health needs of developing countries. In the current study this question is addressed by selecting three areas of regulatory interest as providing the potential to bring a public health balance whilst creating incentives for industry. These areas are

- Extending the models and collaborative initiatives in development of vaccines and biologicals further to other public health interventions
- Harmonization of regulatory environments/practices/capabilities, and
- Clinical trials

It is assumed that the removal of barriers within these areas could translate into industry incentives while strengthening the regulatory capacity in developing countries.
Recommendations

The pharmaceutical industry requires a predictable environment to address specific medical needs. This will be informed by various factors, such as scientific opportunities and regulatory environment and requirements. As an attempt to identify barriers and create incentives for drug development specifically for DDDC, surveys were conducted with MRAs of developing countries as well as members of the industry and civil society. Survey results revealed problems that may serve as barriers, to be administrative, managerial and operational. Based on these results it is developing countries' insufficient capacity to regulate and its associated risks that are a major concern to both industry and regulators. Further, in selected developing countries, the technical requirements for the marketing of FDCs, new medicines and vaccines were shown to be weak and these may be important in bringing new technologies to the market. In contrast, the perceived burden of increased regulatory requirements for new technologies or drug delivery systems or vaccines do not seem to be an obstacle.

Most regulatory authorities have fast track policies that are based on public health priorities and these can be good incentives for R&D in DDDCs. However, there are concerns about safety issues and the required strengthening of safety monitoring by MRAs in support of fast track policies. The models outlined below are proposed based on the lessons learnt from global regulatory arrangements and vaccine initiatives.

Sub-regional harmonization of regulatory functions of countries with similar disease profiles should be encouraged because it would address the medical need, scientific opportunity and faster market access that are of strategic significance for industry.

Part 1. Vaccines and Biologicals:

Experiences of vaccine initiatives and some of their activities have created an enabling environment that would lead to local capacities that will ultimately contribute to accelerated access to vaccines. Overall, these experiences and efforts can be classified as follows:

1. Stimulating/initiating collaboration between various developing countries regulators on various regulatory activities, employing internationally accepted guidelines adapted to suit local needs/circumstances (DCVR). Organizing joint assessments between regulators through sub-regional approaches. For more complex applications e.g. biotechnology products have twinning arrangements with well-established regulatory authorities or the scientific opinion of the EU.

2. Stimulating/initiating collaboration between manufacturers in various developing countries on technological activities (DCVMN) and facilitating partnerships between the industries in developing and developed countries particularly for biotechnology products.

3. Capacity building and training to develop the R&D infrastructure and regulatory/ethical review capabilities necessary for technology transfer. This could be facilitated by collaboration with one or more industrialised nations and international initiatives, or exploring some of the initiatives in the EU.

4. Establishing standard guidelines for various activities related to vaccine R&D (WHO clinical trial guidelines, and training manuals associated with these). These guidelines are available for developing countries to adopt and adapt to local needs and circumstances. At a practical level global training programmes have been developed.

Part 2. Harmonisation:

The regulation of medicines within the global landscape, including recent trends towards international and regional harmonisation of regulatory requirements, have been reviewed and the following are some of the benefits of these initiatives that can be explored further for subregional approaches.

1. Harmonization at the sub-regional level is recommended based on the SADC harmonization initiative and the Gulf Cooperative Council's joint assessments. For example, the AFRO region can be divided into various subregional initiatives. If necessary, some of the
countries with reasonable capacities can be used as nucleus (e.g., in the Gulf model the subregional joint assessment utilizes Saudi Arabia as a central hub).

This will reduce regulatory capacity problems, streamline procedures and pool expert knowledge and resources of developing countries with the aim of creating an environment conducive for facilitating approval and market access to industry.

2. The global initiatives can serve as a resource pool, mainly the WHO prequalification project (with slight improvement) e.g. support by the EU scientific opinion. The WHO prequalification can be slightly improved to incorporate elements of the DCVR network, with a representative of each region participating in the prequalification process. The proposal gives special attention to capacity building based on global networks and global initiatives.

3. A twinning arrangement can further be explored between a sub-region and a well established or well resourced regulatory authority, which already operate within a harmonized environment; e.g., SADC and USA/Canada/EU or ECOWAS and France/EU.

**Part 3. Clinical Trials:**

The following should be in place to support the conduct of clinical trials, if new drugs are to be developed for treatment DDDCs:

1. Ethical review capabilities at the country level must be established and strengthened.

2. Adherence to Good Clinical Practice must take into account local conditions in determining standards of care without compromising scientific principles.

3. Significant investment in infrastructure and technical capacity through creation of centres of excellence at the regional or sub-regional level, several initiatives are referred to in the study

4. Safety monitoring of clinical trials can be strengthened; for example, through the introduction of longer-term safety studies data inclusive of diversified larger patient populations. The challenge for developing countries is resources to do these. Industry can direct resources from phase IV studies considered to be a marketing ploy to more meaningful studies. The following can be further considered for safety monitoring;

   - Requirement of a pro-active pharmacovigilance programme for the registration of any ‘new’ product.
   - A market complaints handling and recall policy should be part of the requirements for compliance with GMP and GDP.
   - Public education campaigns on continuous review of the safety of medicines.
   - Proper evaluation of clinical studies before commencement.
   - Timely publication of cancellation and tighter monitoring of what is on the market.
INTRODUCTION

The pharmaceutical markets of the high income countries\(^1\) differ widely from those in developing countries, they also differ in the extent and effectiveness of medicine regulation. Medicine production is highly concentrated in the industrialized countries, where just five countries, the USA, Japan, Germany, France and the UK account for two thirds of the value of the medicines produced. The major markets especially the United States, Japan, and the European Union accounted for 87% of the audited worldwide pharmaceutical consumption by value in 2001. (IMS Data Group 2002)

The pharmaceutical markets of the world's most populous countries, India and China, show a strong generic sector. India is estimated to have 20 000 pharmaceutical manufacturers that have been inventoried, but only 250 of these are in the organized sector and these account for 70% of the country's total output of branded generics. In China the estimated number of manufacturers is 7500, with those that are GMP compliant said to be 87. Over the years there has been a shift in the production of fine chemicals to India and China due to lower costs of manufacture.

There are approximately 80 000 preparations that are traded worldwide, for which selection must be made for treatment of diseases. These are not accessible across the world. These must be regulated in different markets and the development, manufacture, importation, handling and use must conform to set regulatory standards.

Regulating the pharmaceutical sector, involves complex decision making frameworks and policies. The main objective of government to regulate must be to protect and promote public health.

Ensuring the safety, efficacy and quality of drugs available to the public is the main aim of drug regulation. Different regulatory models exist across the world and these are informed by the size of the pharmaceutical market, the availability of resources as well as public health needs. Histories, cultures and political experiences as well as economic profiles of countries have informed the construction of different institutional arrangements for the regulation of medicines. In addition, to ensure effective medicine regulation, appropriate systems and structures must be in place. (Different regulatory functions and activities receive varying degrees of emphasis. Pre-marketing versus post-marketing (recent events confirm the need to focus on pharmacovigilance and post-marketing surveillance).

WHO has played a significant role in supporting countries, through the assessment of the regulatory capacity of Medicines Regulatory Authorities, and recommending institutional development plans, to address any deficiencies or capacity problems. There are also harmonization initiatives from different regions that have been created and supported by WHO, with noticeable progress.

\(^1\) The World Bank defined low income countries in 2003 as those with GNP per capita of less than $765 per annum at official exchange rates, middle income countries, between $766 and $9385, while it exceeds $9385 for high income countries.
Despite all these developments, global market factors have led to a 30-year absence of serious Research and Development (R&D) in tuberculosis up until recently. Existing drugs in TB treatment involve long duration of therapy, strains of resistance and the challenges of co-morbidity with HIV/AIDS.

Lately concerns have been raised regarding a low yield in general, on innovative medicines. This has been shown in data published by FDA over a 5-year period. Out of a total number of 415 new drugs approved, 133 were new molecular entities, the rest were said to be variations of old drugs. Of the 133 considered new molecular entities, only 58 were priority review drugs.

A detailed study by a clinical team at Prescrire found that only 0.3% of the 2693 new medicines approved, and patented over the past 22 years provide a major therapeutic advance, 2.7% provide important therapeutic benefits with certain limitations, 7.9% have some therapeutic value but do not fundamentally change the present therapeutic practice and 16% provide minimal additional value and should not change prescribing habits, and the rest of all new drugs which is about 1584, are therapeutically superfluous, and a few pose real disadvantages without evident benefit.

Most developing countries lack capacity to undertake research to determine priority public health needs and also capacity to conduct clinical research that meets international standards. There are however differences in the capacities of developing countries. Developing countries are not homogenous in terms of their scientific and technical capacity. It is estimated that 60% of the world’s poor live in countries that have significant scientific and technological capabilities and the great majority of them live in China and India. China and India, along with several other smaller developing countries, have world class capacity in a number of scientific and technological areas including, for instance, space, nuclear energy, computing, biotechnology, pharmaceuticals, software development and aviation. By contrast, 25% of poor people live in Sub-Saharan Africa (excluding South Africa), mainly in countries with relatively weak technical capacity. It is estimated that in 1994 China, India and Latin America together accounted for nearly 9% of worldwide research expenditure, but sub-Saharan Africa accounted for only 0.5% and developing countries other than India and China only about 4%.

A significant development globally has been the rapid growth of active ingredient manufacturers in India and China, with highly specialized manufacturing facilities. These have however not been matched with strengthened regulatory capacity.

In terms of the context of the pharmaceutical industry decision making described above, there is no “generic” method for determining unmet medical need and for creating a product development profile for various developing countries, as each company has different agendas and each country has different needs. Most companies combine commercial market research, competitive intelligence, and therapeutic strategies with scientific development to determine their therapeutic product profile. Decisions about development of new drugs are generally made as depicted in figure 1, within a set of four different contexts, a) scientific opportunity (recent advances in science presents opportunities that must be explored for development of new drugs for diseases that disproportionately affect developing countries), b) market assessment (benefits of having a predictable regulatory environment that can improve access to the market while ensuring the medicines meet set regulatory standards, regulatory trends and requirements and procedures must be understood by industry, sub-regional harmonization of regulatory functions of countries with similar disease profiles should be encouraged because it would facilitate faster market access, c) available and required resources (of relevance are skills of regulatory professionals, the outsourcing e.g. Clinical Research Organizations (CROs) within a developing country context has replaced this, resulting in a missed opportunity for research capacity building) and d) medical need there are a number of diseases that afflict over millions of people for which a medical need exist and a persuasive reason for the pharmaceutical industry to consider for drug development.
**Figure 1**: What drives industry’s decisions on drug development?

Resources for pharmaceutical R&D are predominantly fixed but the needs and demands for health interventions are not, then all decisions regarding R&D resource allocation are based on the prioritization of disease conditions. Warren Kaplan argues that there is no “best” way to prioritize pharmaceutical R&D in a public health context and such prioritization should be viewed, not as a problem to be solved, but as a multidimensional “dilemma”.²

In her recently published book, Marcia Angell is highly critical of the current approaches followed in drug research and development. She suggests alternative programs of vital reforms which include restoration of the pharmaceutical industry’s purpose, changing approach to the conduct of clinical trials, changes to the patent laws, strengthening the FDA as well as the establishment of an institution that oversees clinical testing of drugs.

She has been critical of the incremental approach towards drug development, what she refers to as "me too" drugs. Her views have been echoed by Carlos Correa, who states that innovation is no longer driven by technological breakthroughs. Sydney Taurel, argues that incrementalism has been considered a lower risk venture that has been applied to some extent for line extensions, and new indications or development of late stage molecules.

Centre for Medicines Research International (CMR International) on the other hand suggests yet another approach in clinical development. Where data is sufficiently robust at the end of Phase II a probationary approval for marketing should be possible, with conditions attached to

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² Priority Medicines for Europe and the World, WHO, 2004 (Objective of the report was to formulate a public-health-based development agenda for support by the European Union, and develop a systematic methodology that can be replicated.)
early marketing. These conditions would include studies to confirm efficacy, test the safety hypothesis and risk management programme proposed at the end of phase II. This they state would not be a large phase II trial, but a study in real life conditions. This model is proposed to apply primarily to medicines addressing unmet medical needs (one of the considerations by industry in decision making), and would entail a change in approach from the way data is managed and analyzed to creation of a data warehouse, that would be accessed by regulators and industry. This they suggest would enhance the harmonization agenda.

The research and development programme for drugs can be schematically described below:

Figure 2: Overall Research and Development Process

The final stage of R&D, Pre-approval and Post-Approval

Results of All R&D Activities Are Submitted for Regulatory Approval

Figure 3: Regulatory Activities relevant to the R & D processes
Figures 2 and 3 above depict key activities in R&D, the first being an overall R&D process, while the second highlight areas of relevance for this study e.g. clinical trials, regulatory and marketing authorization, post-marketing activities and pharmacovigilance. These will be referred to later in individual chapters, where the strategies for reducing regulatory barriers and creating incentives for R & D will be discussed and some of the findings of the surveys.

Costs of Research and Development

Less than 10% of global spending on health research is spent on diseases that disproportionately affect developing countries (DDDCs) but which account for 90% of the global disease burden (Remme, et al, 2002). The prime reason, it is argued, is because they do not offer sufficient financial returns for the pharmaceutical industry to engage in research and development. Drug development is estimated to cost an average of almost a US$1 billion per new drug (WHO/EDM/PAR/2004.7), which makes it unlikely that companies will recoup their R&D costs, if they develop drugs solely for the developing world market. Based on Datamonitor study, in 2002, generics companies’ average spent was just 6.3 per cent of sales compared with 14.1 per cent for the top R&D-based players.

Since developing countries are not in a position to offer financial incentives to stimulate R&D in DDDCs, they must devise other strategies to encourage the private pharmaceutical industry to invest in these disease conditions. It is worth noting that most developing countries use generic medicines.

In Europe, the pharmaceutical sector is undergoing major reforms. There are cost containment measures and price regulations with a public health objective, as well as incentives to promote major industries, and more recently initiatives to create regulatory environments conducive for stimulation of R&D.

The high cost of drug development is not only a concern of developing countries but also affects governments of developed nations. Since 1987, the cost of developing a new chemical entity (NCE) has increased from US$231 million to US$800 million in 2000 (DiMasi et al., 2003) and is currently estimated to be US$1 billion. The latter figure has been widely debated, as not exclusively R & D costs, but capitalized costs. Marcia Angell and others dispute this figure, and estimate it at between 200-400 million dollars.

The rising costs, which are eventually passed on to the public, have forced governments of rich countries to subsidize the use of drugs in their communities. A survey done by the Organization for Economic Co-operation and Development (OECD) reported that member countries spent an average of 15.4% of their health budgets on drugs in 1996 (Henry, 2002). Germany’s healthcare expenditure increased by 23% between 1990 and 1997 (HAI-Europe, 2001).

The amount of government subsidization of costs, varied by country, being lowest in the USA (15%) and highest in Norway, Turkey, and the Czech Republic (80% or more). Recent data suggest that drug expenditure is increasing rapidly and creating financial pressures in several countries. The escalating drug prices, which said to be at least partly attributable to rising drug development expenditure, have compelled pharmaceutical companies and government representatives or regulators in different parts of the world to investigate the implementation of systems that will stem the rapid cost increases. (Miosios et al) caution against the pharmaceutical industry's claim that any constraint on profits will threaten truly valuable innovation.

Barriers to Research and Development

A recent World Bank survey, focusing on infectious diseases, identified certain barriers as: (a) lack of adequate information about the basic research that is under way in universities, research councils, and biotechnology companies worldwide that could provide material for industry to screen to generate more product leads; (b) the costs and duration of clinical trials; and (c) limitations inherent in the developing country market for products that could deal with the diseases that primarily afflict those countries. The survey also elicited industry suggestions about ways to lower these barriers.
According to surveys conducted by CMR, regulatory delays and poor communication between the industry and regulatory authority assessors (evaluators) is a major cause of concern. Common problems associated with delays in registration may be due to both industry and the regulatory authority and these include,

**Pharmaceutical Industry related delays**

- Dossiers submitted are sometimes poorly organized, and the quality of submissions may be substandard, and this varies from one applicant to another, some fail to adequately address these deficiencies
- There may be insufficient data to support an application for registration leading to inappropriate use of resources, in some regulatory settings this has tended to be a dossier improvement processes
- Claims for cure especially for alternative medicines which cannot be substantiated, and also due to lack of proper regulatory processes for these category of medicines

**Regulatory Authority related delays**

- Inexperienced members of the medicine evaluation team who are inclined to base evaluation on empirical experience not evidence
- Lack of sustainable financing, with the excessive reliance on contributions from the pharmaceutical industry
- Lack of a critical mass of adequately trained staff with appropriate skills
- Lack of access to information systems, current information for evaluation

All the above factors may contribute to delays and therefore viability in R&D projects.

According to Walker et al the viability of R&D projects are also affected by a number of factors. These include the consistency, objectivity and transparency of decision making by regulatory authorities and decision making models have been proposed. Some tools for decision making, exchange of regulatory reports between different assessors in different geographies may facilitate communication and improve regulatory approval processes.

**Problems associated with lack of incentives for generic manufacturing of medicines for priority diseases**

There are limited numbers of quality-assured sources for specific drugs due to several factors like absence of generic versions of certain products (e.g. some second line ARVs, paediatric formulations, artemisinin derived combination therapies), absence of originators for certain generic Fixed Dose Combinations (FDCs), biogenerics creating unusual challenges for generic companies willing to formulate these products, poor knowledge of pharmaceutical development among some companies, and time taken to do the development work including proper studies to prove the quality, safety and efficacy. It should be noted that even for well resourced generic manufacturers with know how, and human and financial resources available, it takes at least one year to develop a “new” generic drug.

