



Regulatory

EDCTP consultative meeting

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1. Executive Summary

Clinical trials on medicines, vaccines and devices are increasingly conducted in developing countries, including those with the poorest resources. It is important that such studies should meet the highest international standards of clinical trial practice and ethics review. Researchers, clinical trial sponsors, national regulators, ethics review committees (ERCs) and the public, all share responsibility for achieving this. This meeting was convened by EDCTP and brought together other stakeholders including the WHO, DNDi (Development for Neglected Diseases Initiative), International Partnership for Microbicides (IPM) and others to consider what further needs to be done to promote the necessary standards and to make it possible for them to become routine. EDCTP and others aim to encourage capacity development of regulatory authorities and ERCs. Much has already been done as is reflected in the achievements of the Global Training Network (GTN); the establishment of the African Vaccine Regulators Forum (AVAREF); the strengthening of national regulatory authorities (NRA) conducted in collaboration with WHO

The meeting was in agreement that further efforts should address both work in progress and start up novel approaches. By 2010 it is anticipated that all countries will have sound and robust national regulatory systems, and that investigators and regulators would have developed understanding that will facilitate the process of drug development.

To realise these objectives, mapping of the ongoing activities is necessary. This should go on along with , scenario planning, establishment of a database and sharing of information in a manner that protects intellectual property but does not compromise public health. Moreover, we should also capitalise on the available expertise including that from EMEA, the United States FDA, the Canadian NRA and through south-south collaborations. Efforts in the harmonisation process along the lines of regional economic blocks should also be encouraged. However, these initiatives must go with capacity development at both institutional and individual level.

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EDCTP with WHO, DNDi, IPM and other partners will jointly fund a selected number of the activities identified at the meeting. EDCTP has a particular interest in supporting and promoting the regulatory and ethics review capacities especially in countries where it is most directly involved. EDCTP aims at improving the quality of clinical trials, integrity of data collected, safety of the participants involved and ultimately registration of products in countries that need them most. All the participants share an altruistic interest in seeing the essential elements of drug regulation pertaining to clinical trials being strengthened generally in Africa, and elsewhere, thus serving drug development, especially for poverty related diseases.

Overall objective of the meeting:

A consultative meeting aimed at obtaining recommendations on how best EDCTP can support and further strengthen regulatory capacity in Africa.

Specific objectives of the meeting:

- i. To discuss how best EDCTP should collaborate with WHO and other partners to support regulatory capacity on R&D of vaccines, drugs and devices in Africa
- ii. To prioritise regulatory capacity strengthening activities in Africa that are within the EDCTP scope
- iii. To discuss implementation of these strategies and develop timelines
- iv. Identify potential partner organisations in the implementation of these activities.

2. Summary of background documents, presentations and discussions

The following were the highlights from the background documents and presentations:

- EDCTP seeks to identify and review priority activities and approaches to strengthen the capacity of national medicine regulatory bodies in Africa in order to ensure tangible results over the period 2007-2010.
- The way forward is likely to include on agreeing to a working model or models; identifying and essential needs that are to be met; defining leadership; securing of funding; and measuring and monitoring of outcomes.
- The special needs of the vulnerable should be addressed in this process. This includes the very young, the elderly, pregnant women and patients with other diseases such as renal, cardiac, hepatic impairments etc., with particular reference to safety of the medicines and vaccines concerned. Dedicated public health programmes such as malaria, tuberculosis, HIV/AIDS, other poverty related diseases, national immunisation programmes and family planning should receive attention in this regard.
- The special needs of the least developed countries should be addressed.
- Identification of regional cooperation, notably in networking, information exchange, capacity building and technical assistance towards drug regulatory harmonisation at sub-regional and regional levels.
- The progress was noted in developing a framework for strengthening regulatory systems in Africa, and in building national capacity, for both vaccines and pharmaceuticals other than vaccines. And in establishing the African vaccines regulators forum (AVAREF) and developing further the global training network (GTN) for vaccines.
- Wherever possible, systems should be developed that link vaccines with medicines.

The meeting in its deliberations noted the following:

Pharmacovigilance, drug safety monitoring and evaluation as well as laboratory capability to support regulatory functions in sub-Saharan Africa are weak. In general,

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there is a need to address safety issues. There are special issues pertaining to post marketing surveillance /pharmacovigilance and safety monitoring in general (both pre-registration and post registration) in resource-poor countries

- i. There is a general lack in sharing information between national regulatory authorities. This is aggravated by unnecessary constraints in information exchange imposed by confidentiality issues, some of which are unjustified and obstructive.
- ii. There is a plan at WHO (Department of Immunisation, Vaccines and Biologicals) to ensure that all countries in sub-Saharan Africa are assessed against WHO NRA indicators and are fully competent in the review and regulation of clinical trials by year 2010.
- iii. There is a need to establish centres or networks of excellence to address regulatory training and competence in an ongoing and sustained manner.
- iv. The Global Training Network activities and curricula serve as a model for global and regional training efforts developed and supported by WHO.
- v. The core elements of medicines regulatory support necessary for clinical trials include a set of critical activities at country level; activities for regional collaboration; and identification of global issues.
- vi. Capacity development (of individuals and institutions) needs to support the scientific, clinical and ethics basis of new drug development.
- vii. Traditional medicines are a key, and hitherto neglected, concern for clinical trials. Models should be investigated and tested for standard of care and good practices for the use of traditional medicines, and guidelines developed for evaluation of clinical trials for traditional medicines.

