



THE ROAD TO REGULATORY HARMONIZATION FOR AFRICA:

Accelerating Access to Essential Medicines and Vaccines
Nairobi, Kenya, 4 June 2013

DNDi MEETING REPORT
November 2013



DNDi
Drugs for Neglected Diseases *initiative*

CONTENTS

- 1** Introduction
- 3** Part I: What Has Worked Over the Last Decade?
- 7** Part II: Towards Standards for Harmonization
- 11** Final Comment from the Chair
- 12** Conclusions
- 13** Supplementary Information & References
- 14** Appendices



INTRODUCTION

Over the last decade many advances have been made in addressing the neglected diseases which affect patients in resource-poor settings. New effective treatments, vaccines and diagnostic tests are being developed by organizations such as Product Development Partnerships (PDPs), and it has become increasingly apparent that, in parallel with the drug development process, there is also a need for new mechanisms to ensure regulatory processes are swift and efficient in delivering safe, appropriately evaluated products to patients. It is well recognized that developing countries need to have the expertise and capacity to review clinical trial procedures, quality of clinical batches and to monitor trials ongoing in their countries. Drug regulation, in particular registration, requirements have been very heterogeneous across the African continent in the past, but there has been some progress made in moving towards regional harmonization of the process and capacity building.

In June 2013, on the occasion of its 10th anniversary, DNDi and founding partner KEMRI brought together key African decision makers and public health actors to explore the challenges for research and development in Africa at a 2-day meeting entitled "A Decade of R&D for Neglected Diseases in Africa". The first day focused on regulatory harmonization with a view to accelerating access to essential medicines and vaccines in Africa. Representatives from 20 African countries together with 15 others from Europe, Asia and the United States,

including over 360 African regulators, ministers of health, WHO representatives and public health experts, investigators, national control programme representatives, clinical trial and data managers, research and training institutes, and others were present. This resulting document examines the progress made to date, in anticipation of further discussions at the first Biennial Scientific Conference organized by the African Medicines Regulatory Harmonization (AMRH) Partners, to be held in Johannesburg on 2nd – 3rd December 2013.





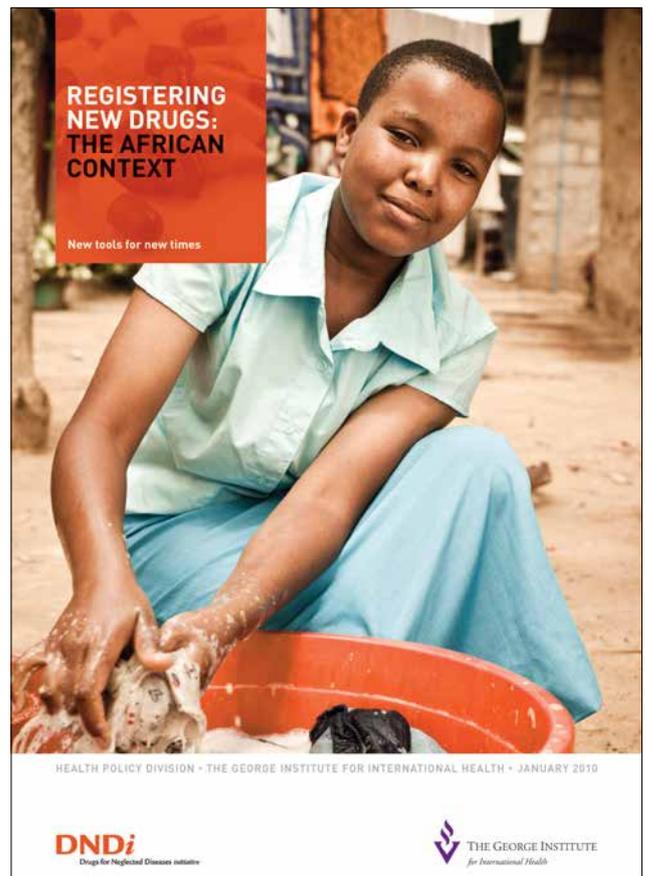
DR NATHALIE STRUB-WOURGAFT

MEDICAL DIRECTOR, DRUGS FOR NEGLECTED DISEASES INITIATIVE (DNDi)