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3 MSH report for Global Fund
An important factor that can contribute to the slow development of new sources of complex generic products that meet international standards (i.e. biotechnological products), is the relative lack of capacity for most local manufacturers to comply with international quality requirements. This does not apply to all generic manufacturers in all countries, as there are different types of manufacturers with different market niche, e.g., commodity generics that are easy to manufacture with no barrier to entry, specially generics, technologically challenging formulations and new drug deliveries, biogenerics or biological generics.

Limited experience with local product development, quality assurance and GMP manufacturing, lack of effective regulatory oversight, and limited resources may complicate the situation in countries where manufacturers are striving to manufacture antiretrovirals or other drugs locally.

So far many local manufacturers have had the possibility to sell their products locally, where, in some countries, regulatory rules were applied preferentially. According to B Santososo there are double standards in some countries for regulating drugs destined for domestic consumption versus those destined for export.

Manufacturers, who have invested and made substantial progress in their capacity to meet international quality standards, have an opportunity to be pre-qualified by WHO. In fact, some such manufacturers have received marketing approvals in major markets, like US and EU. However, incentives to meet international quality standards are not yet created in many developing countries.

The WHO Prequalification process, which has served as a sieve, has shown that only few generic manufacturers can meet international standards, some of them have limited knowledge of GMP and almost no knowledge of product formulation

Adherence to GMP can add significantly to investment and operating costs of a manufacturing operation. Manufacturing should be encouraged in countries that have effective medicine regulation, and where such does not exist it must be established and appropriate investments made. According to the World Bank an ideal environment for a profitable pharmaceutical manufacturing business is in a country with solid regulatory agency, a good business and industrial infrastructure, skilled and qualified personnel, appropriate technology, a domestic market that allows substantial economies of scale in production.

Since the thalidomide disaster decades ago, the regulatory requirements and controls to ensure quality, efficacy and safety, have evolved, and are often perceived to be stringent and characterized by complicated regulatory requirements, rules and control measures. This has been considered to be a disincentive to research based companies, contributing to unnecessary regulatory hurdles and delays. There are also arguments for increased controls and more requirements for improved safety, largely in pursuit of reduced harm and increased benefit to the beneficiaries of these therapeutic agents. The uncertainty and lack of confidence in certain markets that are unregulated are concerns that may explain the pharmaceutical companies’ disincentive. The associated risk of substandard medicines and poor regulation, are equally a public health risk just like they are disenchantment to industry.

**Approach to the Study**

The terms of reference from the Secretariat to the Commission required the team to:

- Review the issues involved in the growth of regulatory requirements for the approval of new products, in particular as these affect the cost of R&D, and the incentives for investment in R&D, particularly with respect to products of particular relevance to developing countries
- Review the impact of international arrangements (e.g. ICH, the WHO prequalification project, WHO EDL) which have relevance for the approval of products, and access to them, in developing countries
- Consider how the challenges posed by new medical technologies could be dealt with by regulatory authorities and the possible implications for developing countries
• Make proposals for consideration by the Commission on possible changes in regulatory approaches, at both national and international levels, which could contribute to faster and more cost-effective regulatory procedures to facilitate the introduction of new medicines, vaccines and other products in developing countries consistent with ensuring the quality, efficacy and safety of medicines.

• Come up with practical proposals about how to strike an appropriate balance between risk and benefit in the construction and application of regulatory frameworks, recognizing that this balance may be different for developed countries compared to developing countries.

• Finally, consider mechanisms to increase capacity for research (including ethical) review.

The following chapters will review some of the regulatory mechanisms that have been introduced to provide incentives to promote faster access to novel and essential medicines and encourage greater investment in R&D, particularly in diseases for which a viable market does not exist. The review will also include an analysis of the regulatory requirements and structures in developed and developing countries and how they compare, case studies and published literature, harmonization initiatives in both developed and developing countries and mechanisms to determine their strengths and weaknesses with respect to promoting R&D in general and for diseases, which disproportionately affect the developing world and the conduct of clinical trials and various approaches to introduce efficiencies.

The approach followed was conducted through literature searches, questionnaires and interviews with relevant people in specific areas. The questionnaires developed were targeted at manufacturers of generic medicines, innovator products, regulatory authorities, civil society. There were also interviews with individuals with extensive regulatory experiences from both a developed and developing country context.
CHAPTER 1: BURDEN OF DISEASE

The developing world, which includes low and middle income countries (LMIC)\(^4\), are plagued by a group of diseases which differ markedly from those that primarily affect industrialized countries. Whereas the diseases that are prevalent in developed countries are non-communicable and lifestyle related, those that occur predominantly in developing countries are infectious. Some of the infectious diseases, which account for a major proportion of the morbidity and mortality in the developing countries, such as HIV/AIDS and tuberculosis (TB), also occur in developed countries, but their prevalence or incidence is significantly less. Their lower contribution to the disease burden in (High Income Countries). HIC, relative to cardiovascular diseases for example, makes them a low priority in developed countries, whereas in developing countries the contrary is the case.

In this report we shall, therefore, refer to diseases that are prevalent in the developing world and which contribute significantly to its total disease burden, as diseases that disproportionately affect developing countries (DDDC). About 14 million people die each year from infectious diseases, and up to 45% of the deaths in Africa and South-East-Asia are considered to be due to infectious diseases\(^5\). Leading causes of death in the poorest countries are respiratory infections, diarrhoeal diseases and perinatal conditions, all of which are preventable and curable, but access to therapeutic agents has been a problem.

Two billion people are carriers of TB, and every year about 8.8 million people develop active TB, and 1.7 million die of the disease, 84% is accounted for by developing countries. The same as HIV/AIDS, deaths have been estimated at 3 million per annum, with new cases at 5.3 million per annum, Malaria, deaths are over a million per annum, 300 million new cases per year, each disease accounting for 92 % and 100% respectively\(^6\). Drug development for HIV/AIDS\(^7\) has received a lot of attention, and WHO has led several projects like Global Alliance for TB\(^8\) Research, Medicines for Malaria Venture\(^9\). Other initiatives have been spearheaded through a UNICEF, UNDP, World Bank and WHO, Special Programme for Research and Training in Tropical Diseases, (TDR), as well as the vaccine research projects coordinated by Initiative for Vaccine Research.

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\(^4\) See previously World bank definition of Low and Middle Income Countries


\(^6\) Scaling up Responses to Infectious Diseases, WHO (2002)

\(^7\) International AIDS Vaccine Initiative (IAVI), established 1996, promotes the development of safe, effective and accessible HIV vaccines for use especially in developing countries. During the 90s several initiatives on AIDS vaccine trials were initiated, mostly conducted in developed countries and some in Africa and Asia (Thailand) As at 2002, a total of 30 experimental HIV vaccines had been tested and were all in the early phases of clinical trials. Other trials have been on microbicides

\(^8\) Global Alliance for TB Drug Development, established in 2000, established in 2000, to develop affordable new drugs for TB by the end of the decade, created by leaders in health, science, industry. The TB Alliance is a virtual R&D company with a social mission.

\(^9\) Medicines for Malaria Venture (MMV), a public venture capital, was established 1999, gets support from numerous sources including WHO, IFPMA,World Bank, Netherlands Government, Rockefeller Foundation, Global Forum for Health Research, DIFD, Swiss Agency for Development and Cooperation, Bill & Melinda Gates Foundation, ExxonMobil, it offers a new perspective to the discovery and development of medicines to treat malaria
All the drugs used in the treatment of these diseases and other related diseases develop resistance. Loss of potency to these drugs is a concern, and possible regulatory issues of relevance and mechanisms to curb these must be explored. Tools to treat, prevent and cure diseases have been available for decades, except for HIV/AIDS treatments, the first regulatory approval was in 1987 in the USA, followed by other regulatory agencies, and more antiretrovirals approved.

There are other diseases like SARS human African trypanosomiasis (HAT), visceral leishmaniasis (VL), an emerging uncontrolled disease, globally estimated to be in 88 countries, with 350 million people at risk. Lymphatic filariasis, a disabling disease which afflicts over 120 million people of India, Africa, the Pacific and the Americas Chagas disease, and Buruli ulcer (BU), i.e., diseases whose prevalence are due primarily to the absence of affordable and effective preventatives (vaccines) or treatment (drugs) mechanisms. The USA and Europe have chosen to pass legislation for “orphan diseases” which require the society to spend substantial funds on a limited number of afflicted individuals who suffer from rare diseases. There are global efforts to address the Drugs for Neglected Diseases Initiative which was established 2003\textsuperscript{10}.

**Therapeutic Interventions used for treatment of disease**

Most developing countries use essential medicines\textsuperscript{11}, which include medicines whose patent has expired, medicines still under patent, vaccines for universal immunization and in some instances biotechnology products, for treatment and prevention of diseases. Interlocked with these are medicines for priority diseases. Although the list of essential medicines has been developed by WHO, the ever-changing public health needs/solutions in various countries (particularly developing countries) require the continuous updating of this list. Examples of public health-related changes that would require updating the list for the pool of essential drugs, either as improved tools of existing therapies, with an aim to simplify complex treatment, new medicines for the treatment of emerging new diseases or variants of old diseases, resistance to existing therapies. The aim may also be for introduction of much safer and more effective drugs, through improvement in current compounds and delivery methods, or innovative approaches to make drugs more affordable and accessible. The logistics and supply pose challenges in developing countries, where simple regimen that can improve handling and distribution can make substantial improvements in the supply management chain.

Dual health systems and the regulation of medicines exist simultaneously for both complementary/traditional medicines and pharmaceuticals in most developing countries. According to WHO, 65 out of 192 its member states have regulatory systems dealing with traditional medicines. These are categories and classes of medicines that will not be specifically addressed in this study.

\textsuperscript{10} DNDI: \url{www.dndi.org}

\textsuperscript{11} The WHO definition of essential medicines, are those medicines that satisfy the priority healthcare needs of the population, they are selected with due regard to public health relevance, evidence on efficacy and safety and comparative cost-effectiveness.
CHAPTER 2: REGULATORY REQUIREMENTS – INCENTIVES (AND BARRIERS) TO THE PROMOTION OF RESEARCH AND DEVELOPMENT

Background
Medicines registration is a process by which Medicines Regulatory Authorities (MRAs) approve the use of medicines based on evidence of their quality, safety and efficacy, with the aim of promoting and protecting public health. Medicines regulation incorporates a number of activities that are performed by MRAs during both the pre- and post-approval or registration periods. These encompass the regulation of pre-clinical, clinical, pharmaceutical and analytical processes, as well as the data submitted to ensure compliance with set standards of Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP).

The regulation of medicines does not end with marketing approval. It continues with ongoing safety monitoring through pharmacovigilance and quality monitoring through random laboratory testing as part of post-marketing surveillance activities. Approved medicines may also be subject to other regulatory measures such as pricing and procurement requirements, etc. Recently, MRAs have been called upon to perform pharmacoeconomic evaluations to determine the cost-benefit ratio of new medicines for which marketing authorization is requested. Although for developing countries with restricted healthcare budgets, this type of analysis may be important, the lack of capacity and resources by the MRAs of many such countries may be a limitation, and there could be priorities needing more attention because of associated risks.

The regulation of medicines occurs within a context of three dimensions, namely technical elements, structural and administrative elements and level of regulation as depicted below (WHO/HTP/EDM/MAC(11)/99.6).

**Dimensions of Drug Regulation**

![Diagram showing the structures and administrative elements of drug regulation](image)

**Figure 4** Key functions and critical elements of medicines regulation
In general, developing countries face significant challenges in fulfilling the basic regulatory functions due to severe resource constraints. There are a number of factors that explain observed weaknesses of drug regulation, and these differ from country to country and depend also on the health system. Countries may vary regarding their registration system and not all of them can implement a comprehensive medicine evaluation and registration system. Drug registration delays may be due to a number of problems. Any inefficiency in the regulatory process delays decision making and may lead to shortages of critically needed medicines, various strategies may be needed to pool resources and increase efficiencies. There are risks associated with poor medicine regulation. On the other hand, there are problems with poor regulatory practices.

The burden of disease in these countries is usually also very high and access to medicines is limited. According to WHO, fewer than one in six of its member states (less than 20%) have a well-developed medicines regulatory system, and those that do are mostly in industrialized countries. Of the remaining member states, about half implement medicines regulation at varying levels of development and operational capacity. The remaining 30% either have no MRA in place, or have only a very limited capacity (WHO, 2003). This situation was once again well-illustrated by another WHO study, conducted in 2002, in which the regulatory systems of ten different countries, including developed and developing were reviewed (WHO, 2002). For description of regulatory status of various countries see annexure 2.

Apart from the differences that exist amongst countries with respect to medicines regulatory capacity, it has been reported that within a country, an MRA will regulate products with different levels of stringency, depending on whether the medicines are destined for the domestic or export market. It is also known that the package insert contents for the same product may vary amongst countries in which the product is marketed, with the indications for the product in developed countries being presented differently by the applicant to that for developing countries.

MRAs of different countries reach different decisions regarding the same application for registration. Similarly, individual assessors arrive at different decisions for the same or similar application. These types of problems are usually minimized with agreements amongst MRAs to exchange evaluation reports and where peer review systems have been introduced. However, Walker argues that a peer review system is not a failsafe mechanism to ensure that balanced decisions are arrived at since dominant members may overshadow their counterparts by the sheer force of their personalities thereby suppressing the views of the less prominent members of the team. Other areas of concern, apart from the manner in which decisions are made, include the structural arrangements of, and communication channels between, the decision-making bodies and advisory committees of MRAs.
Regulatory Capacity, Organizational Arrangements and Structure

Regulatory Capacity and Approaches

A responsive regulatory environment will facilitate an accelerated rate of drug development. This requires that regulatory authorities improve their approval and review processes to match the increasing complexity of applications, such as those for the registration of biotechnology products and other medicines derived from rapidly-evolving technologies, as well as for new drug and vaccine delivery technologies and devices. This may not be achievable by small regulatory agencies and for these some models have been proposed. The regulatory processes of MRAs with high or reasonable capacity should be simplified and, where assessments of complex technologies have been undertaken, the information must be shared with other regulatory authorities, particularly those with limited capacity.

Pharmaceutical markets that are poorly regulated pose significant threats to public health. They are also disincentives to companies that prefer to operate in secure and predictable environments which provide certainty and freedom from unfair competition with counterfeit and substandard medicines. The most common problem in developing countries is the protracted timeline for the registration of medicines, which is a major concern for pharmaceutical companies as well as civil society organizations and even patient groups. All of them, but especially the last two groups, have attempted to influence the regulatory processes, particularly of high priority medicines.

It is apparent that not all countries can implement a comprehensive drug evaluation and registration system. A process, composed of several stages, has been described which an MRA can follow in order to strengthen its capacity. Dukes describes various stages that a regulatory agency may follow to strengthen its capacity and these stages include the following:

Notification procedure

Standard information is obtained on all pharmaceuticals products offered for sale, and these are kept in the register. No judgment is made about appropriateness. The advantage is that if there are product recalls or withdrawals linked to safety concerns and provided basic information has been collected, the MRA will at least know if the product affected is marketed in the country.

The “small MRA” scheme is also structured around an inventory, as described above, of the medicinal products available in the country. Regulation is, therefore, not possible unless information is available about products to be imported and/or manufactured. This is very similar to a “notification” system in which the first step towards regulation of medicinal products is essentially the compilation of the inventory.

Basic authorization procedure

Drugs that are listed in the register are authorized for sale provisionally and new drugs are registered for sale after assessment of efficacy, safety and quality. This process can also benefit from the technical processes of the WHO prequalification scheme, PICS, and harmonization initiatives where reports are shared among regulatory agencies.

Full licensing and registration procedure

In this stage a full evaluation of an individual product is performed by evaluating all data submitted by an applicant and from literature, in order to establish its quality, safety and efficacy. Full drug registration should only be attempted after a country has a significant volume of private-sector drug sales (Quick et al., 1997). Even so, great pressures are placed upon a drug regulatory authority by the increasing numbers of drugs registered, the large number of irrational or unacceptable drug combinations in existence, and demands to shorten the drug approval process. These pressures manifest themselves as attempts by MRAs to simplify and harmonize their technical and administrative procedures. Full registration operates in only a few countries in Africa. One requirement for such registration is evidence for efficacy and safety of the drug in the country itself using approved clinical trial protocols.
These three steps are key for developing countries to strengthen the regulatory capacity of small countries with very limited capacity, the first step may be an option with additional support from established regulatory agencies or those with reasonable capacity, by exchange of scientific reports, and/or regulatory decisions, access to WHO scientific reports and even access to scientific opinions of well established regulatory agencies. For smaller countries which lack a sophisticated drug regulatory system, the drug regulatory agency should be part of the Ministry of Health (similar to the U.S. FDA) and it should be required to report drug registration statistics to the Ministry. The drug regulatory authority should retain all administrative fees. However, to counteract any appearance of undue influence by applicants (pharmaceutical companies), the Ministry of Health should monitor performance and provide funding to the MRA.

For countries with well-established regulatory authorities, the authority should be more autonomous from the Ministry. However, full autonomy has also been criticized as having a potential for bias with no public health safeguards.

A hybrid model with part funding from both the government and industry may be an option. Santoso argues that an efficient drug registration system requires human, administrative and financial resources, which is consistent with findings by WHO.

The functions of any MRA include, as a minimum, procedures for the registration of new medicines as well as for the inspection and control of products once they are on the market (Dukes, Hill, Summers, & Bannenberg 1998). There are several ways in which a MRA can be structured to perform these duties. The entire authority can be an independent, parastatal structure (MCA of the UK), or it can reside as a unit within the ministry of health (TGA of Australia). The evaluation of pre-market dossiers can be carried out largely “internally” (MCAZ of Zimbabwe, ), or largely externally using expert advisory committees (EMEA and MCC).