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- viii. It would be helpful to establish a shared network, in a secure environment, to support joint assessment, including the sharing of expert reports.
- ix. There should be greater community participation in clinical trials design and regulatory review, as well as consideration and implementation of the results.
- x. All efforts should be aimed at establishing a critical number of experts and competent persons in countries, and in this way developing sustainable systems.
- xi. It is important that efforts at harmonisation should not undermine special country characteristics and specific country-related needs and individualities (“harmonise but do not make uniform”).
- xii. There is a need for critical and comprehensive assessment (“mapping”) with a focus on identifying what is in place and who are the players. This needs to look into what is working well as well as identify the deficiencies’. This should form a basis of developing a clear work plan and institutional development strategy.
- xiii. DNDi has established several clinical trial platforms aimed at addressing systems for addressing neglected public health issues, reducing delays, clinical research capacity development and putting a premium on post-marketing surveillance.

Discussion summary of EDCTP funding procedure and timelines for initiating funding procedure

Recommended procedure

Outsource implementation of the priority activities to WHO after getting responses from other partners on activities of interest to be supported by them. It was further

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recommended that both departments of Department of Immunization, Vaccines and Biologicals; and Department Technical Cooperation for Essential Drugs and Traditional Medicine (TCM) of WHO should be involved.

Recommended time to initiate funding procedure (s)

Timelines were not discussed in this meeting, but this should be implemented after successful completion of currently funded activities and on agreeing how to proceed, taking into account the needs of other stakeholders.

Possible funding partners:

Pledged and potential contributions to topic			
Organisation	Country	Amount	Certainty
DNDi	Geneva	To be determined	
IPM	RSA/Belgium/ USA	To be determined	
NACCAP	Netherlands	Expressed interest but was unable to attend meeting	

3. Conclusions and recommendations to EDCTP

The following were the main recommendations that arose from the consultative meeting:

- 3.1. To develop a strategic approach that would facilitate regulatory capacity alignment. This would include mapping drawing from the experience of the WHO RNA assessment and should include institutional analysis and scenario planning in order to link up existing capacities with anticipated needs.
- 3.2. To support training and systems development in pharmacovigilance and in drug safety monitoring and evaluation, particularly in resource-poor countries.
- 3.3. To establish joint training and dialogue between research and clinical scientists, professional members of ethics committees, product developers and evaluators who serve in regulatory authorities, to foster mutual understanding and collaboration and to facilitate the decision making process.
- 3.4. To develop self-assessment tools for national regulatory authorities that would encourage and support capacity development. These should include measurement tools of efficiency.
- 3.5. Systems should be developed for situation analysis and mapping of capacity that would address, inter alia, institutional needs, the legal framework for assessment of clinical trials (including ethics issues), core technical issues, individuals with key functions and responsibilities, and bottlenecks. (Note: much of this information already exists; it needs to be consolidated, organised and analysed.)
- 3.6. A data base with internet access (e.g. share point) would encourage and facilitate these activities, particularly sharing of country information and experience, and access to reports including expert reports from EMEA , Canada, United States Food and Drug Administration, etc. It

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- 3.7. should be noted here that such a database already exists but it needs to be expanded to enable ready sharing of information, cross-cutting activities between vaccines and pharmaceuticals other than vaccines, and complementary activities.

4. Annexes

Annex 1: Back ground, list of participants and agenda

EDCTP REGULATORY CONSULTATIVE MEETING

Venue: Room M105 located in M Annexe of WHO Head Quarters, Geneva

11 June 2007

Background:

The need to strengthen the capacity of national medicine regulatory bodies in Africa is immense and critical. Prioritisation is therefore imperative with investment in specifics other than abstract activities. It is essential that all clinical trials conducted in Africa and the registration of new medicinal products is done by competent, knowledgeable and honest authorities. These bodies should comply with scientific and clinical conditions consistent with GMP, GCLP and GCP, to determine the quality, efficacy and safety of new drugs, vaccines and diagnostic devices, in the interests of public health in their respective countries. It is in the interest of EDCTP to support the regulatory environment in the countries where EDCTP supported clinical trials are at present and will in the future be conducted, and where new products ultimately will be registered.

In response to this, in June 2006, EDCTP and WHO signed an 18 months contract agreement to develop the first phase of capacity strengthening for a regulatory framework to ensure appropriate oversight of clinical trials in Africa. These activities are already underway and are expected to be completed in the third quarter of 2007. They are aimed at strengthening expertise to authorise and evaluate clinical trials, conduct ethical review process, ensure that the legal basis of health research is developed, and that these activities are consistent with international standards of good clinical, laboratory and manufacturing practices. Special efforts in the initial phase are targeting training on clinical evaluation, review of clinical trials applications, inspection of clinical trial sites and developing an African regulators forum to exchange and share scientific, regulatory and ethical information relevant to clinical

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trials ongoing or planned in Africa. There is need to review the priority activities and approaches in order to ensure tangible results over the period 2007-2010. A regulatory consultative meeting is therefore planned by EDCTP to take place in Geneva on the June 11, 2007 to address these issues.