Guests of honour and participants were welcomed to the meeting by Dr Nathalie Strub-Wourgaft, Medical Director of the Drugs for Neglected Diseases initiative (DNDi), who explained that, for many of those developing new therapeutic tools, it is important to know how these tools will be implemented and evaluated, and how the clinical trials that will lead to their development will be carried out. Through a variety of North-South and Pan-African collaborations, involving national ethics committees, the WHO prequalification programme and others, new partnerships have arisen with a view to accelerating the process of developing and regulating new treatments *for Africa in Africa*. Following an initial meeting organized by the Drugs for Neglected Diseases initiative (DNDi) in Nairobi in 2009, a report was generated identifying gaps and obstacles in the regulation and registration of new treatments.¹ Since that time, we have seen the launch and/or development of the African Medicines Regulatory Harmonization initiative (AMRH), the African Vaccine Regulatory Forum (AVAREF), Article 58 of the European Medicines Agency (EMA), and the setting up of regional centres of excellence and European & Developing Countries Clinical Trials Partnership (EDCTP) providing training and support to ethics committees. However, beyond these mechanisms, which provide a working framework for experts, fundamental questions remain unanswered: which aspects still need a fair ethical evaluation? Do we still need universal norms? What does it mean to freely participate in a clinical trial when it represents the only available therapeutic choice?

Dr Margareth Ndomondo-Sigonda, Pharmaceutical Coordinator and Programme Manager of the Medicines Regulators Harmonization (AMRH), New Partnership for Africa's Development (NEPAD) Agency, served as Chair (see p.11) and explained that the NEPAD Agency currently coordinates the AMRH programme. This programme tries to resolve issues around regulatory capacity challenges in Africa, which often hinder the introduction of new medicines

for Africa. The burden of diseases represented by neglected tropical diseases (NTDs) is high in Africa, so it is critical to discuss questions of common interest. While much has been done in terms of R&D and capacity strengthening, it is important to discuss the challenges and successes of the various initiatives and open up discussions on the expected challenges of the next ten years. This session will help us to issue recommendations for the AMRH meeting on 2nd – 3rd December 2013.



PART I

WHAT HAS WORKED OVER THE LAST DECADE?



DR ANNALENE NEL

**MEDICAL DIRECTOR,
INTERNATIONAL PARTNERSHIP FOR MICROBICIDES (IPM)**

IEC and NRS Successful Collaboration in Approving Medical Device Clinical Trials: A Product Development Partnership Perspective

PDPs offer many advantages to global health R&D: they are true partners, have a broad disease profile, implement globally but think locally, focus on good study participant care, and have global quality and standards.

Collaboration with global & local Institutional Ethics Committees (IECs) and National Regulatory Authorities (NRAs) on the regulatory pathway is essential. In parallel with compound development, we also need to think about epidemiology; to engage with communities and traditional leaders to ensure success of the Phase III trial; and to ensure safety, following international Good Clinical Practice (GCP) standards. It is important to know upfront what the dissemination pathway will look like and to think about an access plan.

Many risks were identified during the development of International Partnership for Microbicides (IPM) first microbicide, the dapivirine ring: the focus is often on health authorities in the United States or in Europe, but late stage trials are conducted in high burden countries. It is important to understand the ethical and regulatory pathways in the countries where the product will be introduced, and it is not easy to follow regulatory updates, which vary from country to country. Clinical trial applications and approvals also vary, and it can sometimes result in an expensive process for PDPs with limited funding. In addition, there are language barriers, a lack of CMC (Chemistry, Manufacturing and Controls) expertise (even if excellent preclinical & clinical review staff are available), and differing approaches/views toward trial "insurance" which have to be taken into account. To address all these risks, a collaborative approach was undertaken under the auspices of the EU to implement a risk mitigation plan. This plan was based

on the maximization of networking opportunities amongst NRAs and IECs, enhanced trust and efficient communication, open communication early in the clinical development programme, and consultation of in-country investigators during protocol development. This led to a better understanding of the processes and submission requirements, including the proactive provision of background and supporting documentation and a good understanding of IRBs and local requirements. Proactive participation with continuous updates and open communication lines led to a more efficient process with a shortened review and approval timeline of clinical protocols. A TRUE collaboration is needed: Transparency, Respect, Understanding of Expectations and Enthusiasm.