The ability to regulate medicines effectively is determined by a number of factors, which include the state of economic development, infrastructure availability and the prevailing healthcare system of a country. Because of these factors, countries vary in the manner in which they register and regulate their medicines. Hence, not all countries are in a position to implement a comprehensive drug evaluation and registration system. Those that can serve as benchmark regulatory authorities and they should act as a resource and support to smaller agencies, that are part of a harmonized structure, by making available assessment reports of complex applications and those for new technologies.

**Regulatory Shortcomings Identified in the Survey**

The following shortcomings were identified by generic drugs companies (from the survey) as being the key limitations to an efficient and effective regulatory system in developing countries.

- Long registration time-lines: It takes 2 to 3 years to obtain marketing approval for a generic medicine. Registration requirements for generic drugs which are without benefit
- Inexperienced personnel, lack of technical expertise and training
- Non-collaborative with low service level to industry,
- Absence of interaction between industry and regulator to discuss unique circumstances not catered for in guidance. Reluctance to accept expert recommendations from Pharmaceutical Inspections Convention and Cooperation Scheme (PICS) countries where the product has already been registered
- Inability to meet with evaluators to discuss problems because it is not allowed but practice is permissible by FDA and MCA,
- Absence of guidelines; inconsistent application of guidance’s.
- Choice of ‘best’ guidance’s from a variety of Western regulators (FDA, EMEA) which make for need to develop a ‘unique’ product,
Retrospective implementation of new guidelines at the end of development process.

Communication

Paramount of problems mentioned by respondents is the lack of constructive communication between them and MRAs through more open and frequent consultative meetings that could lead to streamlining the registration process. Apparently some regulatory agencies are inflexible in the application of their requirements. Companies surveyed desire a relationship characterized by a willingness to solve problems as opposed to an adversarial one, which apparently exists in some countries.

Drug companies' experiences with of well-established MRAs, such as the FDA and EMEA, have shown that communication between applicants and regulatory agencies during pre-Investigational New Drugs meetings, i.e., before R&D is undertaken, or other structured meetings between regulators and applicants, are important in resolving misunderstandings and misinterpretations. A recent unpublished survey conducted by CMR amongst developing countries found that very few countries with such a mechanism in place, and where it does exist, is usually very limited. Some investigators, however, believe this type of pre-submission communication to be inappropriate (Garattini and Bertele. According to them it is inexpedient for the CPMP to provide advice to industry participants whilst being charged with the responsibility of assessing applications by industry. Other researchers (Angell) have expressed similar sentiments.

Relationship between industry participants and regulatory agencies

The survey found agreement amongst most industry respondents, that the relationship, which currently exists between regulators and pharmaceutical companies, can be significantly improved. Many companies stated that they would like to meet more often with regulators to clarify evaluator requests. They find telephonic communication difficult since telephones are often not answered or if they do get through to someone it is often not the right person to assist them. They found the system for tracking the progress of new applications and post-registration amendments to be unsatisfactory.

The website of the Medicines Control Council (MCC) was viewed as a positive development since it provides access to the registration guidelines and, hence, cuts down on the number of inquiries to the authority. In order to promote relationship building between regulators and industry participants, the South African Pharmaceutical Regulatory Affairs Association, invites regulators of various countries to their quarterly congress.

The responses of industry participants with respect to their interaction with individual regulatory authorities are summarized in the Table I (R&D companies) and 2 (generic companies) below.
Table 1: Nature of relationship between R&D companies and regulators in the Southern African countries

<table>
<thead>
<tr>
<th>Countries or Regions</th>
<th>Summarized Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>Most respondents claim that their relationship with the MCC is satisfactory. However, some are dissatisfied and claim that although certain departments/directorates are approachable, others prefer contact only through written correspondence. South Africa is also accused of being the last regulatory body to grant marketing authorization due to requirements different from those of other countries.</td>
</tr>
<tr>
<td>Namibia</td>
<td>In general the relationship is described as satisfactory, although the authority is inefficient, possibly due to resource constraints. They struggle to contact the authority and often do not get the desired feedback. Namibia has a policy of only starting the evaluation process once the MCC in South Africa has granted approval. This policy causes unnecessary delays since the South African authority is considered to be the last, worldwide, to approve a drug. Compared to which countries</td>
</tr>
<tr>
<td>Botswana</td>
<td>Generally the same as for Namibia, i.e., the relationship is satisfactory although the authority is under-resourced. Timelines to gain marketing approval are extremely long.</td>
</tr>
<tr>
<td>Kenya</td>
<td>The relationship is described as good and one respondent claim that the registration process runs quite smoothly.</td>
</tr>
<tr>
<td>Malawi</td>
<td>A good relationship also exist with the Malawian authority who responds very quickly to queries</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>The Zimbabwean authority is generally considered to be knowledgeable and helpful. They respond to queries by letter although these are sometimes delayed because of poor postal services between the two countries. The authority is using proposed SADC guidelines for registration requirements although these are not official as yet. Which 2 countries</td>
</tr>
<tr>
<td>Mozambique</td>
<td>The Mozambican authority requires a reputable agent who resides in the country to submit applications for medicine registration. The relationship is still at the experimental stage.</td>
</tr>
<tr>
<td>Central, East and West African countries (Nigeria, Ghana, Uganda, Tanzania, Sudan, Ethiopia)</td>
<td>Interactions with the authorities in these countries are mediated via local agents. The perception is that the authorities in these regions are inflexible in their application requirements. Negotiations for exceptions take long and have a low level of success. The local industry apparently enjoys a higher priority than innovator medicines. There are many logistics problems.</td>
</tr>
</tbody>
</table>

Table 2: Perception by Generic Pharmaceutical Companies of their relationship with Developing Country Regulatory Authorities in Africa

<table>
<thead>
<tr>
<th>Country Authority</th>
<th>Regulatory Quality</th>
<th>Quality of Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Botswana</td>
<td>Poor to good. Difficult to contact agency via telephone.</td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Namibia</td>
<td>Good. Provide timely e-mail responses</td>
<td></td>
</tr>
<tr>
<td>Swaziland</td>
<td>Acceptable</td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td>Acceptable</td>
<td></td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Ghana</td>
<td>No direct contact. Interacts via local agent.</td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rwanda</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mozambique</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Regulatory delays

Delays in product registration by MRAs are due mainly to capacity constraints such as lack of adequate human resources and expertise, lack of access to appropriate information and technology, inexperienced evaluators who use an empirical and/or checklist approach to assessment as opposed to an evidence-base system and lack of transparency in decision making.

Registration delays in developing countries are, however, not only the fault of MRAs. The industry also contributes to the long registration timelines through submission of dossiers that
lack appropriate data to support the application, missing clinical data considered by applicants as irrelevant but important by reviewers and unsubstantiated claims by applicants for a number of indications.

Lengthy and unstructured registration procedures were stated by R&D companies as major regulatory hurdles in developing countries. There is increasing pressure on the pharmaceutical industry by governments, civil society organizations and the general public to lower the cost of medicines, accelerate time to market and improve product performance. Regulatory delays have been cited as a rate-limiting step to the timely market introduction of medicines. This was also confirmed by the outcome of our survey. A major concern of the companies surveyed was that delays in the registration and approval processes reduce the effective patent life of their products. This makes it very difficult for them to recoup their investment in R&D due to shorter patent term protection. It was suggested that enabling legislation be introduced for increased or continued R&D through recognition and "compensation" for delayed marketing through mechanisms like patent term restoration (PTR)

The majority of respondents amongst generic companies also concurred that developing countries have major regulatory hurdles, which increase the cost of bringing medicines to market. Most of these respondents also stated that the regulatory requirements are cumbersome. Respondents further agreed that the differing requirements amongst developing countries, and also from those of developed countries, serve as a deterrent to extend their operations to most developing countries. All were certain that developing countries could introduce mechanisms to increase the efficiency of regulatory review without compromising safety. Surprisingly, respondents were divided on the question of whether regulatory requirements of developing countries were too stringent. Although most agreed with the statement, four of the nine respondents stated that this was not the case.

It was suggested by surveyed R&D companies that co-operation between regulators of developed and developing countries through the exchange of evaluation and inspection reports should be encouraged since this will benefit both developing country regulators in terms of capacity building and, thus, the industry in terms of faster approvals.

The MRA respondents agreed that they could introduce mechanisms that will increase the efficiency of regulatory review without compromising the safety of patients. All also supported the statement that it would be to the advantage of their countries if they collaborated with the MRAs of developed nations. None of the MRAs believed that their regulatory requirements were too cumbersome. Table 3 below is a summary of responses from MRAs on existing technical capacity to evaluate and regulate specific regulatory areas that are of public health importance in facilitating access.
<table>
<thead>
<tr>
<th>Country</th>
<th>Fixed-dose combinations</th>
<th>Multisource medicines (MSM)/Generics</th>
<th>New dosage forms</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>No specific requirements for FDCs. General regulatory requirements are moderately stringent and essential.</td>
<td>No specific requirements for MSMs.</td>
<td>In addition to those required for MSMs, more information required about safety and quality of API. Regulatory requirements are moderately stringent.</td>
<td>Guidelines are being developed.</td>
</tr>
<tr>
<td>Kenya</td>
<td>WHO prequalification used as criteria for FDC approval QC analysis also necessary by laboratory approved by DRA. Requirements for all FDCs are the same. Requirements are regarded as sufficiently stringent and essential.</td>
<td>There are no specific regulatory requirements for MSMs.</td>
<td>There are no specific regulatory requirements.</td>
<td>Accreditation by UNICEF or WHO is a pre-requisite. These are regarded as sufficiently stringent.</td>
</tr>
<tr>
<td>Namibia</td>
<td>No details available</td>
<td>Bioavailability/bioequivalence data required</td>
<td>Bioavailability/ bioequivalence data required</td>
<td>No details available</td>
</tr>
<tr>
<td>Nigeria</td>
<td>No special requirements because rely on WHO prequalification for ARVs. Requirements are not sufficiently stringent.</td>
<td>No special requirements.</td>
<td>Rely on data from developed countries</td>
<td>Rely on WHO standards &amp; pre-qualified sources. Requirements are sufficiently stringent.</td>
</tr>
<tr>
<td>South Africa</td>
<td>Guidelines are available on FDCs. NCE clinical data are required. For a generic to the innovator FDC, bioavailability/bio-equivalence data are required. Requirements are sufficiently stringent and are essential.</td>
<td>Specific guidelines have been developed for MSMs. Requirements for all MSMs are the same. Requirements are sufficiently stringent.</td>
<td>Requires new drug application to be submitted and new evaluation. Requirements are the same.</td>
<td>Guidelines are available. Separate evaluation team with experts in biologicals and vaccines. All vaccines must be batch released by DRA prior to sale. All vaccines must be registered by authority prior to market. Requirements are regarded as sufficiently stringent.</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Requirements for approval FDCs have been included in application guidelines for registration of human medicinal products. Different requirements for FDCs whose APIs are well-established but concurrent use effects are unknown and for FDCs with one or more new APIs. Requirements are sufficiently stringent since non-adherence leads to rejection of registration approval. These requirements are regarded as essential.</td>
<td>Requirements have been include in guidelines and includes pre-registration inspection of production facilities for GMP compliance. Regulatory requirements for all MSMs are the same. Requirements are regarded as sufficiently stringent since failure leads to rejection.</td>
<td>Requirements have been include in application guidelines Requirements are regarded as sufficiently stringent.</td>
<td>Guidelines for registration of biologicals are in place. Training of specialized assessors has been done, but more needs to be done. Requirements include: description of chemistry, manufacturing and quality of immunogenic substance description of chemistry, manufacturing and quality of finished product. Pre-clinical toxicity, clinical safety &amp; efficacy data. Release lot information, whether the facility producing is WHO</td>
</tr>
<tr>
<td>Country</td>
<td>Regulatory Requirements</td>
<td>Stringency Details</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>Guidelines based on WHO &amp; ICH, Developmental pharmacetics &amp; formulation studies, Compatibility studies for different AIs, Bioequivalence studies for oral solid immediate-release FDCs, Clinical trials required for modified release formulations, Formulations with AIs which modify each other’s kinetics, Formulations with AIs in concentrations or ratios different from those whose efficacy was established from clinical trials. These requirements plus approval by WHO prequalification system. Since lapses in bioequivalence data were discovered by WHO, these are regarded as essential. SPC approved by DRA in ICH region are regarded as sufficiently stringent requirements.</td>
<td>Same guidelines used for new and generic products but requirements differ in certain sections, e.g., type of required (or exemption from) toxicology, efficacy &amp; characteristics of AI for generics. Regarded as sufficiently stringent.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td>Requirements have been implemented for FDCs used in treatment of HIV/AIDS, Different requirements for different FDCs. Requirements are not regarded as sufficiently stringent. Requirements are viewed by DRA as essential.</td>
<td>Requirements for MSMs based on WHO guidelines. Requirements regarded as of acceptable stringency. No specific requirements available.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>Clinical data are required for ARVs and anti-TB drugs. These are regarded as sufficiently stringent and essential.</td>
<td>Inspections of manufacturers WHO type certificate to be part of documents required. For some MSMs bioavailability/bioequivalence data. Regarded as sufficiently stringent. Adequate safety &amp; efficacy data required. Regarded as sufficiently stringent.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Regulatory requirements for specific areas of public health importance Survey Results)
Fast track as a means of reducing approval timelines

Most regulatory authorities in both developed and developing markets have introduced fast track policies, regulations and directives. Annexure 3 gives a few examples of those authorities with well-documented fast track mechanisms. In many countries, a fast-track registration system has been introduced to speed up market authorization. The reasons for creating such systems vary from country to country. For example, in some countries it was as a result from pressure from both consumer organizations and the industry. Consumer groups, especially those involved with HIV/AIDS issues, have demanded that products with potential for the treatment of currently incurable diseases should be approved rapidly (Ratanawijitrasin 2002).

In many countries, accelerated registration procedures have been introduced to serve the government’s need to make certain drugs available to the public more quickly (Ratanawijitrasin 2002). Accelerated approval policies have been criticized, primarily on the grounds of potential safety risks since new pharmaceuticals are released well before traditional FDA clinical testing requirements would allow. Thus, quicker review times could allow for the possible approval of unsafe medicines. However, decreased review times could also be the result of a more efficient approval system, which means that fast tracking mechanisms should not necessarily be equated with weakened standards. Some investigators, such as Marcia Angell, disagree in that they believe fast track mechanisms tend to compromise other regulatory functions, which may not be optimally performed because of the pressure under which MRAs must now perform. She advocates increased public funding to be made available to carry out the additional work created by fast track approval systems. Garattini and Bertele support her position since they have found that funding of the EMEA by industry and the European Commission to be disproportionate. In the case of the FDA, industry fees represent only 15% of their overall budget whereas industry fees contribute substantially more to the income of the EMEA than their EC grant. (Annexure 4)

Most MRAs stated that medicines’ approval in their countries is prioritized according to their public health importance. Only one indicated the contrary. In one country priority is granted to products on government tender, to antiretrovirals, and anti-TB drugs, if there is a backlog. Priority for medicines’ approval in most countries is determined by disease condition and/or the essential drugs’ list (EDL). One respondent stated that in their country, priority is also given in the case of compelling motivation by an applicant for a new drug to treat unmet medical needs.

Factors that inform the prioritization process include:

- Disease prevalence and number and type of medicines already available for the disease.
- Need for accessibility and diseases considered a priority as per government policy.
- Availability of the product.
- According to the Minister of Health’s approval for ‘Fast Track’ based on drug either being on the EDL or novel drug for specific disease.
- Shortages on the market, limited registered sources (<4) of any essential drug, and written request from the Director General of Health Services.
- Fast track applications receive first priority. Others are according to ‘first in first out’ principle.
- Most of the participating MRAs believed that the prioritization process is an incentive to industry, which can benefit in a number of ways, as listed below.
- It is a guide to industry on the types of medicines that may be required in the health sector.
- Facilitates faster marketing approval, particularly in the case of innovative medicines and for conditions with high prevalence.
• Faster marketing authorization means quick returns for industry.

One MRA, however, was of the opinion that the process only offers limited benefits to industry. Another respondent claims that industry has attempted to influence their process, but it was never successful unless it met the criteria.

Three MRAs felt that the process contains risk due to reduced evaluation time, resulting in dossiers not being screened stringently enough. Two other respondents, on the other hand, claimed that their processes hold no risk since the application goes the normal evaluation route. The process is the same; it only commences earlier.

Key message: Medicine registration is prioritized or 'fast-tracked' based on public health importance in most developing countries whose MRAs responded to the questionnaire.

The process may benefit applicants in terms of faster access to markets and as a guide to the types of medicines required by developing countries. There may be an element of risk associated with the process in some countries due to incomplete evaluation of dossiers.

Risk Assessment and regulatory requirements

Not all of the MRAs in developing countries have sufficient capacity to perform risk-benefit assessments. Even in well-established regulatory authorities the need for increased regulatory requirements has not been linked to associated risks. The recent withdrawals of the anti-inflammatory COX-2 agents, as a result of potentially life-threatening problems, have raised concerns about the manner in which regulatory decisions are arrived at. More and more data are becoming available concerning the frequency and costs of adverse drug effects. In the US this trend of post-marketing drug safety problems has been attributed to shortened review times.

Pre-marketing studies have a number of shortcomings, such as lack of follow-up of patients over many years after clinical trials, inclusion and exclusion criteria and the ideal environment in which clinical studies are carried out. The shortened timeframes for clinical trials have also been criticized, which have led to suggestions on having mandatory well structured, intensive post-marketing surveillance. Such surveillance programmes have been implemented in the UK (Prescription Event Monitoring) and New Zealand (Intensive Medicines Monitoring Programme) to some extent. Other post-marketing surveillance methods that have been described or proposed include prospective cohort studies, post-marketing cohort studies that are supported by the pharmaceutical industry, special studies on drugs and diseases and the systematic creation of databases through retrospective case controlled studies. Recent developments in pharmacogenomics show that, response to drugs varies among individuals, due to genetic factors (CIOMS). These have been shown through adverse drug reactions to certain drugs by certain population groups, lack of response or in some instances varied responses. Adverse drug reactions and other drug related problems, may result in morbidity and mortality, and have been well documented as contributing to significant proportion of hospital admissions. Many adverse reactions have a genetic substrate and this new area is receiving attention for exploring possible solutions.