Overall objective of the meeting:

This is a consultative meeting aimed at obtaining recommendations on how best EDCTP can support and further strengthen regulatory capacity strengthening in Africa.

Specific objectives of the meeting:

- To discuss how best EDCTP should collaborate with WHO and other partners to support regulatory capacity on R&D of vaccines, drugs and devices in Africa
- To prioritise regulatory capacity strengthening activities in Africa that are within the EDCTP scope
- To discuss implementation of these activities, and develop timelines
- Identify potential partner organisations in the implementation of these activities.

Proposed list of participants:

1. Mr Lahouari Belgharbi: WHO (vaccines)
2. Dr John Marie Okwo-Bele: WHO (vaccines)
3. Mrs Precious Matsoso: WHO (drugs and devices)
4. Dr Clive Ondari: WHO (drugs and devices)
5. Liliana Chocharro: WHO (vaccines)
6. Professor Peter Folb: MRC South Africa (Chair person)
7. Dr Alex Dodoo: National Pharmacovigilance Centre, Ghana
8. Dr Mahamadou Compaoré: Director General NRA¹, Burkina Faso
9. Dr Bernard Pécou: Executive Director DNDi²

¹ NRA: National Regulatory Authority

² Drugs for Neglected Diseases Initiative

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- 10. Dr Aissatou Toure: DCCC³
- 11. Dr Juhani Eskola: PB⁴
- 12. Professor Charles Mgone: EDCTP Sec⁵
- 13. Dr Michael Makanga: EDCTP Sec
- 14. Dr David Coles: EDCTP Sec
- 15. Dr Annaléne Nel: IPM⁶

Meeting Agenda

Agenda items	By	Timelines
<i>Lunch</i>	<i>All</i>	<i>13:00 –13:30</i>
1.0. Welcome	Charles Mgone (EDCTP) and Peter Folb (Chair)	13:30 – 13:50
2.0. Approval of the Agenda	All	13:50 – 14:00
3.0. Brief update on-going regulatory activities in Africa	Lahouari Belgharbi	14:00-14:15
	Precious Matsoso	14:20 -14:35
<i>Coffee break</i>	<i>All</i>	<i>14:40-14:50</i>
4.0. Discussion on how to improve existing regulatory activities	All	14:50- 15:30
5.0. Discussion on priority list of activities	All	15:30 -16:00-
6.0. Chairs remarks on list of priority activities	Chair	16:00:-16:10
7.0. EDCTP funding and procedures	Michael Makanga	16:10:-16:20
8.0. Recommendations on how to proceed in the implementation of the priority activities taking into account time lines	All	16:20-14:50
9.0. Summary of recommendation	.	16:50-17:00
End of meeting	<i>All</i>	<i>17:00</i>

³ DCCC: Developing Countries Coordinating Committee

⁴ PB: Partnership Board

⁵ EDCTP sec: EDCTP Secretariat

⁶ IPM: International Partnership for Microbicides

Annex 2: Discussion paper

EDCTP REGULATORY CONSULTATIVE MEETING – JUNE, 11 2007

Considerable progress has been made in recent years in the discovery and development of novel drugs for the treatment and prevention of diseases prevalent in resource poor countries.⁷ This review focuses on HIV/AIDS, tuberculosis and malaria. These three poverty related diseases (PRDs) together kill over 6 million people each year, and the number of deaths and infections continue to increase. It is necessary to examine critically and fairly whether current systems of national and international drug regulation adequately support the need of communities and national authorities in disease endemic areas for speedy development and provision of critically required drugs. This meeting has been convened to consider the following in regard to possible joint efforts of EDCTP jointly with like minded organizations including WHO, DNDi and IPM⁸ to address the following: (1) realistic areas for change and improvement aimed at developing regulatory capacity in Africa in the different fields of vaccines, drugs and devices; (ii) prioritization of regulatory capacity strengthening activities in Africa in line with the EDCTP mandate; (iii) concrete proposals for action in the implementation of these activities involving key persons in the field; (iv) exploring synergy with potential partner organisations in the implementation of these activities.

Medicinal product regulatory authorities need to be supported to ensure that efficacy, safety and quality criteria for medicinal products (innovative and generic) are high, while at the same time not frustrating efforts aimed at addressing questions of public health importance in Africa. All clinical trials of both non-registered products (drugs or vaccines) and new indications of registered products must be reviewed by competent national drug regulatory authorities. It is in the interest of EDCTP to support the regulatory environment in the countries where clinical trials activities on PRDs are at

⁷. Diseases considered in this category include the following: malaria, schistosomiasis, the trypanosomiasis (African trypanosomiasis and Chaga's Disease), leishmaniasis, the filariases (onchocerciasis and lymphatic filariasis), leprosy, dengue fever, and tuberculosis. In addition, the development and introduction of new vaccines for developing countries are covered in this review.