DR SAMBA COR SARR

RESEARCH MANAGER, MINISTRY OF HEALTH, SENEGAL

Joint Ethics: International Workshop

Dr Carr discussed the joint pre-review of the fexinidazole Phase II/III protocol for sleeping sickness, by a working group made up of members of the Ethical Committee (EC) from the Necker Hospital in Paris, EC members from African countries (some of whom may host trials and others who have regulatory experience but will not host trials), under the auspices of the World Health Organization (WHO), the sponsor, and the involved investigators. In this

way, key actors were able to be brought together whilst avoiding the conflicts of interest which may occur when experts are brought into the study by a sponsor. Initially, a working group consisting of all stakeholders presented and discussed the protocol, with a closed session later in the day during which the EC members deliberated and prepared a report with recommendations, subsequently sent to all participants and local ECs. It shortened the time ultimately needed to review the multi-site protocol, and enabled countries with lower-capacity ECs to benefit from

that available in other countries. In addition to capacity strengthening, the review process itself was reinforced, experience-sharing between different ECs made possible, and it also provided a great networking opportunity for ECs and researchers.

Language is often an issue for joint reviews, such as when protocols in English are reviewed in francophone or lusophone countries, but funding remains the biggest challenge. How can we ensure sustainable review processes are given the level of investment required at the local level?



© Simon Tsiamala, DRC/DNDi



HIITI B. SILLO

DIRECTOR GENERAL, TANZANIA FOOD & DRUGS AUTHORITY (TFDA)

WHO Prequalification Programme: Facilitating Regional Approval and Patient Access to Treatments

The main challenges of medicines regulation in Africa are:

- Adequacy of legislations to address all regulatory requirements and mandates
- Management structures and processes – good regulatory practices
- Human resources capacity (number and skills) and resources (financial and infrastructure)
- Lack of harmonized GMP requirements and inspection procedures among regulators in importing and exporting countries, and within the same region
- Market control
 - Inspecting all consignments/batches imported
 - Control of substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products.

The WHO prequalification programme (PQP) was established in 2001 as a UN programme managed by WHO to ensure that medicines procured with international funds are assessed and inspected for quality, efficacy and safety. Capacity building is a core value of the programme and WHO has provided support to NMRAs in Africa.

The WHO-East Africa Community (EAC) joint pilot project was launched in 2010 with two products, Abacavir sulfate and Amikacin sulfate, which were submitted to WHO PQP and the EAC NMRAs at the same time. A joint review was conducted in Denmark, and the products were prequalified and registered in the participating countries (Kenya, Tanzania and Uganda) simultaneously, i.e. with accelerated access. It is hoped this reduction in time will be repeated during the second

phase of the pilot project, due to start in ten countries in July 2013.

The procedure is voluntary for manufacturers and NMRAs, and is beneficial to both parties; the PQP shares full PQP assessment and inspection outcomes with interested NMRAs, and provides advice to facilitate national regulatory decisions (registrations, variations, withdrawals). It does not interfere with national legislation, decision process or regulatory fees. Cooperation between the PQP holder (the manufacturer), the NMRA in the interested country, and PQP is necessary to overcome confidentiality issues, and to assure information flow and product identity. The registration dossier in countries is, in principle, the same as that approved by the PQP. The aim is to reduce the time taken to arrive at a decision on registration to 90 days, with the option to decline to adopt the procedure for individual medicines, and to come to a different decision from the PQP (but to inform and clarify the reasons for deviation to the PQP).

Prequalification provides regulators in the region with improved technical knowledge and skills, practice and experience, practical tools and guidelines and helps to build more credible regulatory systems whilst saving resources. In parallel, it enables industries to access international funds and, through better quality production, better products and increased regulatory knowledge, better access to markets.

In conclusion, the PQP is a powerful and effective mechanism to promote access to quality medicines and a major contributor to capacity building both for regulators and local manufacturers. In addition, it promotes collaboration and cooperation amongst regulators and leads to a reduction in duplication. The PQP played a significant role in the EAC Medicines Regulation Harmonization Project launched last June in Arusha. It is anticipated that once capacity has been built, local regulators can take over from the PQP.