MRA respondents to the survey conducted amongst regulatory agencies of the southern African region made the following suggestions to minimize the risks associated with cancellation of marketing authorizations.

• Requirement of a pro-active pharmacovigilance programme for the registration of any ‘new’ product.
• A market complaints handling and recall policy should be part of the requirements for compliance with GMP and GDP.
• Public education campaigns on continuous review of the safety of medicines.
• Proper evaluation of clinical studies before commencement.
• Timely publication of cancellation and tighter monitoring of what is on the market.

Two agencies indicated that they do not have mechanisms in place to ensure that medicines whose marketing have been cancelled are in fact withdrawn from the market. The other respondents claimed that they do have guidance on conducting a product recall and product withdrawal. One respondent stated that the Law Enforcement and Inspectorate directorate of their MRA oversees and monitors activity in the market. The Director-General of Health or the MRA can issue a media release on the marketing withdrawal and warn the public if the company was slack. The MRA can also declare the medicine undesirable and make it known by Government Gazette.

Risk-benefit assessment of a drug can be made by examining the risks of the disease being treated, the chance of improvement by the drug and the risk from the treatment. Risk-benefit analyses can also be comparative between two or more treatments for the same indication. It is acknowledge, however, that the risks aspects of a drug are likely to contain incomplete, controversial and anecdotal data compared with the benefit data that comes from clinical trials for efficacy (Edwards, et al., 1996).

According to a CMR review, there are very few models described in the literature on criteria and methods applied by regulatory agencies for benefit-risk analysis. Amongst the published models are those of Edwards et al. (1996), Amery (1998) and Beckmann. However, these methods have mainly been developed for pharmacovigilance purposes and currently, no well-established validated methods for risk-benefit analysis exists. Other methods, including mathematical models, have been described but they too have certain limitations. It is further acknowledged that risk cannot only be assessed based on scientific and statistical factors alone. Recently, decision-analytical methods have been proposed as a framework for risk-benefit quantification (Walker, 2004).

Risk assessment by drug regulatory authorities

The greatest risks identified by MRA respondents due to poor regulatory requirements and systems include:
• The appearance of substandard medicines on the market that can jeopardize public health.
• Mushrooming of unauthorized market dealers in pharmaceuticals such as unauthorized drug outlets, hawkers and smugglers of medicines.
• An environment conducive to trade in counterfeit medicines.
• Poor healthcare systems due to the use of ineffective, poor quality and counterfeit medicines and products.
• Wastage of resources on procurement of unsafe and poor quality medicines.
• Negative reputation of the regulatory authority by the public.
• Some of the risks the MRAs associated with neglecting specific areas of medicine regulation due to capacity constraints were:
  • Leaving loopholes in the drug regulatory system that can be utilized by counterfeiters
  • Promoting distortions and an ‘unfair economic playing field’ in the market.
  • Reducing the impact of the regulatory system that was implemented.
  • Putting public safety at risk.
  • Exploitation of clinical trial subjects.
  • Increased risk of drug resistance.
Three MRAs have not implemented mechanisms to assess the risks due to possible deficiencies in their regulatory control systems. One MRA, that participated in the WHO assessment of regulatory capacity, reported that it applies the risk assessment tools developed by the WHO. Another MRA respondent monitors the appearance of substandard and counterfeit medicines on their market as well as treatment failures. This MRA stated that it used both qualitative and quantitative measures of risk assessment and have applied the results to inform regulatory decision-making.

Additional risk assessment measures that have been implemented by other MRAs include:

- Qualitative assessment based on safety, quality and efficacy requirements
- Following the level of interest in the market by applicants/suppliers.
- Monitoring complaints and dissatisfaction about MRA services from the public and clients.
- Determining the extent of unapproved, poor quality and counterfeit medicines on the market.

One MRA reported that although they have not done specific internal or external qualitative or quantitative assessments of the risks, they do address risk-related issues in their MRAs quarterly and annual reports. The MRA also organizes meetings with stakeholders (at least once a year) to provide opportunities for feedback and their website has a facility to receive comments from the public.

A significant majority, consisting of six MRAs, denied that they lack the necessary regulatory resources to prevent unfair competition from counterfeit products and that this discourages R&D investment in diseases that are prevalent in their countries. Three MRAs, however, conceded that this might be true in their countries.

**Key message:** The greatest risk associated with poor regulation in developing countries is the appearance of substandard and counterfeit medicines on their markets. Competition from counterfeit products is a major deterrent to investment by R&D companies. The majority of MRAs, which participated in this study, claimed to have the resources to prevent the sale of counterfeit medicines in their countries.

**Industry viewpoint**

The pharmaceutical industry is becoming increasingly concerned at the risk-averse nature of regulatory decision-making, particularly by MRAs of industrialized countries, which they believe, are bowing to pressure by the public due to the perceived toxicity of conventional medicines and vaccines by the latter. The recent withdrawals of certain medicines from the market due to safety issues have further fuelled the public’s perception and have led to accusations that MRAs approve medicines too rapidly and without due consideration of the harmful effects the medicines may have on public health. The result has been that MRAs have become more stringent and less flexible in their requirements for marketing authorizations.

A recent submission by GlaxoSmithKline (GSK) emphasizes the industry’s stance with respect to the new extremely cautious approach of MRAs to medicines’ approval. GSK states that regulatory authorities have become more risk-averse and do not exercise any flexibility in their existing regulatory requirements. Instead they accuse MRAs of making unreasonable and expensive requests such as the requirement for expanded studies to quantify potential serious adverse events. This risk aversion is also manifested in requests for additional data after submission of a marketing application and an ‘increasing tendency for approval of more restricted indications (with requests for increased data for broader indications)’...” This can lead to delays in gaining marketing authorization and patient access to innovative medicines.
GSK points out further that the shift in focus of industry to chronic diseases has made research more difficult because of the increasing costs associated with newer regulatory demands and the difficulties experienced in undertaking clinical trials in such disorders. This is because a clinical ‘event’ is not realized for many years in a number of chronic diseases. There is, thus, an urgent need for validated surrogate endpoints and biomarkers for chronic disorders. New biomarkers in particular have the potential to speed the development process "...if they can also be used for regulatory decision making." GSK also argues that improved dialogue with regulators in the EU would help to foster better data packages for regulators on which to make risk-benefit judgments and improve predictability for companies with respect to the approval process.

Pharmacovigilance (extent of implementation and effectiveness)

Critics of the fast track policy for medicines’ approval maintain that it has an inherent potential to cause safety problems. In order to reduce the likelihood of such an eventuality, it has been suggested that fast track mechanisms be linked with good pharmacovigilance programmes. Concerns have been raised in cases where significant risks exist and pharmacovigilance programmes were lacking.

In recent years a significant rise in the conduct and funding of post-marketing studies, which are styled as phase IV clinical studies, have been observed. These studies have been criticized as not adding value but as merely a strategy, used by companies, to promote and market medicines. However, it may represent an avenue for putting resources to good use by simply Redirecting post-marketing or phase IV studies to focus more on safety aspects. It should, however, be borne in mind that very few MRAs, particularly those of developing countries, monitor phase IV clinical studies.

Medicines’ safety has been an issue as far back as the mid-1930s when 107 children died from diethylene glycol poisoning that was used as a solvent for a sulphanilamide elixir in the US. Subsequent to that was the thalidomide disaster in the 1960s in Europe, which caused birth defects in several children, multiple tragedies in India and Haiti as a result of paracetamol elixirs contaminated with diethylene glycol and 2500 deaths in Niger due to fake meningitis vaccines. In South Africa reports appeared of several cases of infant mortality due to non-sterile intravenous fluids.

The tightening of registration regulations for medicines as a result of the earlier disasters have, however, not translated into safer drugs being introduced in recent years. This is attested to by the increasing incidences of medicine-related morbidity and mortality that have been reported across Europe and the United States. Many prescription medicines have been withdrawn from the world market over the last few decades because of unacceptable adverse or toxic events. Most of the medicines whose marketing authorizations have been cancelled belong to three therapeutic classes, namely, central nervous system drugs, musculoskeletal agents and cardiovascular medicines. The most commonly seen adverse reactions involved the hepatic, haematological and cardiovascular systems. Although teratogenic and carcinogenic related problems of innovative drugs are regulated through pre-clinical studies, concern still remains because the pharmacokinetic profile of a drug may differ between humans and animals because of underlying species variations. There are a number of drugs withdrawn from the market as a result of adverse reaction and this has, lately, raised concerns from a public health perspective.

Withdrawal also has implications for the pharmaceutical industry.

A number of developed countries have well-established medicine safety monitoring centers or programmes, such as registries in the US, prescription event monitoring in the UK and IMPM in New Zealand. This is unlike the situation in developing countries, particularly those in Africa. The WHO has helped to offset this shortcoming with the establishment of a collaborating centre in Sweden, the Uppsala Monitoring Centre, which has linkages with over 70 countries for central data collection on safety.
An issue, which has recently been debated, relates to the submission of periodic safety update reports (PSURs) by companies to MRAs in developing countries. The contention is that this regulatory practice must be reviewed since developing country MRAs do not have the capacity to carry out a detailed assessment of these reports. Regulatory agencies from limited resource settings are, thus, not in a position to enforce conditional marketing approvals on all products. In addition companies, that meet their regulatory obligations, may question the justification of investing in studies that will not be thoroughly evaluated. Hence, a balance must be struck between protecting the public through ensuring that safe products are approved for registration and minimizing requests to research-base companies for inappropriate studies. The implications of such requests that will lead to additional costs to R&D companies must be carefully assessed with respect to global drug development for medicines that will be used for diseases that disproportionately affect developing countries.

Finally, the relatively scant attention that is being paid to phase IV post-marketing studies in developing countries needs to be re-considered. South Africa is in the process of implementing registries such as those established by the FDA. Such registries will have data on both incidence and exposure to medicines, which will be obtained from observational/epidemiological studies that use electronic patient-level data. Long term, post-marketing risks and benefits of medicines will therefore need to be evaluated. It may, thus, be best to integrate such pharmacovigilance activities into public health programs instead of leaving their management to the regulatory authority. There challenges will be resources to establish such initiatives in developing countries.

US FDA and incentives for research and development

The FDA has initiated processes to support speedy approval of priority medicines, such as the orphan drug regulatory framework and, lately, mechanisms to promote innovation for medical therapies.

In March 2004 the FDA produced a document entitled "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products". The FDA analysis of the pipeline problem in this publication reflects a slowdown in innovative medical therapies reaching patients and also recognizes the problems inherent in the development of products for priority health needs in developing countries. New product development toolkits are suggested in this document, which are aimed at improving predictability and efficiency. These toolkits contain new scientific and technical methods, such as computer-based predictive models, biomarkers for safety and effectiveness and new clinical evaluation techniques. Furthermore, some of the issues raised in this white paper are consistent with issues highlighted by Croce, in particular, the drug discovery process based on animal models and its poorly understood clinical relevance. Some have referred to these models as pre-clinical regulatory rituals.

The FDA also suggests earlier "proof-of-concept" trials that seek to confirm activity in humans before a commitment to full-scale development is made. They identified a need for new genomic, informatics, and imaging technologies that could provide tools to reliably detect safety problems early, identify patients likely to respond to therapy, and lead to new clinical endpoints. The FDA also identified a need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints, and analyses. The FDA acknowledges that "... most of the tools used for toxicology and human safety testing are decades old... and may fail to predict the specific safety problem that ultimately halts development" Moreover, clinical trials may not uncover such issues, as the safety issues may be uncommon, the trials may be run with too few patients or with patients that are not representative of the target population (i.e., trials lacking the elderly, women, ethnic groups, etc.). Predicting and subsequently demonstrating medical benefit is quite challenging as available pre-clinical animal models have limited predictive value in many diseases.

Emphasis is being placed on the importance of research into the entire regulatory process and the value that scientists working in drug regulatory authorities can add to such a research agenda.
EU incentives for research and development

In the EU, the European Agency for the Evaluation of Medicinal Products (EMEA), launched a consultation exercise in April 2004 to develop a strategy that will allow the EMEA to better facilitate drug regulation in an expanded Europe within a setting of increasing innovation and research. Pre-clinical and clinical scientific assessment, post-marketing issues and improving interactions with patients are important challenges faced by the EMEA. The EU proposed a new comprehensive approach to drug development that identifies “bottlenecks/barriers in the current drug development process” and solutions to overcome them. The project contains two components:

- A comprehensive strategy with a detailed roadmap to reduce the drug development time, encompassing the whole path from discovery of a new drug target to the validation and approval stages of new drug compounds, ensuring high levels of drug safety and efficacy as well as fast availability of innovative medicines to the patients.

- A strategy to develop exploratory and demonstrative research activities within one or two of the major chronic progressive disorders, where novel concepts for accelerated drug development can be tested and evaluated.

No such well-documented strategies were available from the developing countries that were surveyed. Singapore has already been identified as a research site for drug development for Dengue fever and tuberculosis. Singapore has introduced regulatory measures to stimulate R&D, which include the following:

1. Introduction of effective regulatory practices and systems;
2. Promotion of life sciences innovation;
3. Promotion of interaction with stakeholders; and
4. Utilization of information technology and acceptance of assessment.
CHAPTER 3: THE CHALLENGE OF VACCINES AND NEW TECHNOLOGIES

Challenges of biotechnology
Since 1988, the development of medicines has undergone a major transformation, moving from a synthetic, chemistry-based to molecular biology based processes. Biotechnology is already posing a regulatory challenge to developing countries that are likely to share the benefits of biotechnology products but lack the regulatory capacity for evaluation and approval. According to the International Pharmaceutical Review report published in 2003, biotechnology and genomic approaches to drug discovery and development will present substantial challenges to regulatory and standard setting bodies and safety and efficacy criteria will remain pivotal for approval of marketing authorization. The limited capacity of medicines regulatory authorities of developing countries will remain a problem and certain approaches and procedures would have to be considered.

Accelerated rates of development require an accordingly responsive regulatory environment. Regulatory authorities must step-up their approval and review processes to match the complexity of applications for the registration of biotechnology products and rapidly evolving technology, as well as new drug delivery technologies.

Regulatory approval processes must be simplified as far as possible, without compromising quality, particularly where the risk/return profile (from an investment standpoint) justifies simplification. This is even more important for vaccines, since efficacy trials usually take longer than in drug trials. Furthermore, the criteria for approval of medicines could be adapted to reflect the particular risk/benefit profile (from a public health standpoint) in the endemic countries. This could lead to less stringent criteria in favor of providing access for thousands and millions at risk in these countries. Naturally, changing approval criteria can only be undertaken in settings with adequate ethical and regulatory capabilities. In addition, where assessment of complex technology has been undertaken, this information must be shared amongst regulatory authorities thus advocating for a system of information interchange without violating confidentiality.

Vaccines
In recent years there have been increased efforts to promote vaccine R&D in developing countries. In March 2000 WHO convened a meeting with the Public Sector Vaccine Manufacturers (PSVM), to define their role within the changing world of vaccines.

PSVM has expanded its activities beyond the production of traditional vaccines and put more emphasis on R & D.

There have been some considerations for prioritization of vaccines for the developing world and the Global Alliance for Vaccines and Immunization (GAVI) has, as one of its main objectives, accelerated R&D efforts for vaccines needed primarily in developing countries

Disease Prioritization
WHO's Initiative for Vaccine Research (IVR) has embarked on various projects to advance public health and improve access to vaccines for vaccine-preventable diseases. IVR has prioritized various infectious diseases of public health importance using a "filter system" with three categories for disease priority efforts, namely IVR watching list, IVR developing list and IVR facilitating list.

• Watching list: between12-14 identified priority diseases, IVR's role is mainly that of monitoring, these diseases are e.g. cholera, typhoid fever, Buruli ulcer.

• Developer list: includes 5 priority diseases, and IVR directly supports and sponsors the development of specific vaccine candidates, e.g. malaria, leishmaniasis or measles
WHO Role in Developing New delivery systems

WHO IVR has strategies for new delivery systems, which include novel technologies to improve delivery of vaccines, immunogenicity, etc.

In addition to disease-specific research activities, IVR performs capacity building and monitoring activities including training and workshops (e.g., in Africa) to build capacity for research and development across all disease areas.

Regulatory capacity for vaccine R&D

Given the public and private sector efforts to develop vaccines for the diseases in developing countries there is an urgent need that regulatory requirements for clinical trials, registration and regulation of biotechnology products and vaccines (particularly against the diseases such as TB, Malaria and HIV/AIDS) be formulated. Currently, there are few developing countries with such requirements and the ability to regulate all activities from clinical trials to registration.

The political and regulatory environment is a key determinant of investment in local vaccine production. A study involving 21 respondents, from local vaccine production facilities, showed that the key motivators for investing in local production were political and strategic and not economic. WHO identified among other factors the necessity for the establishment and the strengthening of National Drug Regulatory Agencies (NDRA) and commitment by the government to implement necessary changes. Developing Countries Vaccine Regulators Network (DCVRN) has been organized by WHO to facilitate inter-country collaboration towards collective regulatory capacity. Global Training Network for vaccines, an institutionalized programme for training and capacity building, was established by WHO in 1996, it provides training to both regulatory, laboratory and production staff. Similarly, WHO-initiated Developing Country Vaccine Manufacturers Network (DCVMN) has been established to encourage collaboration between various countries. DCVRN is a similar network for regulators.