⁸. IPM: International Partnership for Microbicides

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present, and will in the future, be conducted at the highest standards achievable. EDCTP intends to support this through facilitation of information and expertise transfer by regional networking and matching support from European national counterparts, and in particular regulatory expertise from the European Medicines Agency (EMA).

In order to address urgent needs in drug discovery and development of medicines critically required for diseases (usually infectious diseases) that mainly affect the world's poorest people, there is need to support and develop a pragmatic, public health minded and clinically relevant approach that would expedite new drug development and drug regulatory activities in Africa, and in general.

How might essential standards of new drug review and of conduct of clinical trials be defined that meet necessary requirements for determining quality, efficacy and safety, that fully address the expectations of the countries concerned, and that allow for NRAs fully to exercise their autonomous duty to protect and advance the public health? They would need to be consistent with those applied by the WHO in its new drug evaluation processes (*vide infra*), and that do not conflict with ICH guidelines. *Such essential standards describe might be defined as those scientific and clinical conditions necessary to ensure that patient needs are met, guided by GMP, GCLP and GCP, to determine the quality, efficacy and safety of a new medicine (including generic medicines), vaccine or diagnostic tools, to ensure public health benefit to the population or populations concerned, in a manner that is appropriate for the severity of the disease and the availability (or not) of alternative treatments.*

The World Health Organization has an overarching and coordinating role in new drug and vaccine development and evaluation. The WHO presently exercises this in three distinct ways – prequalification of medicines for acquisition and use in developing countries by United Nations agencies, compilation of the WHO essential drugs list and its implementation at country level, and support for and capacity development of national regulatory authorities. Building capacity is a paramount function of the WHO. Mutual collaboration and recognition might strengthen the concepts of essential standards referred to above. The role of the WHO is reflected, *inter alia*, in the World Health Assembly resolution on Essential Health Research and Development in May 2006 which called for public leadership in R&D strategy and which proposed an inter-

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governmental working group of interested member states whose mandate would be to produce a new global strategy for poverty related diseases by 2008. This resolution links with the 2005 WHA resolution on regulatory issues, aimed to advance the role of regulators in essential health R&D at national level.

The importance of pharmacovigilance also needs to be considered. New and progressive ways of assuring drug safety through pharmacovigilance would reduce the need for defensive, costly and often unnecessary studies of safety in the development of new drugs. That would be consistent with WHO policy and WHA resolutions such as the 55th World Health Assembly resolution in 2003 (WHA resolution 55.18); namely:

Recognizing the need to promote patient safety as a fundamental principle of all health systems, [The WHA] urges Member States:

- i. To pay the closest possible attention to the problem of patient safety; and,*
- ii. To establish and strengthen science-based systems necessary for improving patients' safety and the quality of health care, including the monitoring of drugs, medical equipment and technology.*

The above resolution has a significant bearing on the introduction of new medicines for neglected diseases. Drug regulatory authorities have come to depend increasingly on their national pharmacovigilance centres (those countries that have centres) for ongoing review of the safety (and efficacy) of medicines subsequent to licensing for general use, and of their rational use – particularly in the public sector. Pharmacovigilance underpins dedicated national programmes such as tuberculosis or malaria control and treatment rollout of anti-HIV medicines, schistosomiasis, human African trypanosomiasis and immunization coverage. It can support the introduction of new vaccines and medicines, and provide an infrastructure for essential drugs programmes. Health ministries, health professionals and the public are reassured to know that there is a competent and functional system in place that monitors the safety of medicines, when they are introduced into the health system

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and subsequently.^{9, 10} The special needs of the vulnerable should be addressed (the very young, the elderly, pregnant women, and patients with other diseases such as renal, cardiac, hepatic, etc), and dedicated public health programmes such as malaria, tuberculosis, HIV/AIDS, schistosomiasis, national immunization programmes and family planning.

The WHO, NRAs, EMEA, EDCTP, DNDi, IPM and other organisations concerned with the development of new drugs for poverty related diseases have in their different ways an enormous role to play in achieving the various objectives identified for consideration at the meeting.

⁹ For a country to rely on its own pharmacovigilance programme a number of elements need to be in place:

- i. A dedicated pharmacovigilance centre, independently funded (usually by the State), and staffed by persons with expert knowledge of drug safety and evaluation of adverse drug event reports;
- ii. Links between the pharmacovigilance centre and the WHO, specifically Uppsala Monitoring Centre;
- iii. Close ties with the national drug regulatory authority that meet the mutual needs of the NRA and the pharmacovigilance centre in monitoring safety; and,
- iv. Access to unbiased drug information relevant to the medicines available.

¹⁰ The future of pharmacovigilance, assuming that the resolution of the WHA referred to above is carried forward, (Waller and Evans, 2003; Risk Management Public Workshop, 2003; Wilson *et al*, 2003; Verstraeten *et al*, 2003) is envisaged to include the following: (i) access to databases by practitioners, and linkage or integration of databases for the purpose; (ii) quality control of pharmacovigilance, ensuring its support by robust and independent drug information systems; (iii) use of a common technical language that is supportive of WHO programmes; (iv) integration of vaccines and medicines in a common system; (v) education in the universities, and advancement of the discipline by incorporating it into curricula with the scientific and clinical elements that underpin it – pathology, epidemiology, immunology, pharmacology, toxicology, and clinical practice; (vi) strong collaborative arrangements; and (vii) extending the systems and expertise of pharmacovigilance to the countries where presently they do not exist, especially to Africa.