WHO PREQUALIFICATION PROGRAMME ESTABLISHED IN 2001

- Aims to make priority treatments available for those in need of treatments for HIV/AIDS, TB, malaria, reproductive health, some paediatric medicines, neglected tropical diseases and influenza
- Currently 28 active pharmaceutical ingredients (APIs) prequalified, all of which can be used for the manufacture of UNITAID priority products
- Prequalification of 19 medicines quality control laboratories (QCLs) ensures coverage in all 6 WHO regions
- Joint pilot project initiated in 2010 by the WHO-EAC to simultaneously prequalify and register treatments ongoing in 10 countries: Abacavir sulfate and Amikacin sulfate registered in Kenya, Tanzania and Uganda.



DR MARIE-HÉLÈNE PINHEIRO

PRINCIPAL REGULATORY ADVISOR, EUROPEAN MEDICINES AGENCY (EMA)

Article 58: Collaboration between the European Medicines Agency and WHO

Article 58 of Regulation (EC) No 726/2004 was introduced into European Legislation in 2004–05 to enable Europe to participate in global public health beyond its own borders. Through this mechanism the European Medicines Agency is able to issue a scientific opinion on human medicinal products intended for the markets outside the community, in cooperation with the WHO. Back in 2005, there were many discussions with WHO on how to implement such legal provision, given that this was a new tool established for medicines that will not be used in Europe. What should be the scope of the procedure? What should be the standards for evaluation? What will be the details of the evaluation procedure?

It was clear that there were some medicinal products which were no longer available in the EU market but which were still needed in other parts of the world to protect public health.

Article 58 scientific opinion should be seen as a tool to provide scientific assistance in the context of cooperation with WHO, which should lead to rapid, or accelerated, access to important new vaccines and medicinal products for WHO target diseases. The principles agreed with WHO and NMRAs involved at the time was that the same process, standards, and timelines as those for EU centralized registration should be applied.

Upon receipt of an application for Article 58 scientific opinion, with WHO confirmation of the high public health need in the NMRA concerned, the EMA and its EU network of expert teams initiate the scientific evaluation of such products, in order to target the needs and specificities of the patients and countries where the medicine is intended to be used.

ARTICLE 58 OF REGULATION (EC) NO 726/2004 OF THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION

The Agency may give a scientific opinion, in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organization, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply.

- Five European public assessment reports (EPARs) have been published to date:
 - Aluvia (lopinavir/ritonavir), Lamivudine ViiV, and Lamivudine / Zidovudine ViiV for HIV/AIDS
 - Pyramax (pyronaridine/artesunate) for malaria
 - Hexaxim, a multivalent vaccine
- A further 16 products are currently in the medicinal products pipeline
- Following its positive scientific approval from the EMA in February 2012, Pyramax[®] was immediately considered by the WHO for prequalification, which it received 3 months later.

To date, all products being reviewed have been prequalified by WHO. However, since 2005, only 5 products had gone through Article 58 (including Pyramax[®]) and discussions were held to explore if the NMRAs could be involved even earlier, at the joint scientific advice stage. Since 2010, the EMA and WHO Vaccine prequalification department have been discussing streamlining procedures in order to further accelerate these two review processes and enable an even earlier access to medicines.

Collaboration between EMA with NMRAs and WHO is essential, as EU experts may not be familiar with the specific epidemiological characteristics and other particularities of the disease. It is crucial that NMRAs be involved in the

evaluation Article 58. However, it should be highlighted that such evaluation procedures are to be used for new products where scientific and regulatory expertise is currently unavailable in the NMRA concerned. This is a facilitating tool to collaborate, exchange and share regulatory and scientific expertise amongst regulators.

Discussion:

Most access to these products comes through funding agencies, so information on differences in pricing between products that are prequalified and those that are not is not necessarily available. There is a need for post-marketing studies on quality. This process is not suitable for all products, e.g. generics. Local NMRAs have more expertise on certain products.

PART II

TOWARDS STANDARDS FOR HARMONIZATION



DR BERNHARDS OGUTU

SENIOR CLINICAL TRIALIST (INDEPTH NETWORK),
KENYA MEDICAL RESEARCH INSTITUTE (KEMRI)

Are Current Biological Norms Adapted for Clinical Research in Africa?