Public Sector Vaccine Manufacturers (PSVM)

There is an array of vaccine portfolios produced by Public Sector institutions and a range of activities in vaccine research and development. In recent years, challenges posed by the complexities of vaccine production, increasing regulatory demands and strengthened international patent enforcement, were discouraging public sector manufacturers from investing in new technologies and, hence, worsening the already widening technology gap between the public and private sector. To address these problems, Public-Private sector partnerships and collaborations through joint ventures and technology transfers were considered as a viable solution and Global Training Network an institutionalized programme for training and capacity building were established as a means to facilitate it.

In addition to Public-Private sector partnership, coordinated efforts among public institutions through direct partnerships or regional arrangements to share technical expertise would be of benefit to public sector institutions. DCVMN, a voluntary public health driven alliance of developing country vaccine manufacturers, aims to provide a consistent and sustainable supply of quality vaccines at an affordable price to developing countries.

Further considerations by PSVM could be the production of combination vaccines and plan to meet global vaccine needs. WHO would drive the capacity building to ensure requirements for quality, efficacy and safety were complied with and purity and consistency were maintained. An information sharing network would be initiated that would build on strength and expertise of PSVM.
<table>
<thead>
<tr>
<th>Country</th>
<th>Producer</th>
<th>Status</th>
<th>R &amp; D</th>
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<tr>
<td>Mexico</td>
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<tr>
<td></td>
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<td>Brazil</td>
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<td></td>
<td>Instito Butantan - Fundacao utantan</td>
<td>Government; Not-for-profit</td>
<td>Partnerships</td>
<td>DTP, BCG, HepB, rabies, influenza</td>
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<tr>
<td>India</td>
<td>Serum Institute (DCVMN)</td>
<td>Private</td>
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<td>Hlb, Hepatitis B, DTP, BCG, influenza, etc</td>
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</tr>
<tr>
<td></td>
<td>Bharat Biotech (DCVMN)</td>
<td>Private</td>
<td>R&amp;D</td>
<td>HepB, Typhoid</td>
<td></td>
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<tr>
<td>Cuba</td>
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</tr>
<tr>
<td>Egypt</td>
<td>Vacsera (DCVMN)</td>
<td>Government</td>
<td></td>
<td>DTP, BCG, cholera, typhoid, polio, measles, HepB, rabies</td>
<td></td>
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<tr>
<td>Senegal</td>
<td>Pasteur Institute (DCVMN)</td>
<td>Government</td>
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<td>Tunisia</td>
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<tr>
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<td>Independent international organization</td>
<td>R&amp;D</td>
<td></td>
<td>GMP, QC and QA</td>
</tr>
</tbody>
</table>
Developing Countries’ Vaccine Regulators (DCVR) Network

Many new vaccines are being developed either in developed or developing countries but almost exclusively for the needs of the latter. The critical review of proposed clinical trials and eventual registration and licensing will depend more and more on the national regulatory authorities (NRA) of countries that use these vaccines. Many developing countries that import vaccines either do not have an NRA or if they do have one, it is unlikely to have adequate capacity for critical review functions. Many such countries rely on the registration of vaccines and GMP oversight of the manufacturers’ facilities by developed countries with well-recognized MRAs or depend on regulatory oversight by other developing countries with more established MRAs and which have implemented critical regulatory functions. The latter approach (reliance on the NRA of other developing countries) has led to the establishment of the Developing Countries Vaccine Regulators (DVCR) Network on September 17th 2004, in Bangkok, Thailand.

The Network does not, as such, have any separate legal status or decision making powers. It may identify the needs of each participating NRA for internal strengthening and training in clinical trial evaluation, and may make proposals for achieving this. To this end, the Network may also consider the needs of other countries that may seek advice from the Network.

The discussions at and outcome of the Network meetings do not, however, commit the participating in any way, but constitute a reference for guidelines, recommendation for policy, information sharing, training, or other action, as appropriate, under the responsibility, and according to the prerogative, mandate and internal rules and procedures of each participating NRA. The founding member countries are Brazil, China, Cuba, India, Indonesia, Korea, Russia, South Africa and Thailand.

Strategy for developing countries: technology transfer of biotechnology products

Various efforts have been made by international initiatives with the aim to build regulatory and manufacturing capacity for biologicals in developing countries. Technology transfer involves activities with respect to several relevant areas: building the infrastructure, production capacity, R&D capacity, GCP and GMP capabilities, etc. For example, WHO has established vaccine related networks such as DCVR and DCVMN. WHO has also developed guidance documents on the subject of evaluation of clinical trials and clinical trial data. Similarly, as mentioned earlier, the global training network aims to build capacity for MRAs of developing countries and vaccine manufacturers.

Addressing production issues

Several initiatives have been considered for technology transfer, for example the technology transfer model for Meningitis Vaccine Project and the Programme on Appropriate Technology on Health. This meningococcal conjugate vaccine is targeted for Africa\textsuperscript{12}. The approach followed was technology transfer, from an established manufacturer in an industrialized country to a manufacturer in a developing country. There are several factors that were considered, namely capital investment, sale of vaccines in Africa with a low profit margin, and how the acquired capacity could be used to create other vaccines. Serum Institute of India

\textsuperscript{12} \url{www.meningvax.org}

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was a contractual partner and phase I studies are planned for 2005. The vaccine has a target price of US$ 0.40 per dose a fifth of the cost of similar vaccines developed in the industrialized countries.

**Addressing clinical research ethical issues**

As a result of unresolved issues regarding ethics in clinical research in developing countries, some flexibilities are needed within the context of ethical principles of respect, beneficence and justice. The multi-country typhoid vaccine research project highlights the systematic application of ethical principles and good clinical practice in a developing world public health setting. GCP as it applies to vaccines in developing countries falls into three categories (World Report on Knowledge for Better Health, WHO, 2004)

1. Clearly applicable and full compliance
2. Clearly applicable as stated with interpretation and application within the context within which it is applied (standard of care is not global but local, but general standard of care in research may be defined). Local requirements and conditions must be clearly defined and complied with 3. Clearly applicable as stated but requires capacity building.

This approach of the multi-country typhoid vaccine has expedited broader access to a needed vaccine.

**Challenges posed by new technologies**

Pharmacogenetics is defined as the study of inter-individual variations in DNA sequencing related to drug disposition or drug action; it includes applications of single or a set of multiple gene sequences to investigate variations in DNA sequencing that may influence drug response.

Pharmacogenomics is defined more broadly as the application of genomic technologies to elucidate disease susceptibility, drug discovery, pharmacological function, drug disposition and therapeutic response.

Biogenerics, are considered to be targeting highly complex compounds and the technological and regulatory challenges have been considered to be enormous. This may be an area for further work, where strategic alliances between biotechnology and generic companies can enter into development partnerships for biotechnology products that can be used for the treatment of DDDCs.

It has been shown that as a result of genetic factors, response to drugs varies among individuals. Therefore, diagnosis, treatment and safety can be improved by considering the interaction of medicines and the genetic make-up of individuals. The poor success rate in drug development, as a result of aborted projects, may be improved. There are a number of drugs withdrawn from the market as a result of adverse reaction and this has, lately, raised concerns from a public health perspective.

Withdrawal also has negative implications for the pharmaceutical industry and regulatory credibility. It is for this reason that among other factors pharmacogenetics and its role must be assessed. This has drug development as well as regulatory implications. The implications must be assessed from drug research and development through to post marketing. Most drug regulatory authorities, from developed countries, have the capacity to regulate and provide guidance documents on genetic factors and their influence on new products, for which applications for marketing authorization have been filed.

**Implications for drug development**

Genotyping of all subjects and patients participating in clinical trials would result in additional costs, which are considered to be a very small fraction of the total costs. This is considered a cost-effective investment, from a safety and efficacy point of view, but has ethical and practical challenges.
It is suggested that a protocol of every clinical trial in man could include a section on variability in drug pharmacokinetics and pharmacodynamics. Clinical studies should provide for the assessment of genetic, and these should be considered for various phases of clinical trials, e.g. prospective genotyping in phase II studies for dosing recommendations, and Phase III may give further evidence on the role pharmacogenetics factors, in determining drug response.

It has been suggested that phase IV studies should be conducted through collection of blood and DNA samples, as part of a pharmacovigilance program.

Even though this is a new area, some companies have already started submitting pharmacogenetics data to the regulatory authorities, as part of their applications; a recent CMR survey reported nine companies having this experience. According to the United Kingdom Secretary of State for Health, although gene therapy was a new branch of medicine, more than 600 trials had been approved world-wide.

Despite all these efforts, the capacity to generate and assess pharmacogenetic data will remain a challenge in developing countries. There are ethical, social and legal challenges that require attention. Increased public confidence and acceptance of using genetic testing are needed worldwide to make the progress. This can be achieved through better communication and education.
CHAPTER 4: HARMONISATION AND GLOBAL INITIATIVES

Background
In the past there were many ‘roadblocks’ to the rapid development of quality products, because of the need to comply individually with each nation’s regulatory requirements. Duplication of effort and attempted leveraging of various databases for multinational product registrations were often fraught with delay, excessive expenditures and frustration (Hoff, 2000). Thus, there has always been interest to promote as much similarity as possible in the form and content of registration dossiers in multiple countries.

Harmonization was initiated with an aim to achieve a reduction of development and regulatory review times, which would translate into significant cost saving to the industry and quicker access to new (and improved) therapies at more affordable prices. Harmonization is, however, not an easy process. It depends largely on the successful implementation of a model, which acknowledges and incorporates the sharing of regulatory burden between the participating countries. There have been increasing trends towards harmonization globally. There have been a number of regional activities of harmonizing guidelines, forms and regulatory requirements.

The European Union, with its reciprocal and mutual recognition procedures to enable one dossier to serve for all 15 Member States, is the longest established model of harmonization. The first European Pharmaceutical Directive (65/65/EEC) was issued in 1965 but it was not until the 1990s that effective methods for sharing regulatory processes and structures were really in place (Hill and Johnson, 2004). The European Union is the most successful and well resourced harmonization initiative.

The other major model is the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The pace of harmonization has been galvanized through the efforts of the International Conference on Harmonization established by the representatives of trade associations and medicines regulatory authorities of the three regions namely US, EU and Japan.

There have been other activities involving the Eastern and Central European countries and of harmonization of Accession States with the European Union. The other sub regional and regional efforts have been initiated with an aim to achieve harmonization in 6 of the WHO regions, the SADC as part of AFRO, ASEAN, the Gulf region as part of EMRO, PAHO/AMRO, PANDRH and EURO.

There have been efforts by WHO to support the harmonization initiatives in most of these regions although to varying extents. Other efforts by WHO entail support to the United Nations Procurement Agencies, through the pre-qualification of products by assessing them based on certain standardized regulatory requirements. Different experts from both the well established regulatory settings and limited settings have been pooled. This experience can be expanded further to strengthen regulatory capacity of developing countries for complex technologies whilst retaining certain elements for regional and country control and activities.

Significant progress has been made towards harmonization of regulatory requirements and standards in different regions of the World Health Organization. There are still obstacles to the mutual recognition with the EU and the implementation of ICH guidelines. The implementation of the Common Technical Document is mandatory in the EU while it is voluntary in the US. The EU mutual recognition system for its members was a lengthy process, but a lot has been achieved through the harmonized approach.
Harmonization of different regions

European Union

The activation of the Maastricht Treaty in November of 1993 transformed the European Community into the European Union. A new pharmaceutical registration system was soon established in which drug manufacturers were able to gain marketing authorization for medicinal products in countries of the European Union (EU) in three ways.

1. They could use the “traditional” route by approaching the medicines licensing authority of each Member State (MS) individually to obtain separate national licenses. This was known as parallel national application and did not involve the European Commission.

2. A second route was, and remains, the EU’s mutual recognition procedure (also known as the decentralized procedure), which enables manufacturers to seek simultaneous marketing authorization in two or more Member States, known as the Concerned Member States (CMSs), providing that they have an existing marketing authorization for that drug in at least one Member State, known as the Reference Member State (RMS). Under this procedure the CMSs are encouraged to mutually recognize the marketing authorization of the RMS. (EEC, 1993a, Abrahams and Lewis, 1999).

3. The centralized procedure is managed by the European Medicines Evaluation Agency (EMEA), which was established in London on 1 January 1995. The EMEA chooses which Member State acts as the rapporteur for the centralized procedure and plays a central role in the mutual recognition procedure (EEC, 1993a, Abrahams and Lewis, 1999). Biotechnology products, must follow the third route, known as the centralized procedure, which is also for highly innovative new chemical entities (NCEs). (EEC, 1993b).

The harmonization procedures in the EU have created a number of concerns, particularly amongst consumer organizations and even some regulators. They claim that too often drug regulatory systems do not safeguard public health sufficiently (Abraham, 2004). It has also been claimed that regulators excessively accommodate the interest of the pharmaceutical industry at the expense of patients’ interest in safety because of “too close” a relationship and that governmental efforts to hasten drug approval could jeopardize safety considerations (Lexchin, 1994).

A study by Abraham and Lewis (1999) sought the opinions of regulators, on harmonization in the EU. The majority of those interviewed felt that faster approvals might well undermine safety. Swedish regulators, who have in the past taken longer to approve drugs because they imposed tougher standards on manufacturers, showed the greatest concerns. Half the British and German regulators also thought that harmonization would entail a “leveling down” in safety standards. In contrast sources from industryoptimistically welcomed the new EU competitive and harmonizing processes and believed that they will not compromise safety.

The EU has created a mechanism to issue a scientific opinion for the evaluation of medicinal products intended exclusively for markets outside the Community. Article 58 of Regulation no726/2004 established a mechanism whereby the EMEA may give such a scientific opinion in the context of cooperation with WHO for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. It serves as a response to the need for protection of public health and provision of scientific assistance to non-member countries within the context of cooperation with WHO, while at the same time allowing rapid access by those countries to important new medicinal products (intended to prevent or treat diseases of major public health interest). This is an interesting development that can be explored further for regulatory support to developing countries.
SADC

The Southern African Development Community (SADC) is a regional trade bloc with 13 member states and a population of 191 million people. The countries display significant variability in the level of development, capacities, infrastructure and expertise.

The harmonization of regulatory requirements was initiated through the South Eastern African Medicines Regulatory Authority Conference (SEAC) initiative, which included both SADC member states and a few countries in the Eastern African Region. This initiative mainly focused on specific issues that were of interest to the medicine regulators and the pharmaceutical industry: labeling, package inserts, patient information leaflet, scheduling and therapeutic classification and standardization of terminology. The first harmonization process was initiated in 1995 through SEAC, and was largely driven by the South African Pharmaceutical Manufacturers Association and Medicines Control Council as well as the Zimbabwean Pharmaceutical Manufacturers Association and Medicines Control Authority...

SADC medicines regulatory authorities, following a directive of SADC Ministers, have undertaken several activities involving the control of quality of pharmaceutical products at various stages of distribution and the registration of medicines. A paper based analysis of legislation, regulations and guidelines of some of the member states was conducted based on all documentation that was provided. Nine out of fourteen SADC member states submitted their legislation, regulations and guidelines on registration and control of medicines. Some legislation dated as far back as 1965 in one country with the latest laws having been recently passed in 2002. The legislative provisions differ in emphasis but basic elements exist, and are implemented to varying extents. The approach followed by the SADC medicines regulatory authorities was the adoption of the EU application format, which has since been replaced by the ICH Common Technical Document.

The Gulf Region

A formal structure, the Cooperation Council for the Arab States, was created in 1999 which is responsible for central registration of medicines. It consists of two members from each state and is located in Saudi Arabia, and has so far approved 73 companies and 214 products. There are harmonized guidelines on GMP, bioequivalence, and stability that have been published and implemented. The observation made is that only local companies are allowed to submit applications for product registrations. This model can be further explored for other regions with limited capacity.

The Gulf regional experience reflects a more practical but different approach to harmonization. A study was conducted in 2001 by CMR involving 11 pharmaceutical companies, 9 countries in the Middle East\(^\text{13}\) and 7 health authorities of the region. A few issues from the findings of this study reflect that there was lack of understanding of requirements by the pharmaceutical industry, the review timelines are reduced and certain authorities used a priority review system for important products. There was also increased dialogue between companies and regulatory authorities,

\(^\text{13}\) Bahrain, Egypt, Jordan, Kuwait, Lebanon, Oman, Qatar; Saudi Arabia, United Arab Emirates
ASEAN Region

In Asia and the South Pacific, the Association of South-East Asian Nations (ASEAN) countries have undertaken work to attain a common approach to medicines regulation.

The Pharmaceutical Product Evaluation Group, with membership from both the pharmaceutical industry and the Drug Regulatory Authority, of ten member states was formed September 1999. The Consultative Committee for Standards and Quality (ACCSQ) is tasked with the development of harmonized scheme among ASEAN members, and to facilitate and complement the objectives of the ASEAN Free Trade Area, without compromising public health by ensuring quality, efficacy and safety of medicines.

Pan American Network for Drug Regulatory Harmonization (PANDRH)

This is a continental forum that deals with harmonization, it includes Drug Regulatory Authorities in the region as well as representative from the trade organizations, namely CARICON, MERCOSUR, TLCA, Latin American Association for Integration (ALADI) and the Andean Community. Also included are academics, regional professional associations and other interested groups. The aim of the conference is to disseminate the decision of drug regulatory harmonization of global initiatives, e.g. International Conferences of Drug Regulatory Authorities (ICDRA) and the ICH. It also supports harmonization processes and analysis of guidelines. It has technical working groups, selected by the Steering Committee which assists with assessing countries and implementing international standards.

Co-operative networks and systems: Developing Countries’ Vaccine Regulators (DCVR) Network

WHO initiated the establishment of Developing Countries’ Vaccine Regulators (DVCR) Network on September 17th 2004, in Bangkok, Thailand. The mission of the DVCR is to promote and support the strengthening of the regulatory capacity of MRAs of participating and other developing countries in the evaluation of clinical trial proposals (including pre-clinical data and product development processes) and clinical trial data through expertise and exchange of relevant information. The Network provides a forum for discussion, advancement of knowledge and exposure to policies and procedures pertaining to evaluation of clinical trial proposals (including pre-clinical data and product development processes) and clinical trial data. The Network does not, as such, have any separate legal status or decision making powers. It may identify the needs of each participating NRA for internal strengthening and training in clinical trial evaluation, and may make proposals for achieving this. To this end, the Network may also consider the needs of other countries that may seek advice from the Network.