Annex 3: Background document prepared by the WHO's Department of Immunization, Vaccines and Biologicals (IVB) activities conducted in 2006-2007 and those planned for the period 2007-2010

Background and rationale

Activities conducted by WHO's Department of Immunization, Vaccines and Biologicals (IVB) in the African region in the area of vaccine regulation have focused since 2005 on strengthening national vaccine regulatory systems (NRAs), building capacity to regulate vaccines (through the Global Training Network, GTN) and supporting introduction of new vaccines by developing appropriate regulatory oversight of clinical trials (through regulatory pathways, RP). The first agreement (1st phase of the project) with EDCTP and WHO/IVB was signed in March 2006 and activities started to be implemented soon thereafter. During the 2nd semester 2006, all activities funded by EDCTP were implemented as per the initial workplan and are listed below:

Regulatory Pathways

In view of the increasing number of trials being conducted in the African Region, it became clear that there was a need for strong support of National Regulatory Authorities for the oversight of these trials. Three areas of work were identified: a) clinical trial authorization, b) clinical trial monitoring and c) evaluation of clinical data for licensing purposes. It was noted that most trials conducted in Africa did not have the approval of the NRA of the countries where they were conducted, and that only ethical approval was given. There was usually no link between the Ethics Committees and the Regulatory Authorities. Once the trials were started, no regulatory oversight was in place. The NRAs in most countries in Africa did not have the expertise to review and evaluate the data from these trials as submitted in the licensing dossiers. The first workshops organized in the Region were targeted at identifying the gaps: areas where specific immediate expert support was required, training needs and regulatory procedures to be developed. Soon after, the development of basic model regulatory procedures started, examples of which are the model procedures for submission and review of clinical trial applications (CTAs) and for importation and release of clinical batches. These were pilot tested to authorize clinical trials for the Conjugate Meningitis A vaccine in Mali and the Gambia. In addition, joint review of applications by several countries was organized

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with the support from expert advisers; these joint reviews included the two countries that had already received the submission as well as other countries targeted for clinical trials in 2007 and 2008.

The African Vaccine Regulatory Forum (AVAREF) was established as a forum for discussion and exchange of information on aspects to be considered for the clinical evaluation of vaccines ready to be licensed and others on the research pipeline. It is intended to provide ongoing support to regulators in the field of clinical trials. Nineteen countries participated in the initial meeting of the forum (September 2006), with designated representatives from the Regulatory Authority and the Ethics Committee of each country. The first meeting was supported by experts from the Regulatory Authorities from the USA (Food and Drug Administration, FDA) and from Europe (European Medicines Agency (EMA)). AVAREF meetings are envisaged to take place at least once a year. It is proposed to establish AVAREF support centres (Centres of Excellence) in the region to provide ongoing support between meetings and to respond to needs identified in the meetings.

Global Training Network (GTN)

Both the NRA assessments and the meetings convened in the context of strengthening clinical trial expertise in the region; identify training needs in the countries of the Region. These are then translated into course curricula, which when appropriately developed and approved are delivered in English and French to target both English and French speaking countries in Africa. Similar needs exist in some other parts of the world, and WHO is able to draw on experiences elsewhere in the development of training material. As an example, a basic course on Clinical Evaluation was developed in 2002 and delivered first in Brazil, and later in Thailand and then South Africa. On the basis of this basic training, the curriculum was upgraded and split to address the different aspects of clinical trial regulation: a) authorization, b) monitoring and c) data evaluation. A training course on authorization/approval of clinical trials has been delivered from 11-15 December 2006 in Ouidah (Benin) to 10 French speaking countries (Benin, Mali, Niger, Togo, Senegal, Algeria, Rwanda, Cameroon, and Guinea & Burkina Faso). The course was attended by representatives from the national regulatory authorities, ethics committees and principal investigators designated by EDCTP and who are involved in vaccine clinical trials. The training course ended with some recommendations that all participants agreed to share with their relevant authorities and to implement within a defined timeframe. The training was led by WHO (both Headquarters, HQ and

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Regional Office, AFRO, staff) and facilitated by clinical experts from the French Regulatory Agency (AFSSAPS), the Tunisian National Centre for Pharmacovigilance (CPT, Tunis) and the French NGO Association pour la Médecine Préventive (AMP, Paris). EDCTP also participated in this training as co-facilitator.

Planned activities for 2007-2010

It is proposed to build on the satisfactory outcomes of the first phase of the project, and to continue, and expand, both the GTN and Regulatory Pathways activities. The objective is the same; the target is all African countries. Activities for the period 2007-2010 are planned along the same lines and are briefly described below:

AVAREF provides a forum for networking, exchange of information, and discussion of questions related to the specific issues involved in regulating trials for vaccines. At least one plenary meeting a year is planned to provide significant support to the authorities of the Region; The Forum provides a way for knowledge to be discussed and transferred to the NRAs of individual countries to make their own informed decisions regarding authorization of trials or licensing of products. It is expected that the Forum will identify training needs, needs for development of guidance documents, proposals for changes in regulations to provide support to ensure that these needs are met; Centres of Excellence (see below) are proposed.