Global biological norms are accepted values of specific parameters used to guide the health status of persons, their clinical care, the classification of adverse events and the determination of study end points. They are based on a variety of data sources, including surveys, clinical trials, routine check-ups and pre-trial evaluations. However, they may be misleading. Haematological, biochemical, immunological, spirometry, anthropometric, and cardiovascular variables are commonly considered, but can be confounded by the age and physiological status of participants, the time the sample was obtained, the use of pooled data, and the genetic constitution of the target population. Regulators must adopt normal ranges for their country in order to optimize treatment for patients.

For Africa, few studies have looked at normal ranges, and most of those are linked to clinical trials; there are no longitudinal normal ranges, and age bands are not wide enough for specific

areas. In addition, there are variations in normal ranges even within the same country (e.g. Kenya). Some values may be considered as out of range values, meaning that valuable participants to trials could be missed.^{3,4} Similarly, otherwise healthy participants could erroneously be considered to have experienced an adverse event, because of unadapted normal ranges, leading to a good product not being registered.

The development of region/age/gender specific reference values is essential to good clinical research. Such parameters are likely to change and will need to be updated on a regular basis.

Discussion:

However big the task is, it would be good to establish reference ranges in different regions. How to consolidate all the differences to establish a general different “normal” range?

Q: There is a huge gap when we want to conduct operational research on reference ranges. Is it possible to get a protocol from KEMRI to help other countries collect the information?

A: KEMRI and other partners have tried to put together a protocol to help other countries. They are setting up a platform that should help sharing and harmonizing.



© Benoît Marquet, Kenya / DNDi



DR MICHAEL MAKANGA

DIRECTOR SOUTH-SOUTH COOPERATION AND HEAD OF AFRICA OFFICE, EUROPEAN & DEVELOPING COUNTRIES CLINICAL TRIALS PARTNERSHIP (EDCTP)

Priority Areas to Be Addressed in Ethics and Regulatory Reviews in Africa

Dr Makanga discussed priority areas from an EDCTP perspective. Currently, the EDCTP is working with 30 countries in Africa. The core function is to support clinical trials integrated with capacity development and networking. This goes together with creating an enabling environment in ethical and regulatory areas.

Health research is rapidly increasing in quantity and complexity in Africa, and ethics and regulatory review capacity is very heterogeneous on the continent. An increase in both quality and efficiency of ethics and regulatory activities is required, and the functionality and independence of ethics and regulatory structures in Africa need to be promoted through strengthening local infrastructure and human resources.

Local ownership and sustainability strategies are sub-optimal in many African countries.

Many capacity development initiatives have been launched in recent years, including ethics training in sub-Saharan Africa, the establishment and strengthening of ethics capacity at both the institutional and national level, and the mapping of African Research Ethics and Drug Regulatory Capacity (MARC Project: COHRED). Regulatory pathway capacity has been greatly strengthened by setting up the African Vaccine Regulatory Forum (AVAREF), a platform that brings together NRAs from different countries to share experiences, but also to standardize procedures in preparation of market authorizations. Clinical trials activities are rapidly expanding in Africa, including in central Africa, which was long neglected. The ethics environment in Africa is very heterogeneous: some

countries need to strengthen NRAs and there is a need for help to coordinate such initiatives.

The EDCTP has identified a number of capacity gaps: shortage of human resources and infrastructure; lack of coordination amongst ethics and regulatory structures, and among funders and donor agencies; lack of awareness of existing capacity and gaps; and a lack of collaboration and appropriate integration of ethics, regulatory and clinical trial registration. It is also important to think about sustained change, which is also in the hands of the funding agencies. There is a need to think differently in terms of how success is reported, through new metrics to report on activities and obtain more funding.

Discussion:

Q: How many countries have the development of new drugs in their national health action plans? If they do, why don't they do it?

A: This is something that is being addressed through AVAREF, by involving regulators in protocol development for clinical trials that are of potential national and regional policy relevance. Also, through the AVAREF platform different countries are facilitated to develop institutional development plans, which may include national regulatory authority (NRA) capacity development for review of clinical trials, and evaluation of dossiers for new products developed and authorized for use in different countries.