The discussions and outcome of the Network meetings do not, however, commit the participating MRAs in any way, but constitute a reference for guidelines, recommendation for policy, information sharing, training, or other action, as appropriate, under the responsibility, and according to the prerogative, mandate and internal rules and procedures of each

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14 Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic, Malaysia, Mynmar, Phillipines, Singapore, Thailand, and Vietnam
participating NRA. The founding member countries are Brazil, China, Cuba, India, Indonesia, Korea, Russia, South Africa and Thailand.

**The WHO prequalification project**

The prequalification project, set up in 2001, is a service provided by the World Health Organization (WHO) to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. From the outset, the project was supported by UNAIDS, UNICEF, UNFPA and the World Bank as a concrete contribution to the United Nations priority goal of addressing widespread diseases in countries with limited access to quality medicines (WHO, 2004).

Prequalification was originally intended to give United Nations procurement agencies, such as UNICEF, the choice of a range of quality medicines. With time, the growing list of products that have been found to meet the set requirements has come to be seen as a useful tool for anyone bulk purchasing medicines, including countries themselves and organizations such as MSF (Médecins Sans Frontières) and other NGOs.

The specific tasks of the prequalification project include:

a) to assess the quality of essential drugs, produced by generic and brand name companies, through the evaluation of product dossiers submitted by companies, and

b) To assess manufacturing sites to comply with Good Manufacturing Practices.

The Prequalification outcome of the WHO site inspection reports is a signal for a need for tight regulatory controls. It is argued that under-resourced regulatory authorities do not have capacity and harmonization approaches make it necessary for close collaboration.

**International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)**

The ICH is an initiative that was largely driven by industry to reduce time and cost in drug development. It was established in 1990 and brought together the drug regulatory authorities of the European Union (EMEA), Japan (Ministry of Health and Welfare), and the United States (FDA) as well as representative associations of the pharmaceutical research-based industry in the three regions (European Federation of Pharmaceutical Industries, Japanese Pharmaceutical Manufacturers Association, International Federation of Pharmaceutical Manufacturers Association and Pharmaceutical research and Manufacturers of America). The overall objective was to find ways to harmonize technical guidelines and requirements for medicinal product registrations. The pharmaceutical industry was keen to provide a more cost-effective use of human, animal and material resources and to eliminate delays in global development and registration of new drugs, while keeping an appropriate level of quality, safety and efficacy (McCarthy, 2001).

The International Federation of Pharmaceutical Manufacturers Association (IFPMA) provides the ICH Secretariat. The World Health Organization (WHO), Canada (represented by Health Canada) and the European Free Trade association (EFTA) hold observer status in ICH and its Steering Committee (WHO/EDM/QSM/2002.3).

To date, ICH has produced more than 45 guidelines describing technical requirements related to specific components of the drug registration process. The cost related to full implementation of the guidelines may in some cases be considerable but it is argued that this is offset by more rapid registration of new drugs in the ICH countries.

As part of this expanded phase of ICH activities, the Steering Committee of ICH has established a Global Co-operation Group. The terms of reference of the Group include the provision of information on ICH, its activities and guidelines to any country, regulatory authority or company that requests such information. Thus, the Group’s aim is to disseminate finalized ICH guidelines in order to encourage their acceptance and adoption in non-ICH countries (WHO/EDM/QSM/2002.3).
The challenges posed by ICH guidelines are not limited to non ICH members only. The following is a summary of the results of the survey of ICH members in the implementation of ICH guidelines.

**Experiences of ICH countries in the implementation of ICH guidelines**

In a survey conducted among ICH members, the following implementation challenges were highlighted

- Each member state will have to make regulations to accommodate ICH
- Training was needed in the interpretation of guidelines
- There were systems requirements, which meant some revision was needed to accommodate the ICH Common Technical Document
- There were still differences among ICH members, and stability was cited as an example
- The respondents considered the following as benefits,
  - Closer collaboration with other regulatory authorities
  - Viable solution to modern regulatory challenges
- The ICH Common Technical Document was considered a means of having efficient review process, with an overall improvement in presentation, integration and analysis of data
- The ICH CTD was seen as a way of reducing delays through filing applications and this would contribute towards availability of medicines
- The ICH harmonization has established a basis on which one global development programme can be achieved, and this can serve as an incentive for identification of medicines targeted at diseases affecting developing countries.
- Several concerns, however, have been expressed about ICH, with particular reference to developing countries

Concerns are with particular reference to developing countries, and examples of specific technical areas will be discussed below.

The public health implications of the application of guidelines of greater technical complexity in developing countries may be far-reaching. In many countries, essential drugs required for the prevention and treatment of locally endemic conditions are not supplied by the major multinationals, but by local industry or generic manufacturers. If these suppliers are unable to meet these new quality standards, the adverse impact of the withdrawal of these drugs on the health of the population might have far more impact than that of any potential risk posed by failing to achieve the ICH standard (WHO/EDM/QSM/2002.3).

Complying with ICH standards may require local generic companies to make greater investments in new technology and training of personnel, which will force them to substantially increase the prices of their products in the local market.

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15 ICH Conference Japan
If local companies in developing countries, whether research-based or generic drug producers, become ICH compliant they may, like multinational corporations, target global diseases because of the prospects of earning much greater returns. Country-specific diseases may, thus, become totally neglected.

The ICH process has involved only 17 industrialized countries in the decision-making process. Developing countries lack an effective mechanism by which to influence the process to ensure that their needs are addressed.

Finally, ICH is harmonizing standards that reflect the priorities and resources of the highly developed countries. Even with improved efficiencies, new drugs are likely to remain expensive for most developing countries because ICH-harmonized regulations will still impose significant regulatory costs on pharmaceutical companies. Outside the ICH, even harmonized quality standards developed by WHO contain costly GMP requirements that many drug manufacturers in developing countries cannot afford. These factors suggest that international harmonization of drug development is unlikely to create incentives for pharmaceutical companies to shift resources towards therapies for diseases prevalent in the developing world or reduce materially the investment of new drugs for developing countries (Fidler, 1999).

**Survey Results**

All MRAs except one, agreed that implementation of ICH requirements and standards are likely to increase the cost of operating their regulatory agencies. A mixed response was received to the statement that the higher cost associated with meeting ICH standards was a disincentive to investing in R&D in their countries. All responding found WHO guidelines to be acceptable and not costly, lax or too stringent. It was also stated that a number of provisions under the ICH guidelines have been adopted in national drug regulatory guidelines and in the guidelines of most of the MRAs in the region.

Interestingly, the majority of respondents from generic industry wanted ICH requirements to be applied to generic medicines. Respondents were, however, split on whether adoption of ICH requirements by a developing country regulatory authority would increase their cost of operations.

**Other harmonization structures**

A number of other regional drug regulatory organizations/initiatives that exist worldwide. In Europe, the Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries (CADREAC) members are now officially collaborating with EU unified procedure. In Africa, in addition to the SADC harmonization described above, there is the Common Market for Eastern and Southern Africa (COMESA), which began in 1995 with a commitment, like that for SADC, to pursue harmonization of registration procedures with a mutual recognition process akin to that in Europe.

The successful harmonization arrangements, such as ICH and that of the EU, have all taken a considerable amount of time and money to develop. There is now a single dossier format that is generally used in EU countries, and countries such as Canada and Australia have also adopted this. In addition, a number of ICH guidelines have become accepted standards. Manufacturers, therefore, no longer have to prepare completely different versions of the same dossier for each authority. In addition registration time has decreased which is a prominent measure of efficiency for the industry (Trouiller, et al., 2001).

**Survey Results**

All MRAs concurred that harmonization of regulatory requirements amongst regulatory agencies in specific regions, such as the Southern African Development Community (SADC), would be beneficial. Most also agreed that regional harmonization will release resources that can be applied to research on diseases that disproportionately affect developing countries. The majority of MRAs also stated that differences in regulatory requirements amongst developing countries and between developed and developing countries are a deterrent to market access. MRAs are busy mapping out ways of harmonizing registration processes and
efforts within the East African and COMESA regions are ongoing. It was reported that most of the national DRA regulatory requirements are based on WHO guidelines in the East African and COMESA region. This has facilitated similarity, which can serve as the basis for harmonization efforts.

**Strategies**

Lessons learnt from harmonization efforts of countries with resources and developing countries regional efforts, are that the regulatory frameworks created and approaches followed have overcome some barriers. There are several initiatives from the SADC region, where 13 regulatory agencies have harmonized their technical requirements. The achievement has been standardization of regulatory requirements. Standardization benefits both regulators and the industry that researches, manufactures and produces medicines. It can be shown that savings can be achieved; administrative burden can be reduced from both regulators and industry. The preliminary results of the survey from the research based industry and generic industry reveal that.

The challenge is the model for implementation of these harmonized guidelines. A significant amount of harmonization with some of the ICH guidelines has been achieved, not only for the SADC harmonization process but also other regions. The EU model is unaffordable, while the ICH implementation process has not been completed and may not meet the needs of developing countries. There are WHO initiatives, including the DCVR network that involves 9 national drug regulatory authorities across 5 continents; another model may be the improvement of the WHO prequalification system, to draw on the technical pool of experts. Harmonization initiatives have been explored with a regulatory model that reduces regulatory burden and draws on a pool of available experts, The Gulf regional experience reflects a more practical but different approach to harmonization of joint assessments. It is one of the few if not the only collaborative initiative with procedural and structural arrangements that have been operational for decades.

The DCVR network and Prequalification are initiatives worth considering. While it is acknowledged that it they are not multi-country regulatory authorities, the prime purpose is to support and strengthen the critical skills needed to review applications in importing countries in which the requisite expertise is lacking because of resource constraints. The independence of the participating MRAs is, thus, not compromised. This can be extended for complex biotechnology products and new chemical entities.

Financial and other resource inputs can be obtained from member states through their MRAs and from industry through registration and licensing fees to offset administrative costs. This can be a good model for strengthening regulatory capacity, and some twining arrangements can be considered.
CHAPTER 5: CLINICAL TRIALS

Drug development and trends in the conduct of clinical trials

Drug development has become a global activity that is aimed at launching each new drug in three major global markets (US, EU and Japan) It is under the influence of economic factors, scientific progress and increased regulation. Key players in drug development are the MRAs, Ethics Committees, research institutions and the pharmaceutical industry( which has various players e.g. discoverers, developers, Contract Research Organizations (CROs), etc. ).

According to Brummerlen, the aim of drug development is to provide information on the optimal use of a new drug, in the treatment or prevention of disease, and it also includes documentation of the quality aspects of pharmaceutical products. Although efficacy and safety are the main criteria for granting marketing authorization, clinical studies are generally not sufficient to guarantee the safety of a new drug thus the need for post marketing surveillance or pharmacoepidemiological studies during and after sufficient exposure to the drug(s) in medical practice.

There are different approaches to drug development, including an approach considered to be a label driven development plan. This is an approach where a target profile of the compound is defined, which follows a format of a package insert with indication, patient population, usage, safety, dosage and administration.

There are different stages to drug development including preclinical, clinical and post-marketing trials (phase IV). Clinical trials, in their progression, include phase I (safety with a few volunteers), phase II (safety and dose confirmation with a larger number of volunteers) and phase III (safety and efficacy with large numbers of volunteers) trials. Phase IV (confirmation of safety and efficacy in large numbers) is for post marketing surveillance and is initiated by the pharmaceutical company or it can be investigator driven studies.

Clinical Trials in developing Countries:

There has been an upsurge in the number of Clinical trials in developing countries. Reasons why sponsors have expanded into uncharted territory include:

- Accessibility of human subjects
- Ease of recruitment
- Population without previous access to treatment (Naïve patients).
- Low cost
- Ease of study approval.
- Some countries require local clinical trial data for product registration e.g. Brazil, China, Nigeria, Philippines etc.

Different models have been proposed to review the clinical trial approaches. The traditional model of clinical development is currently a subject of debate, from a public, commercial, scientific and regulatory point of view. There are emerging trends about the current regulatory models for assessing safety and efficacy of biotechnology products, whereby critiques discount the approach of using animal models and extrapolating safety data to humans. There are also proponents who call for increased new studies. A case is made in the EU study (priority medicines for Europe and the world that every aspect of the regulatory process should be re-examined and that evidence-based regulatory practices should be critically analyzed using modern methodologies e.g. The submission of data from alternative randomized trials, a change in approach from the "pre-clinical rituals", historical controls, and alternative analytical statistical techniques using Bayesian statistics is one school of thought that has been advocated. The authors argue that most of the tools used for toxicology and human safety testing are decades old and fail to predict the specific safety problems, other authors argue strongly against vivisection and the use of animal models. It is important that these issues be explored further and the economy of resources that are normally dedicated to these
studies be assessed. There may be limitations on the strength of the evidence that have been raised in several publications.

**Clinical trials and the current regulatory frameworks in developing countries**

Requirements for the conduct of clinical trials have evolved quite significantly both in and outside the EU. According to Richard Kingham, reports of clinical trials conducted outside US could not in the past be submitted to fulfill even the most basic requirements for the US marketing authorization process. This improved with the signing of memoranda of understanding between the US and EU. The picture is different in regulatory settings of developing countries in that very few regulatory authorities have set requirements for approval of clinical trials. Some regulatory agencies do not have the capacity to approve clinical trials nor have Institutional Review Boards or Ethics Committees. It is a challenge for sponsors of clinical trials in these countries to demonstrate reliability of data and confirm that clinical trials were conducted in accordance with Good Clinical Practice.

**Views of regulators (survey results)**

A significant number of respondents claimed that their countries have the required infrastructure and expertise to conduct clinical trials. The results of our surveys of regulatory agencies in some of the developing countries suggest varying views among these MRAs on the sufficiency of existing levels of expertise and infrastructure for the evaluation of clinical trials. However, in spite of this, many regulatory authorities conceded that they do not have the capacity to regulate clinical research in their countries. Although this may be an incentive for companies who do not want close regulatory scrutiny of their research, it was also recognized as a major deterrent to those who want to use the data to support registration of their products in countries with strong MRAs.

**Views of the Industry (survey results)**

The companies surveyed primarily conduct clinical research in developing countries. Many of the industry respondents surveyed also see these shortcomings as root causes of regulatory problems in developing countries. The majority of participants felt that although developing countries offer many advantages as readily available sites of clinical trial research, the process of gaining approval to conduct clinical research is cumbersome, time-consuming and costly. In some instances it apparently takes so long to enroll patients in one country that by the time the trial starts, enrolment and the trials in the rest of the world have been completed. Many of the problems are due to a lack of expertise and infrastructure in most developing countries.

Survey results also suggest most regulatory and industry respondents to believe that the approval processes in developing countries are cumbersome, time-consuming and costly. However, it appears from the responses that lack of support for clinical trials is not viewed as a disincentive in most of these countries.

Overall, the views regarding the opportunities offered by developing countries for clinical development are partially countered by the reality regarding the lack of expertise and regulatory infrastructure.
Ethics in Clinical Trials in Resource-Limited Countries

This perhaps remains the most controversial or contentious area in the debate on how best to conduct clinical trials in developing countries. Several questions come to mind in addressing this issue:

- Should the differences in healthcare needs, infrastructure and financing justify different ethical standards in the resource-limited countries?
- Should ethical standards differ or be modified in order to accommodate local beliefs, customs, socioeconomic and the level of sophistication of the health system?
- What should be the minimum acceptable standard?
- Does the non-existence or inadequate independent ethics Committee or Investigation Review Boards (IRB) affect Research and Development (R&D) in developing countries?

While these questions are still under review and debate, it is a known fact that the numbers of clinical trials in developing countries have also increased tremendously over the last decade. Concerns have been voiced that vulnerable populations are being exploited for benefits that accrue to people elsewhere. The dilemma is how to protect against exploitation without unduly constraining much-needed health research that could, in fact, benefit vulnerable populations.

It is equally disturbing to note from a recent survey of more than 200 health researchers that a quarter of clinical trials conducted in developing countries do not undergo ethical review. This was a survey that was commissioned by the former US Bioethics Advisory commission (journal of medical Ethics 2004). As recently as 2004, C. Gulhati, editor of an independent Pharmaceutical journal reported more than 400 women in India who were enrolled on Letrozole (an anti-cancer drug) in a study to evaluate letrozole for induction of ovulation were not aware nor did they consent.

Ethics and International Requirements.

The ICH defines the role of an Independent Ethics Committee (IEC) in some settings referred to as Institutional Review Board (IRB) to be: to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial among other things, reviewing, approving and providing continuing review of trials, to be used in obtaining and documenting informed consent of trial subjects. The adaptation or adoption of ICH guidelines by non-member countries, particularly resource-poor countries faces a lot of challenges since the views, priorities and needs of these countries have not been fully taken into consideration. The variability of financial and human resources, infrastructure and political will in the resource-poor countries further complicates the implementation of ICH guidelines.

The FDA regulation previously required that studies submitted to the FDA must have been conducted in a manner consistent either with the declaration of Helsinki or any local laws, whichever is more protective for patients. FDA’s current proposal however now requires that submitted studies only be consistent with GCP guidelines of the ICH. Conducting clinical research in developing countries presents challenges that make compliance with the ICH-GCP guideline difficult. These challenges include differences in language, medical practice, culture, infrastructure and resources.