Development of Centres of Excellence. It is proposed to identify Institutions within the Region who can support, between the meetings, the needs identified by AVAREF. This could for example include developing guidance on regulatory procedures, deliver training and expand this information to other countries not included in AVAREF. It is proposed that the South African National Regulatory Authority can constitute the first of such centres. The rationale for proposing South Africa is two fold: a) available expertise in the area of regulation of clinical trials and evaluation of clinical data for registration of vaccines, and infrastructure to adequately provide the service and b) since South Africa is one of the member countries of a global initiative, the Developing Countries Vaccine Regulators Network, they are well suited to establish a link between the Regional needs and global development. This Centre(s) can be used to deliver the required training and develop materials. A second Centre of Excellence will be established in a Francophone country to be defined.

Training activities are much needed and efforts conducted to train African regulatory staff, ethics committee representatives and relevant African scientists involved in vaccine clinical trials will expand. The overall demand is based on 46 countries

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targeted to develop and strengthen their vaccine regulatory systems. The number of staff estimated to be trained for a period within the next 5 years is about 300 staff. The average cost per trainee is about 3500- 4500 US dollars. In order to build regional capacity, it will be required to develop a roster of trainers and facilitators to conduct the training. WHO will need to deliver training of trainers courses to ensure that adequate training techniques to assure the quality and consistency of training.

Continuity of training on Clinical Trial Authorization and Clinical Trials Inspections needs to be ensured for Anglophone and francophone countries. It is proposed to conduct for each one course per year, alternatively in English and French in the next two years.

Additional training curriculum needs to be developed to address the third step of clinical evaluation, which is the evaluation of clinical data for licensing purposes.

So far activities were mainly coordinated at WHO/HQ Geneva and AFRO was providing the necessary logistic support for their implementation at regional level. The need to expand the project and to cover a wider range of activities suggests that appropriate staff resources needs to be allocated for regional coordination of the project. It is therefore suggested to assign one WHO international staff member who will lead the project and coordinate the regional activities, ensure coordination with WHO/HQ and EDCTP and will follow up for preparing the adequate reporting and feedback to both WHO and EDCTP when necessary. The terms of reference for this position will be shared with EDCTP and will include monitoring of impact of the EDCTP grant on improving oversight and quality of clinical trials conducted in Africa. He/she will be also responsible for advocacy and fundraising for the next phase of the project. It is desirable that progress and the overall experience in Africa are reflected in international publications.

NOTE: Wherever possible, links with medicines will be made.

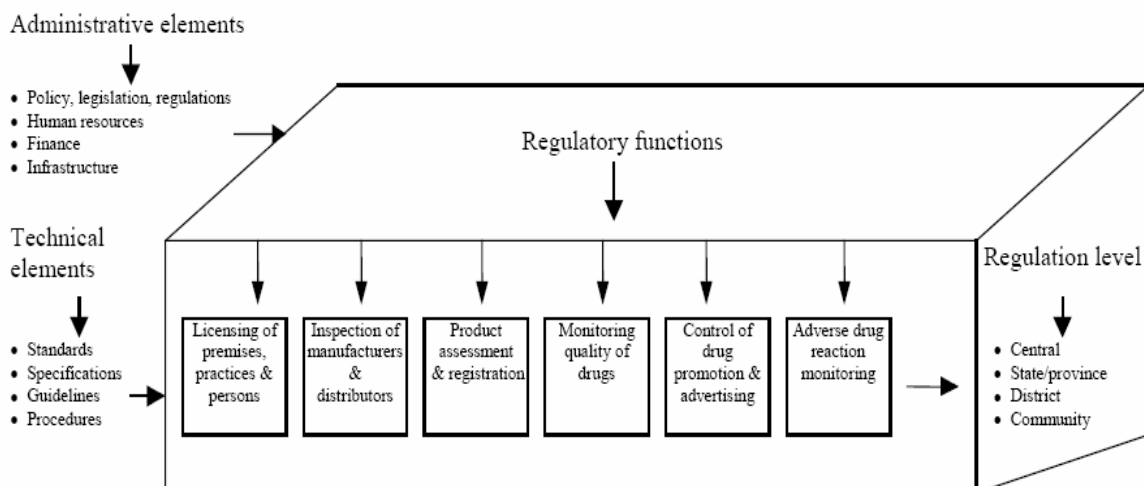
**Annex 4: Background document prepared by
Department Technical Cooperation for Essential Drugs
and Traditional Medicine (TCM) of WHO**

**Clinical trials and regulatory capacity building in
developing countries**

Background

National governments are responsible for establishing strong national drug regulatory authorities (NDRA), and it is the role of the NDRA to guarantee the quality, safety and efficacy of the drugs that it allows on the national market, as well as their ongoing quality assurance and pharmacovigilance. In a number of countries drug regulatory procedures are largely ineffective due to chronic shortages of human and technical resources. In fact, only 20% of WHO's 193 Member States have a well-developed drug regulatory system, and those that do are mostly industrialized countries. About 50% of remaining Member States implement medicine regulation at varying levels of development and operational capacity, and the remaining 30% either have no drug regulatory authority in place, or operate one with very limited capacity (WHO, 2003). This means that in many countries, medicines that have not passed through the marketing authorization process will circulate freely.