EDCTP ESTABLISHED IN 2003

- Aims to accelerate the development of treatments against HIV/AIDS, tuberculosis and malaria
- Brings together European partners involved in developing new drugs, vaccines, microbicides and diagnostics with those in countries which are the worst affected by the diseases
- Unites 14 EU countries, Switzerland, Norway, and 47 countries in sub-Saharan Africa
- Focuses primarily on Phase II and III trials.
- Currently working with 30 countries in Africa
- Clinical trial support as a core function, but also regulatory and ethical issues
- Current EDCTP programme will end in May 2015, expected to be renewed under the EU's Horizon 2020 Framework Programme.



ESNAT MWAPE

DIRECTOR, PHARMACEUTICAL REGULATORY AUTHORITY, ZAMBIA

Capacity Strengthening Initiatives for Regulatory Authorities in Africa

Most NMRAs are not fully functional – they cannot carry out all the functions recommended by WHO. Legal frameworks are not always aligned with current best practices, and there is limited expertise in terms of finance and skills. The majority of NMRAs are organized in departments within the relevant Ministry of Health, but are poorly funded with limited budgets, although some are able to get resources from the charges they apply. Cooperation among the member states can still be enhanced.

The African Medicines Regulatory Harmonization (AMRH)⁵ Programme aims to promote sustainable capacity building strategies in the African Region. Supported by NEPAD and the EU, it targets capacities such as awareness, analytical skills, decision-making and institutional capacity. It wants to ensure that both human and institutional capacities are available, through identifying needs and building on existing capacities; relying on locally existing expertise and those in the diaspora who may be involved in the design and implementation; and by reviewing other programmes being undertaken. It is mapping existing capacities, and identifying centres of excellence, and provides technical and

financial support to sustain, expand and improve capacity building programmes. Through education, networking and long- and short-term projects, the AMRH aims to build a critical mass of people that can sustain the capacity building programmes. Expected results include a comprehensive report on short-term and long-term regulatory training programmes in Africa, a database of regulatory training institutions and partners/stakeholders involved in regulatory training programmes in Africa, a database of regulatory science expertise in Africa and elsewhere, as well as carefully designed capacity building programmes at the national, regional and African level, and regional centres of excellence (RCoREs) will be established.

THE AMRH INITIATIVE ESTABLISHED IN 2009

AIMS

- Reduce the approximately 50 different National Medicines Regulators Authorities (NMRAs) working independently across Africa down to 5–6 regional groups, each with harmonized technical requirements
- Harmonize registration and technical documentation, procedures, and decision-making processes
- Stream-line processes to reduce time taken
- Build a critical mass of people that can sustain the capacity building programmes
- Improve transparency.



© Marietta Furrer, South Africa / DNDi



DR SAMVEL AZATYAN

MANAGER, MEDICINES REGULATORY SUPPORT PROGRAMME,
WORLD HEALTH ORGANIZATION (WHO)

Can We Define Essential Technical Standards for Dossiers Necessary for Regulatory Harmonization?

The lack of capacity of NMRAs in Africa causes a lot of problems to applicants, and means that there is a corresponding lack of medicines and products being made available to patients. Could registration harmonization increase regulatory efficiency?

Ideally, the NMRA should be able to administer the full spectrum of regulatory activities, including market authorization for new products and variation of existing authorizations; GMP, GCP and GLP inspections; licensing and post-license control of manufacturers, wholesalers and other distribution channels; quality control laboratory testing; adverse reaction monitoring; provision of drug information and promotion of rational

use; enforcement operations; and monitoring of drug utilization. Currently only 30% of NMRAs globally have limited capacity to perform all core regulatory authorities; 90% of African NMRA's lack the capacity to guarantee quality, safety and efficacy. This means that sponsors and manufacturers face a landscape of disparate regulations, frequent delays and limited transparency.

Introducing essential technical standards would improve public health, by increasing timely access to safe and effective medicines. This could be done by reducing the time taken to registration in-country, without compromising quality, and therefore the time taken for essential therapies to reach patients in need. This will require capacity building to ensure transparent, efficient and competent regulatory activities, including assessments and inspections.

Different technical requirements mean that timelines are longer. A Common

Technical Document (CTD) format with harmonized technical requirements is becoming the gold standard, and would be adaptable to most, if not all, submission types as it is based on an international format and structure rather than on content. It could contain built-in flexibilities (similar to the ICH-CTD) so that it could be appropriately tailored to local circumstances and preferences, and to "generics". The logical order of presentation follows the development scheme and leads to a reduction in resources needed to compile applications, facilitating the regulatory assessment process and information exchange between industry and the regulator, and between regulators, and is an important step towards electronic CTDs.