Several international organizations such as the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) and its sub-group Pan-African Bioethics Initiative (PABIN) are currently reviewing the ethical environment for clinical trials in the developing countries. A program called, Networking for Ethics on Biomedical Research in Africa (NEBRA) was created January 2005 to understand ethical issues arising in individual African countries and to identify people already involved in reviewing ethics of research and identify their needs.
The Changing Approach of Industry

Several scandals and public enquiries on some clinical trials in resource-limited countries have forced some pharmaceutical industries and other biotechnology research organizations to review their stand on pertinent ethical issues. There is the zeal to ensure that all trials conducted during drug development will stand the scrutiny by both national and trans-national health authorities. Three major pharmaceutical companies have addressed the issue of the Ethics of conducting clinical trials in developing countries as follows:

Pfizer: in order to ensure that appropriate ethical standards are observed, a qualified Independent Ethics Committee or IRB must review all company-sponsored studies. If a study is being conducted in a country that lacks adequate human subject protection/IEC/IRB infrastructure, the study should undergo ethical review in both the host and Pfizer sponsoring country (i.e. US, UK, Japan), where possible. Review in the sponsoring country shall be obtained through IEC or IRB that has an understanding of the ethical and medical practices in the host country. This review in the sponsoring country will evaluate the actual protocol and clinical trial design and informed consent, but may not have an oversight function on the monitoring of the clinical trial.

Roche: there are no geographic distinctions in the design or ethical standards of its clinical trials, regardless of whether they are conducted in the developing countries or developed countries. The ICH GCP guideline is applied internationally in all Roche trials and is augmented by each country's specific legal requirements. Thus, all patients are protected by independent ethics committees and informed consent requirements regardless of geographic location. It should also be noted that many Roche trials are multi-centre and also multi-national projects. The same protocols and the same standards are used throughout the study and at all locations, thus ensuring uniform levels of compliance and patient protection.

GlaxoSmithKline: they always seek formal approval for trials in the developing countries from local ethics committees and health authorities. The composition and organization of these committees may vary; however GSK ensures that they are all composed in line with regulatory requirements. Due to inadequate capacity in some countries, the sponsoring countries do ethical reviews. GSK is working with local regulators and sponsors to develop local capacity in ethical reviews. GSK is equally working with the WHO to develop capacity for ethical review worldwide.

Approaches to building capacity in ethics review

According to the Nuffield Council on Bioethics, difficulties in ethical review in developing countries may arise where ethical committees are in place, members may lack the training and resources to assess the ethical acceptability of the research protocol. Misunderstandings can occur when those in the country or countries sponsoring, designing and conducting the research are unfamiliar with the cultural traditions in the host country. For instance, a woman might be required to seek permission from her husband before agreeing to take part in a trial. Equally, in some societies, taking sample of blood or hair is taboo. These and several socio-cultural differences demonstrate that the universal application of the ICH guidelines or approval of a clinical trial by an ethics committee in a sponsor country may fall short of the necessary ethical considerations. To ensure that the activities of the investigators are guided by a sense of beneficence, assessing risks and potential benefits to individuals and the society, a proper informed consent process and the exercise of justice and fairness, local ethics committees must be involved. The lack of capacity and consensus on the ethical approach for conducting clinical trials in developing countries has left a void and room for manipulation:

- Some pharmaceutical industries, biotechnology companies and governments take advantage of nonexistent or inadequate ethics review processes and prey on vulnerable populations.
- Some organizations with higher moral standards and obligations use the ICH-guidelines or ethics committee from the sponsor country.
• Others proactively build capacity setting up and training of ethics committee members) that will subsequently be used for approval of their protocols (possibility of bias by such a committee has been invoked)

• Lack of clarity, has hampered several other research companies from conducting clinical trials in developing countries.

• Capacity building in developing countries in all areas of clinical research will be a sustainable approach to developing a high standard of clinical research culture in the respective countries. 

International organizations, such as WHO, SIDCER, PABIN and NEBRA must develop a consensus document to tailor the ICH guidelines to developing country setting taking into consideration issues such as post-study medication to trial subjects, availability and affordability of trial medication to the community or country, informed consent and training of ethics committee members.  

The following need to be addressed in resource-poor countries in the area of ethics in order to properly adapt and adopt the ICH guidelines: 

• Formation of a National Ethics committee or regional and/or institutional IEC where feasible.

• Ensure that the IEC is truly Independent and competent.

• The right composition (proper representation).

• Understand the functions and operations of the IEC

• Understand the legal requirements for the protection of subjects.

• Protection of vulnerable populations

• Continuous monitoring of ongoing studies

• Ensure adequate funding for the smooth running of the IEC

• Training of IEC members

• Continuous review of biases and conflicts of IEC members.

**Clinical trials and the clinical research organizations (outsourcing and associated problems)**

There has been a rapid growth in the use of Contract Research Organizations, (these are private firms that conduct clinical trials on behalf of pharmaceutical companies, through the use of network of doctors (with 25% of R&D going to CROs), who perform almost 50% of clinical development activities. The main reasons for the use of CROs are to reduce overhead costs and speed up development. M Angell argues that CROs concentrate particularly on Phase IV studies, and these studies have been considered as the fastest growing segment of clinical spending with little added value. 

More than 1000 CRO exist worldwide and the number is said to be growing and of which only 100 are estimated to be operating regionally e.g. either in one continent or several countries. These CROs differ in size, capability and capacity, scope, profile as well as geographical distribution in relation to their research activities in specific regions or territories.

There are CROs that offer a full range of services, across the entire area of pharmaceutical development, S Wolfgang argues that even though many CROs claim to offer a full service, in reality they do not. The services range from clinical, pharmaceutical process design, development, manufacturing and production issues. A few others offer services in the clinical area, e.g. conduct of clinical trials but some with no analysis of samples. The remaining are more specialized, offering services in specific therapeutic areas, specific methodologies or application of certain software technologies (e.g. Electronic trial management applications) or only a particular phase of clinical trials.
The skills and capacity of CROs have been raised as a key concern. The majority of CROs in developing countries are offices that may not necessarily carry out certain services, skilled staff may be located in one country or continent while the services may be required elsewhere. Skilled staff may not be available for a range of services and for all therapeutic areas. Wolfgang identifies the weaknesses of today's CRO market\(^\text{16}\). The transparency seems to be an issue as most CROs do not prefer this as it is detrimental to their business.

**Clinical Trials: A regulatory model for resource-limited settings**

There has been a considerable increase in the number of clinical trials in developing countries but still very disproportionate to the burden of disease, improvement of the healthcare infrastructure, capacity building and benefit to the communities and countries.

The question remains: what regulatory model for clinical trials can be used to stimulate R&D, build capacity, transfer skills and technology, improve the healthcare infrastructure and ensure a mutually beneficial outcome for the study sponsors/researchers and the communities and countries of research?

Infectious diseases, tropical diseases, maternal and childhood diseases and malnutrition have been the major areas of morbidity and mortality in developing countries. There has been more discussion on the inadequacy of clinical trials in this area than actual innovative intervention measures to slow down or halt the morbidity and mortality. At the same time, the chronic diseases becoming a problem. This poses a new challenge of emerging epidemics of non-communicable diseases and injuries that not very long ago were the "privilege" of affluent societies. Now heart disease, mental illnesses, strokes, and chronic respiratory diseases are fast emerging in low-income countries as the economic level rises and traditional life styles are replaced by riskier ways of life.

Clinical trials constitute a prerequisite for the development of new and improved therapeutic tools in medicine. It is therefore of utmost importance that such trials be designed to fulfill high scientific and ethical standards and also be meticulously conducted, recorded, terminated, and reported according to pre-established criteria detailed in the study protocol. Several incidents of scientific misconduct have caused widespread concern within the medical community and among involved authorities and have spurred the development of rules for the conduct of clinical trials. The reason for scientific misconduct can be factors such as pressure to publish in order to get funding, personal ambition, vanity, or direct financial gain. There are three broad approaches to prevent scientific fraud and misconduct: education, training, and the establishment of ethical standards. Additionally, adherence to the principles of Good Clinical Practice (GCP) would constitute added insurance that fraudulent or negligent clinical findings do not lead to ineffective or harmful medical products.

**What is the profile of clinical trials in Sub-Saharan Africa**

Isaakidis and colleagues could identify only 1179 eligible randomized controlled trials conducted in sub-Saharan Africa over the past 50 years. A total of 795 trials (67.4\%) focused on treatment rather than prevention. The median sample size was 90 (interquartile range 42-238). Only 535 trials had over 100 participants; 154 trials had over 500 participants; and 79

\(^{16}\) Applied Clinical Trials magazine Vol 12 No 4 April 2003
trials had over 1000. Almost half of the trials had been done in South Africa (n=565). Four other countries accounted for another quarter (Nigeria=98, Kenya=89, Gambia=56, Tanzania=50). Only 19 countries had more than one trial per million population. South Africa accounted for over 90% of all trials on malignant, respiratory (31/33), digestive (69/76), musculoskeletal (27/27), and congenital (2/2) diseases and 75-90% of trials on diabetes (10/13), endocrine (9/10), cardiovascular (75/99), and genitourinary (29/34) diseases and injuries (26/31), but for only 14% of trials on infectious and parasitic diseases (74/150). However, in considering these statistics, it must be remembered that the absence of national directories of research activities in most Africa and other developing countries make the magnitude of research to be underestimated.

**Who is sponsoring/conducting Clinical trials in the developing countries?**

According to an FDA report, the number of foreign clinical investigators conducting drug research in other countries under Investigational New Drug (IND) Applications increased 16-fold in the past decade, from 271 in 1990 to 4,458 in 1999. FDA inspections of foreign clinical investigators conducting drug research outside the US have tripled, from just 22 in 1990 to 64 in 1999. The number of countries in which drug research tracked by the FDA is conducted increased from 28 in 1990 to 79 in 1999. Among the countries that have experienced the largest growth in clinical investigators are Russia and countries in Eastern Europe and Latin America.

In a survey conducted in Kenya, Thirty-four percent (34%) of sponsorship for clinical studies comes from international aid, 37% from research funding agencies, 10% from universities (local and foreign), and 13% local and multinational pharmaceutical companies.

In Nigeria, five categories of research and researchers are easily identifiable. Individual or institution-supported research is done by students, clinicians (including resident doctors) and other scientists. This category constitutes a significant proportion of research in tertiary academic and health institutions. Industry-sponsored research is undertaken by researchers for pharmaceutical companies to promote new or old drugs. Such research protocol may be indigenously developed or be a part of multi-centre trials with other countries. Collaborative research with colleagues from the developed countries is often externally funded. It includes hospital and community-based trials and mostly involves experimenting with drugs or vaccines. Of particular ethical concern in collaborative research is the fact that external sponsors may differ in their motives for conducting research and there may be limited applicability of research benefits to the country or local community. Another category of research is that which occurs through indigenous government-funded agencies. An example of such an agency is the National Institute for Medical Research, which has been carrying out research in Nigeria for more than thirty years on parasitic, infective and non-infective diseases. Non-Governmental Organizations (NGOs) are also involved to variable extents in both clinic and community-based research.

**What Challenges do the sponsors face in developing countries?**

Lack of technical capacity and the absence of a viable economic level to provide the needed infrastructure and to support the industry are some of the more commonly cited obstacles to drug development. Because of these obstacles and other perceived deterrents, drug companies do not sponsor clinical trials in developing countries proportionately with the burden of disease. Although patients with diseases may be readily available, patient recruitment in some areas remains a challenge. Recruitment procedures are, in general, similar to those of a typical clinical trial elsewhere; however, significant differences occur in how informed consent is obtained in the rural areas where the literacy level is lower than elsewhere. Some of the problems encountered in recruitment include illiteracy, inadequate transportation, differing cultural backgrounds and taboos, fear of adverse events, and uncertainty about confidentiality. In these places, prior to recruitment and study commencement, investigators may need to initiate intensive awareness programs in local languages through local administration and community outreach, for example, churches, adult literacy groups, and women's groups.
Problems confronting clinical trials

A conference focusing on addressing the future of clinical research in the changing environment was convened in the US. The recommendation was to organize a national summit of key stakeholders in the domain of clinical research and as a result in 1998 a Clinical Research Summit was held at Graylyn, USA. It identified some problems that confront the clinical research enterprises and also developed a set of goals that were fully described in the Report of the Graylyn Consensus Development Conference (1998). The summit's final report, "Clinical Research: A National Call to Action (USA-November 1999)", identified the core problems and made recommendations to solve these problems.

The following core problems were identified:

• Lack of clear definition of clinical research;
• Clinical research not being adequately understood or valued;
• Lack of data on clinical research funding and productivity;
• Insufficient funding for the conduct of some types of clinical research;
• Insufficient numbers of clinical investigators;
• Insufficient emphasis on incorporating research findings into clinical practice;
• Inadequate coordination of clinical research among research entities and disciplines
• Lack of comprehensive, dynamic and clinical research agenda.

These core problems are not only relevant to the US but are more peculiar in developing countries.

Considerations for Optimizing Clinical Research

Following are considerations related to problems and inefficiencies in the purpose, design, approval and conduct of clinical trials.

• Clinical research should be promoted and supported by the EU and EU Member States. Investment in infrastructure including training and creating posts for suitably qualified staff should be a priority.

• Alternatives to randomized controlled trials should be investigated. This requires an experimental approach with formal comparisons of the results of studies comparing novel and traditional (RCT) designs. 16 They include various designs, including decision based and risk-based designs, observational studies, including historical controlled trials that confirm or refute the circumstances under which they might be useful.47, 48 In this regard, historical controls might be used to good effect in phase III trials since one can create a large number of prospectively collected historical controls that follow the natural history of clinically important diseases.

• It is possible to merge clinical phases. Indeed, once multiple dosing in phase I healthy volunteer’s starts, there is no reason not to go directly into perhaps 20-30 patients and merge this with a phase II trial.

• As suggested by the Centre for medicines Research International (CMR International), where data is sufficiently robust at the end of Phase II a probationary approval for marketing should be possible, with conditions attached to early marketing. These conditions would include studies to confirm efficacy, test the safety hypothesis and risk management programme proposed at the end of phase II. This they state would not be a large phase II trial, but a study in real life conditions. This model is proposed to apply primarily to medicines addressing unmet medical needs, and would entail a change in approach from the way data is managed and analyzed to creation of a data warehouse, that would be accessed by regulators and industry. This would enhance the harmonization agenda.
• To improve drug safety, phase III trial requirements could be altered to clearly demonstrate efficacy and phase IV monitoring be expanded to include active case detection (numerator) as well as reporting of all drugs dispensed (denominator).

• Bayesian analytical approaches should be considered as, in principle, they can allow clinical trials to be terminated sooner.\(^{17}\) Certainly it is possible to retrospectively analyze clinical trials using Bayesian and “frequentist” approaches. Its flexibility makes the Bayesian approach ideal for analyzing data from clinical trials.\(^{49}\) In carrying out a Bayesian analysis for inferring treatment effect, information from the clinical trial and other sources can be combined and used explicitly in drawing conclusions. The ability to calculate predictive probabilities for future observations is a distinct advantage of the Bayesian approach to designing clinical trials and other decisions.

• Increased use of biomarkers and surrogate clinical end points to improve “translational” research (e.g., new scanning methods, micro-array assay technologies and high throughput screening).

• Review current technology opportunities and use of biomarkers/surrogate end-points in marketing authorization applications with a view to encouraging the use of bio-markers of drug effect (e.g. in dose ranging studies) or surrogate end-points likely to be predictive of clinical benefit.

• Improving communication between the industry, physicians and regulators during drug development would help to reduce requests for additional data and regulatory questions following submission. This could increase predictability of outcomes for marketing authorization applications. Industry should interact with payers at early stages in the development process in order to provide industry with sufficient information to know that payers would be looking for in order to reimburse a medicine.

• Continue to improve regulatory procedures in Europe, including piloting new processes to speed up the system (e.g., rolling submissions, accelerated assessment for innovative products).

• Increase the dialogue between patients and regulators. Patients have a different assessment of the risks and benefits of medicines, especially for products that are going to be released conditionally.

\(^{17}\) A definition of Bayesian methods in the present context might be: the explicit quantitative use of external evidence (prior judgments), in the design, monitoring, analysis, interpretation, and reporting of a health technology assessment. Bayes's theorem is a formula that shows how existing beliefs, formally expressed as probability distributions, are modified by new information. For instance, in diagnostic testing, the evaluation of a diagnostic test requires the prevalence of the disease to be specified, and a Bayesian analyst will specify a probability distribution expressing the relative plausibility for this unknown quantity, before taking into account any evidence from a study. This “prior” distribution can then be combined with actual evidence from the study.
Approaches for an acceptable clinical trial model

There are few areas of science that cross as many boundaries as does clinical research. Therefore, expanding clinical research cannot succeed without the wholehearted support of academia, industry, regulators and civil society. It is vital to develop robust mechanisms for co-operation between these stakeholders.

WHO-sponsored study recommendations

A WHO study on “Priority Medicines for Europe and the World – A public health approach to innovation” commissioned by the Dutch Government as President of the European Union (2nd Semester 2004), showed that on one hand, R&D investments per new molecule are becoming exorbitant. On the other, the willingness to pay a fair price for new medicines, particularly in Europe, is rapidly decreasing. Arguably, both trends could be altered through changes in the policy and regulatory framework that constitutes the operating environment of pharmaceutical industry. Additional data is often requested after a marketing application has been submitted. For example, in the past six years (1998-2003) 73 percent of drug approvals by the US FDA involved some form of post-marketing commitment by the company, compared with 25 percent in the period 1970-84. This group also recommended increased dialogue with drug regulators during the clinical trial process and prior to registration and the need to involve other stakeholders such as patients in the regulatory review process in order to accommodate their view on the risk they are prepared to take. Furthermore, the EMEAs ‘road map to 2010’ proposes establishing ‘centres of excellence’ in scientific assessment in a set number of national agencies, coordinated by the EMEA. If implemented, some important benefits could proceed from this model if there was early appointment of Rapporteur and assessment agency to allow the company to maintain ongoing dialogue with the assessment team during development. The study group also suggested that Evaluation of the long term and real life benefits and risks of medicines after launch should use information from randomized clinical trials and from observational/epidemiological studies that use electronic patient-level data (e.g. data from medical records). It is therefore important that databases containing this information are developed and these resources made available for academic and industry research.