Sound, consistent standards, existence of laws, regulations, guidelines and their effective implementation are necessary for avoiding above scenarios and for ensuring that only medicines that meet set standards are available on the market. The promotion of a common drug registration and regulation systems across national borders, would greatly contribute improve the quality and safety of pharmaceutical products, and notably, contribute to ensure an effective approach to achieving the health-related Millennium Development Goals, more particularly goal no 4: *reduce child mortality*; goal number 5: *improve maternal health*; goal number 6: *combat HIV/AIDS, malaria and other diseases*; and goal number 8: *develop partnership for development*, particularly target 13, *address the special needs of the least developed countries*; target 17: *in cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries*; and target 18: *in cooperation with the private sector, make available the benefits of new technologies, especially information and communications*.



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- Policy, legislation, regulations existing in the country, that addresses all the relevant issues and carries appropriate sanctions for violations;
- Human resources - resources should permit employment of a sufficient number of staff with the appropriate skills to undertake the functions that have been designated by the government;
- Finance - appropriate financing which have to ensure that all important regulatory functions are conducted properly;
- Infrastructure - premises, computers, archiving - to perform regulatory functions properly.

2. Technical elements, including:

- Standards
- Norms
- Specifications
- Guidelines
- Procedures

3. Functions and processes:

- Licensing
- Evaluation and registration
- Inspection
- Quality control
- Control of information and promotion
- Surveillance of safety and efficacy

4. Levels at which the regulatory activities are performed:

- Central
- State/province
- District/region
- Local community

The WHO's strategic approach in supporting countries is how to target specific dimensions of medicines regulation, taking advantage of existing regional structures. Each of the WHO regions has regional integration and economic blocs and some have been targeted for harmonisation related activities. In Africa, out of the 14 Regional blocs WHO will support four, namely SADC, EAC, CEMAC, and UEMOA. In West Africa, 5 Anglophone countries within ECOWAS will be supported. Initiatives to strengthen regulatory capacity in specific technical areas are underway.

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Major obstacles in addressing the regulatory functions by the DRAs are due to the lack of skilled personnel, lack of appropriate technology, lack of financial resources, lack of regulatory capacity, lack of regulatory tools and guidelines, and lack of requirements that are publicly available.

No Drug Regulatory Authority (DRA) will be successful in performing its functions if it does not have full and continuing government support, including when the government changes. The appropriate level of financial support depends on what functions the government intends the DRA to undertake. The WHO's role in this regard is:

- To provide advocacy;
- To assist in development of the legislation and regulations;
- To provide training and other technical support;
- To formulate regulatory and registration packages with an aim to help countries pool their resources and have joint activities.

Support for increased harmonization and integration in general is expressed in a number of regional and national fora. For example, among the key recommendations of the new African Health Strategy for 2007-2015¹¹, which was discussed during the African Union Conference of Ministers in April 2007, were stronger collaboration between health and other sectors and increased regional and intergovernmental collaboration among African nations.

Regional and sub regional approaches and global initiatives are considered for:

- Pooling resources, to deal with capacity challenges,
- Reducing duplication of effort, redirect resources (GCC, PAHO, good experiences in procurement)
- Standardizing requirements
- Streamlining regulatory processes
- Legal mechanisms to jointly negotiate
- Promotion of good governance

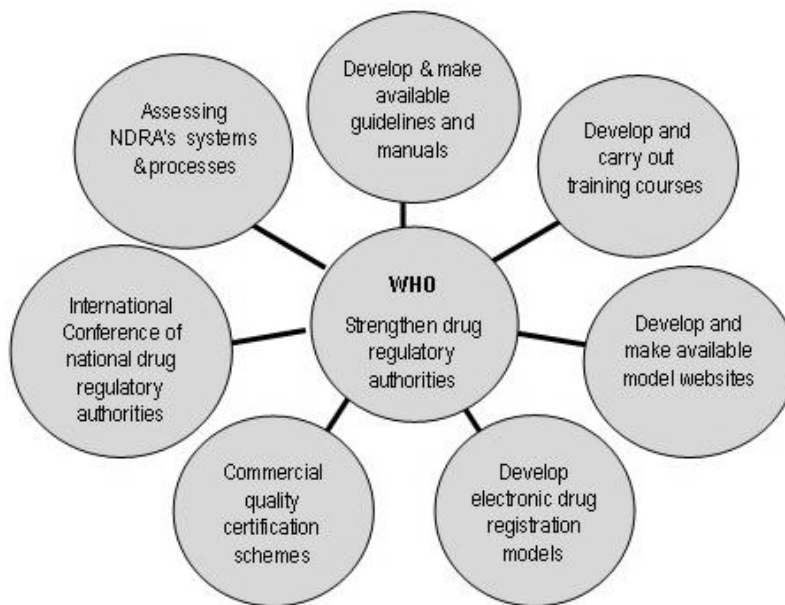
¹¹ Third Session of the African Union Conference of Ministers of Health, Johannesburg, South Africa, 9-13 April 2007. African Health Strategy: 2007-2015

3.8. What has been done so far?

WHO has a long history in providing drug regulatory support both to national governments, and regional and international initiatives, primarily by developing internationally recognized norms and standards and guidelines and providing guidance, technical assistance and training in order to enable countries to adapt global guidelines to meet their specific drug regulatory environment and needs.