The group also put forth the following proposal to address potential barriers to innovation:

- Member States should be encouraged to promote and support clinical research – for example, the UK government has recently announced an increase in public funding for clinical research.
- Patients need to be educated about the benefits of participating in research.
- More clinical scientists should be trained and posts created for them to fill once trained. Career structures also need to be developed.
- Investment needs to take place to ensure adequate infrastructure within hospitals and universities is in place to conduct clinical research.
- Increased public funding should be provided to develop academic expertise in biomarker and surrogate end point technologies. If the WHO Priority Medicines Report leads to more public funding being used for this type of research, in the diseases identified to be priorities, this could make a real impact.

Netherlands African Partnership for Capacity Development and Clinical Interventions against Poverty Related Diseases model

The Netherlands African Partnership for Capacity Development and Clinical Interventions against Poverty Related Diseases (NACCAP) was developed as a new national programme. Although governed nationally, NACCAP has been designed to make a direct contribution to the EDCTP Joint Programme, in close cooperation with the EDCTP bodies. NACCAP especially aims at strengthening the position of African R&D centres in the EDCTP activities by making an early start with investing in joint African – European R&D and capacity building
activities in Africa. The active participation by the Pharmaceutical industry in public-private partnerships is certainly encouraged. The NACCAP objectives are twofold:

- Development of African owned, internationally recognized research centres capable of conducting clinical trials for clinical interventions against HIV/AIDS, malaria and tuberculosis
- Clinical testing of promising candidate interventions against HIV/AIDS, malaria and/or tuberculosis in Africa, taking into account the needs and interests to the African stakeholders.

According to Esparza of the WHO Vacinology group, "What is really needed is to develop and coordinate African trial sites. Such a site would have a population with the appropriate epidemiology of the disease being studied. "Then you need scientific infrastructure, political support and community support in the region. The concept of a 'site' is "something that is evolving" says Esparza. "In the past a site was where foreign investigators could come to a country and do research to take their samples back home and publish a paper. That concept has gone. The sites we're talking about, that EDCTP wants to develop, are ones with ownership in the country, as that's the only way to ensure continuity, and the appropriate investment of time and resources.

**India Forum for GCP model**

The India Forum for GCP (Info-GCP) was launched recently. Info-GCP plans to take a lead to develop such linkages to facilitate growth of clinical research in India.

The main objectives of this new initiative include:

- Facilitating a discussion of ethical and GCP related issues.
- Offer a platform to update guidelines and working practices for the purpose of improving clinical research standards.
- Create and spread awareness of ethical principles in research and promote efforts towards its integration in GCP while conducting such research.
- Stimulate a closer relationship and improve understanding between key stakeholders of clinical research field, and also individual members of the Forum while sharing best practices.
- Foster the development of clinical research professionals through various means including training and continuing education programs in biomedical research and related areas, promote the development of Indian guidelines/directives based on these discussions and interactions, and share updates on new legislations/guidelines to key stakeholders in clinical research.
- Provide a national platform for all key stakeholders in clinical research by dealing with matters brought to its attention by the members.

**European & Developing Countries Clinical Trials Partnership model**

The European Parliament and Council have formed European & Developing Countries Clinical Trials Partnership (EDCTP) in response to the combined political will and health priorities of both the developing and developed world. Its objective was to contribute to the development of new and affordable therapeutics and prophylactics for HIV/AIDS, tuberculosis and malaria. Initially, EDCTP will focus on the countries most severely afflicted, primarily Sub-Saharan Africa. The EDCTP comprises 14 EU member states plus Norway and is funded by the European Union to promote a more integrated approach to health research amongst European countries. The EDCTP is about partnership, pursuing a common platform to optimize synergies. It is also forming strategic alliances with like-minded organizations in the public and private sector towards achieving common goals. It is poised to provide a platform for the conduct of large-scale clinical trials and the development of the required capacities in developing countries. Furthermore, it aims at improving synergies of, and collaboration amongst, national and international research programs.
EDCTP believes that their clinical trials in host countries must be relevant to these countries' health needs. For example, they work with the African Center for Clinical Trials, a nonprofit organization of African researchers working to attract foreign research.

The present capacity for conducting clinical trials is, however, insufficient or even nonexistent in virtually all countries in sub-Saharan Africa. Strengthening the R&D capacity in developing countries by investing in African owned health research centres capable of conducting clinical trials has thus been identified as an international priority to improve public health and, indirectly, development. Efforts should be focused on the establishment and strengthening of locally controlled and managed research centres able to pursue their own priorities and R&D agenda. The existence of internationally recognized institutes will also strengthen the position of African R&D priorities in international initiatives, and increases the ability to influence cash flows. Eventually, a strong and equal position in international partnerships will offer the best opportunities for a focus on local needs and interests. In this case, the aim for equal partnership requires the ability to provide balanced input in all aspects of the joint action, including scientific input at international level and the ability to attract co-funding. At present, far too few research centres in Africa are in this position, precluding true equal partnership.

**Recommendations**

Developing countries face the challenge of being in various regions of the world at various levels of economic development, socioeconomic, health care infrastructure, particularly research capability and drug regulation, governance and government structures. Individual countries of the regions also differ; however, there are more similarities than are differences between countries of the same region.

A regional approach such as the activities of EFPIA and EMEA for European countries will strengthen R&D and regulatory matters. This will require the following:

- For purposes of proper management, large regions such as Africa could be subdivided into its sub regions e.g. Ecowas, SADC etc. with the goal of feeding into AU model similar to the EU in the near future.
- This advocates for harmonization of R&D and drug regulation activities for each sub-region and establishment of centres of excellence.
- Partnerships such as that of EDCTP and NACCAP should be with the regional centres rather than individual countries.
- There should be emphasis on gathering pharmacoepidemiolgical data on recently approved drugs (such as now seen with the FDA and proposed by EFPIA). This will avoid delays and may account for country differences if any.
- Capacity building in the areas of medical bioethics and drug regulation should be part of science training and school curriculum.
- Capacity building and efforts to retain researchers in those regions should be part of its mandate.
- Develop and tailor ethics and informed consent issues to the needs, culture and beliefs of the region.
- Harmonize the various groups that are undertaking the task of training in the area of ethics and developing IECs and IRBs.
- Embark on on-going patient and community education in the region about clinical trials.
- Involve patients’ views in the drug regulatory process such as suggested by EFPIA.
- Adaptation and adoption of ICH guidelines.
CHAPTER 6: INTELLECTUAL PROPERTY RIGHTS

The condition for registering pharmaceutical products requires the submission of data relating to quality, efficacy and safety and its physical and chemical characteristics. In some jurisdiction, data submitted for registration are subject to protection, based on temporary rights to exclusive use of data by the first applicant. In other countries, this is not the case, authorities are permitted to rely on data submitted by the first applicant to process and approve third party's subsequent application for a similar product. (WHO, South Centre)

The US has a system of granting patents through the US Patent and Trademark Office (USPTO) and granting exclusive marketing rights through the FDA. The exclusivity granted by the FDA is different from patents, in that, it is granted at the time a drug is approved for marketing which may be later than when the patent was first granted by USPTO. During this period, no approval of the same drug made by a different applicant may be granted, this is a means of protecting clinical trial data. Companies are supposed to list relevant patents with the FDA in a publication referred to as the Orange Book.

As a means to stimulate generic industry, a law was passed referred to as Hatch-Waxman, this also provided for mechanisms for additional exclusivity for brand name products to make up for the long development times and regulatory approval time. The law introduced measures that simplified the approval of generic medicines. There are reports highlighting problems with the implementation of this law and some of the provisions, these include delays in approval of generic medicines, which may be over and above patent period, additional exclusivities that have been identified. The Federal Trade Commission identified the widespread anticompetitive activities within the pharmaceutical industry and the challenges faced by the FDA in enforcing legal restrictions on the listing of patents in the Orange Book. The challenges, included lack of resources and expertise to check on the Orange Book listing. Following this and public reaction, there were legislative reforms.

In the EU data protection for mutual recognition procedure and centralized procedure applies. Subsequent applicants can submit once the original product is authorised for eight years. If it is about new indications that promise significant benefit over existing therapies, then 10 years plus one are a requirement. The most interesting development is the submission of appropriate scientific literature for products with well established medicinal use instead of submission of trial and test results. This new directive has a potential for early generic entry where there are public health priorities especially for diseases considered a high burden, where there are no available therapies.

There has been increasing requests for countries to have requirements to confer exclusive rights on originators of marketing approval data, some of these may be in the following manner:

1. A proposal to extend the term of a patent in exchange for “early registration of generics”.

2. A proposal that forces drug regulatory authorities to notify the patent owner of the identity of any company that is seeking approval to market a generic version of the patented invention while the patent is in effect.

3. A proposal to allow the sponsor company to have five years of exclusive rights over clinical data supplied to the drug regulatory authorities for the purposes of obtaining market authorization. (Cohen 2002)

The developing countries have different priorities, the first being to have a functioning regulatory system. The priority of developing countries is to facilitate access to priority medicines and to protect the public from unsafe and poor quality medicines. The majority of developing countries use generic medicines. Some countries do not have capacity to evaluate clinical data and the results of the survey reveal this to be a major challenge. For priority health problems, the approval of generics may be granted, with provisions for voluntary
or compulsory licensing for purposes of marketing. The recent experience has been that of Aspen Pharmaceuticals for which marketing authorization has been issued and voluntary license by a competent authority. The exclusive marketing rights do not apply, as there are provisions for early working in the patent law.
CHAPTER 7: CONCLUSIONS AND RECOMMENDATIONS

In terms of the strategic context within which industry makes its decisions (figure 1 in Introduction), medical need, scientific opportunity, market assessment/regulatory environment and available/required resources are key.

The strategy proposed in this document focuses on: harmonization, clinical trials and the use of new technologies and interventions for treatment of DDDC.

Operational, managerial and administrative issues identified in the surveys require attention by regulators. Equally, shortcomings that currently exist in the regulatory systems must be improved.

The regulatory framework proposed must address regulatory concerns of strategic importance. These involve strategic issues such as infrastructure, technical and regulatory capacity as well as technology transfer. The approaches outlined below (figure 5) could address these issues of strategic importance:

Figure 5: The proposed framework on how innovation can be encouraged

The global landscape of pharmaceutical regulation and some of the regulatory concerns can be addressed within some of the proposed harmonization models. The vaccine experience and lessons from some of the initiatives is a good framework that aligns various elements and integrates them together in a coherent form.

The study attempted to determine if constraints to the efficient regulation of medicines and vaccines exist in developing countries, and if so, whether these constraints contribute to the lack of investment by innovator companies in research of diseases that are prevalent in the developing world. The findings support the contention that most, if not all, MRAs conduct their operations with limited resources at their disposal, both in terms of required infrastructure and human resources with the necessary expertise. Mechanisms that would enhance the efficiency of the regulatory review process are suggested and one such mechanism is harmonization of their regulatory requirements at a sub regional, regional and/or international level. Sub-regional harmonization of regulatory functions of countries with similar disease profiles should be encouraged because it would address the faster market access that are of strategic significance for industry. This must translate into increased access to safe, effective and quality medicines needed for the treatment of DDDC at affordable prices.
The achievement of harmonization of regulatory requirements by a group of neighboring countries within a region should in principle, therefore, be coordinated and supported by global initiatives through twinning arrangements and direct support and streamlining each country's already closely-related requirements. The WHO Prequalification of medicines for three priority diseases HIV/AIDS, Malaria, Tuberculosis, has created opportunities and means for the industries in developing countries to strengthen their capacities. The EU role in preparing scientific opinions can be considered as another available international arrangement with a resource pool of experts.

In an effort to overcome the challenges and obstacles identified in the survey, mechanisms to facilitate communication whilst maintaining integrity should be explored. This will require commitment on the part of the regulators and pharmaceutical industry. Appropriate structure and advisory bodies as well as technical working groups must be established.

The greatest challenge is the practical implementation of the guidelines, (for regional or sub regional harmonization efforts) the creation of a sustainable structure that is fully funded for the implementation of the guidelines, formalization of harmonization

The experience of the Gulf region and their approval processes could be used to address this challenge through joint assessments and decision making as well as means by which they exchange information. Any or all of these components could be adopted by a sub-region, based on the political, economic, social settings.

Clinical trials play a pivotal role in the overall R&D continuum. They constitute the major component of the so-called “critical path”, i.e., the part of the R&D process, which begins when candidate products are selected for development, and includes pre-clinical and clinical studies. Developing countries offer many advantages as sites for clinical trials. However, the required infrastructure and expertise to conduct clinical trials is lacking.

It is of importance that trials meet scientific and ethical standards and that they must be meticulously conducted recorded, terminated and reported accordingly based on established criteria in line with good clinical practice standards. The standard of care must be determined based on local conditions and best available practices.

Partnerships with EDCTP and NACCAP should be through the sub-regional, rather than local, initiatives to strengthen harmonization, pool resources and share benefits.

Limited experience with local product development, quality assurance and GMP manufacturing, lack of effective regulatory oversight, and limited resources may complicate the situation in countries where manufacturers are striving to manufacture antiretrovirals or other drugs locally. The experience on technology transfer sets a basis on which capacity of companies with potential can be built. This will largely address areas not addressed in sufficient detail in this paper, which need further work. Process and formulation development may be areas where developing countries with capacity and technical skills can invest. The WHO scientific reports and guidance documents, and training courses as well as meeting materials on GCP and GLP, can be a basis for companies applying to improve their quality.
Specific Recommendations

Most regulatory authorities have fast track policies that are based on public health priorities and these can be good incentives for R&D in DDDCs. However, there are concerns about safety issues and the required strengthening of safety monitoring by MRAs in support of fast track policies. The models outlined below are proposed based on the lessons learnt from global regulatory arrangements and vaccine initiatives.

Sub-regional harmonization of regulatory functions of countries with similar disease profiles should be encouraged because it would address the medical need, scientific opportunity and faster market access that are of strategic significance for industry.

Part 1. Vaccines and Biologicals:

Experiences of vaccine initiatives and some of their activities have created an enabling environment that would lead to local capacities that will ultimately contribute to accelerated access to vaccines. Overall, these experiences and efforts can be classified as follows:

1. Stimulating/initiating collaboration between various developing countries regulators on various regulatory activities, employing internationally accepted guidelines adapted to suit local needs/circumstances (DCVR). Organizing joint assessments between regulators through sub-regional approaches. For more complex applications e.g. biotechnology products have twinning arrangements with well-established regulatory authorities or the scientific opinion of the EU.

2. Stimulating/initiating collaboration between manufacturers in various developing countries on technological activities (DCVMN) and facilitating partnerships between the industries in developing and developed countries particularly for biotechnology products.

3. Capacity building and training to develop the R&D infrastructure and regulatory/ethical review capabilities necessary for technology transfer. This could be facilitated by collaboration with one or more industrialised nations and international initiatives, or exploring some of the initiatives in the EU.

4. Establishing standard guidelines for various activities related to vaccine R&D (WHO clinical trial guidelines and training manuals associated with these). These guidelines are available for developing countries to adopt and adapt to local needs and circumstances. At a practical level global training programmes have been developed.

Part 2. Harmonisation:

The regulation of medicines within the global landscape, including recent trends towards international and regional harmonisation of regulatory requirements, have been reviewed and the following are some of the benefits of these initiatives that can be explored further for subregional approaches.

1. Harmonization at the sub-regional level is recommended based on the SADC harmonization initiative and the Gulf Cooperative Council's joint assessments. For example, the AFRO region can be divided into various subregional initiatives. If necessary, some of the countries with reasonable capacities can be used as nucleus (e.g., in the Gulf model the subregional joint assessment utilizes Saudi Arabia as a central hub).

This will reduce regulatory capacity problems, streamline procedures and pool expert knowledge and resources of developing countries with the aim of creating an environment conducive for facilitating approval and market access to industry.

2. The global initiatives can serve as a resource pool, mainly the WHO prequalification project (with slight improvement) e.g. support by the EU scientific opinion. The WHO prequalification can be slightly improved to incorporate elements of the DCVR network, with a representative of each region participating in the prequalification process. The proposal gives special attention to capacity building based on global networks and global initiatives.
3. A twinning arrangement can further be explored between a subregion and a well established or well resourced regulatory authority, which already operate within a harmonized environment; e.g., SADC and USA/Canada/EU or ECOWAS and France/EU.

Part 3. Clinical Trials:

The following should be in place to support the conduct of clinical trials, if new drugs are to be developed for treatment DDDCs:

1. Ethical review capabilities at the country level must be established and strengthened.
2. Adherence to Good Clinical Practice must take into account local conditions in determining standards of care without compromising scientific principles.
3. Significant investment in infrastructure and technical capacity through creation of centres of excellence at the regional or sub-regional level, several initiatives are referred to in the study
4. Safety monitoring of clinical trials can be strengthened; for example, through the introduction of longer-term safety studies data inclusive of diversified larger patient populations. The challenge for developing countries is resources to do these. Industry can direct resources from phase IV studies considered to be a marketing ploy to more meaningful studies. The following can be further considered for safety monitoring;
   • Requirement of a pro-active pharmacovigilance programme for the registration of any ‘new’ product.
   • A market complaints handling and recall policy should be part of the requirements for compliance with GMP and GDP.
   • Public education campaigns on continuous review of the safety of medicines.
   • Proper evaluation of clinical studies before commencement.
   • Timely publication of cancellation and tighter monitoring of what is on the market
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## ANNEXURES

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<sup>18</sup> No vaccine manufacturers responded to this questionnaire. One vaccine manufacturer instead completed the generic manufacturers questionnaire