Below chart summarizes WHO's efforts to strengthen national drug regulatory authorities & harmonize national and regional drug regulatory requirements.

Drug regulatory models are conditioned by the size of the pharmaceutical market, the availability of resources as well as public health needs. Drug registration procedures vary from country to country and ranges from simple notification or authorization to full registration.



A number of initiatives have already been initiated at regional and sub-regional level to standardize, or harmonize regulatory requirement & processes, in SADC, EAC, CEMAC, UEMOA.

3.9. What needs to be done now?

WHO's role in medicine regulation is guided by its constitutional mandate and the various resolutions the World Health Assembly passes¹². In collaboration with other

¹² Of most relevance are resolutions: WHA45.28 on harmonizing drug regulations; WHA47.16 on ethical criteria for medicinal drug promotion; WHA47.17 on safety, efficacy and quality of pharmaceuticals; WHA49.14 on the revised drug strategy and WHA54.11 on WHO medicine strategy.

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international organizations, WHO has over the years provided technical support to a number of countries to establish, or to strengthen drug regulatory systems, especially in developing countries. Given that the level of drug regulatory activities, and regional harmonization of drug regulatory authorities vary enormously among the regional groups, WHO has identified a strong need for increased regional cooperation, notably in networking, information exchange, capacity-building and technical assistance towards drug regulatory harmonization at sub-regional and regional levels.

There are areas identified for support and strengthening of capacity in the regions (see table below).

Table Summarising WHO/TCM Activities on Clinical Trial and Regulatory Capacity building in Developing Countries

Problem statement	Proposed Activities
<p>Capacity building of developing countries to conduct clinical trials, based on the existing models for clinical trials</p> <ul style="list-style-type: none"> ▪ Lack of clear definition of clinical research ▪ Lack of human and financial resources ▪ Lack of regulatory expertise and capacity ▪ Lack of transparency in decision-making 	<ul style="list-style-type: none"> ▪ Situation analysis and mapping of clinical regulatory activities and regional structures with an aim to pool resources
<p>Regulatory capacity/infrastructure in developing countries</p> <ul style="list-style-type: none"> ▪ Lack of human and financial resources ▪ Frequent regulatory delays ▪ Poor communication between industry and regulation authority evaluators ▪ Lack of political commitment and leadership ▪ Risk-benefit and market authorization decisions are not in line with local health needs ▪ Poor quality of drug sources used for clinical trials ▪ Poor quality of submissions 	<ul style="list-style-type: none"> ▪ Establish regional network for effective exchange of regulatory information and support regional economic blocs with the installation of information repositories
<p>The clinical and social implications of strengthening clinical trials and regulatory capacity</p> <p>Studies / documented activities demonstrate the importance of strengthening clinical trials and regulatory infrastructure in developing countries, in particular, sub-Saharan Africa e.g.:</p> <ul style="list-style-type: none"> ▪ WHO (1999) showing that only 1/3 of WHO Member States have adequate regulatory environments ▪ Failed quality testings can be up to 90% in 	<ul style="list-style-type: none"> ▪ Build capacity of local communities and civil society through advocacy on informed consent and safety monitoring ▪ Strengthen quality related

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Problem statement	Proposed Activities
antimalarials in some African countries	aspects of medicine regulation
<p>Conducting clinical trials for traditional medicines</p> <ul style="list-style-type: none"> ▪ Systematic documentation, interpretation, harmonization of concepts and practices remain a major challenge in most systems of traditional medicines 	<ul style="list-style-type: none"> ▪ Develop guidelines for evaluation of clinical trials for traditional medicines ▪ Investigate models for standard of care and good practices for the use of traditional medicine
<p>Safety issues to be considered during the clinical trials in developing countries</p> <ul style="list-style-type: none"> ▪ Risk benefit, consider harmonized approach to meet needs of developing countries ▪ One of the needs to focus on should be on early release with improved safety and monitoring 	<ul style="list-style-type: none"> ▪ Assist countries in building national and regulatory capacity for recording, reporting and analysis of serious adverse events. ▪ All clinical trials in developing countries have to be designed, conducted and reported in accordance with the principles of WHO Guideline for Good Clinical Practice.
<p>Ethical issues on community rights and consent</p> <ul style="list-style-type: none"> • What should be the minimum acceptable ethical standard? • Ensuring same ethical standards for conducting clinical trials in industrialized and developing countries • Ethical standards must accommodate local beliefs, customs, socioeconomic and the level of sophistication of the health system? 	<ul style="list-style-type: none"> ▪ Assist countries in developing their national ethical standards for biomedical research in accordance with Helsinki declaration and WHO GCP ▪ Facilitate communication between Ethics Committees in Countries and Drug Regulatory Authorities, and promote mechanisms for exchange of information