In conclusion, the future is regulatory harmonization, and a common application format is the cornerstone of a harmonized regulatory system. The CTD is the logical standard to adopt.



© Mariella Furrer, South Africa/DNDi

FINAL COMMENT FROM THE CHAIR



DR MARGARETH NDOMONDO-SIGONDA
PHARMACEUTICAL COORDINATOR AND PROGRAMME MANAGER
OF THE MEDICINES REGULATORS HARMONIZATION (AMRH),
NEW PARTNERSHIP FOR AFRICA'S DEVELOPMENT (NEPAD) AGENCY

It is essential to have reference ranges for the region, and also to have harmonization across the continent. Regulatory tools, such as EDCTP, Article 58 and WHO PQP have been developed.

How best can we use these tools, how can they themselves be harmonized? Also, there is a need for sustainability, through capacity building and a sustainable funding mechanism.



© Benoît Marquet, Kenya / DNDi

CONCLUSIONS

Much progress towards harmonization in Africa can be seen, with many of the recommendations of the George Institute report implemented or ongoing (Appendix 3), thus expediting the time taken to deliver safe, stringently evaluated treatments to patients.

There is a need for sustainable funding (e.g. joint review committees). This will require income-generating models with long-term growth prospects, reducing the dependence on external charities or grants support and allowing African governments to take responsibility.

Further streamlining of the regulatory process could be achieved by twinning the EMA's Article 58 with WHO prequalification, so that treatments given a positive scientific opinion under Article 58 would be automatically considered for prequalification, as effectively happened with the review of Pyramax®.

Understanding the local NMRAs, ethics requirements, language and culture is key to successful clinical trial design and implementation, with proactive communication leading to more efficient review and approval timelines of clinical protocols. Communication can be an issue when ethics committees and experts speak different languages. It is also important to promote medicines registration harmonization whilst respecting national sovereignty with regard to regulatory decisions.

A number of specific problems still need to be addressed:

■ Regulatory

- Continue harmonization efforts across all countries
- Implementation of changes post Article 58 opinion at a national level
- Harmonize GMP requirements and inspection procedures among regulators in importing/exporting countries and within the same region
- Adoption of a Common Technical Document (CTD) in countries/regions.

■ Coordination and cooperation

- Increased coordination needed among ethics and regulatory structures, and among funders and donor agencies
- Collaboration and appropriate integration of ethics, regulatory and clinical trials registration
- Establish mechanisms for site reviews and joint inspections by more than one national ethics committee for multiple site studies across countries. Determine a mechanism for dealing with ethical issues for multisite projects
- Reporting/collecting information on adverse drug reactions (ADRs)
- Increased transparency.

■ African norms

- Development and regular updating of region/age/gender specific reference values

■ Capacity building

- Shortage of skilled human resources: need quality control and accreditation standards for short- and long-term training programmes. Promote local resources whilst leveraging collaboration

■ Funding

- Need for sustainable funding
- New metrics needed to report on activities and increase funding

■ Time

- Reduce the time required for the Clinical Trial Application (CTA) and other regulatory processes, and for import/export licenses
- Limited CMC expertise experience leads to delays in product development.

SUPPLEMENTARY INFORMATION

Full information on the event is available at:

www.dndi.org/media-centre/events/216-media-centre/events/1574-a-decade-of-r-d-for-neglected-diseases-in-africa.html

In particular:

■ **Programme and Speaker Bios are available at:**

www.dndi.org/images/stories/events2013/DNDi_June4_programme_bios.pdf

■ **Powerpoint presentations are available at:**

www.dndi.org/media-centre/events/216-media-centre/events/1574-a-decade-of-r-d-for-neglected-diseases-in-africa.html?showall=&start=4

■ **Videos of the event are available at:**

www.dndi.org/media-centre/events/216-media-centre/events/1574-a-decade-of-r-d-for-neglected-diseases-in-africa.html?showall=&start=7

REFERENCES

1. Moran M, Guzman J, McDonald A, Wu L, Omune B (2010) **Registering New Drugs: The African Context**. Sydney. Available: http://ghtcoalition.org/files/Regulatory_report_George_Institute_DNDi_Jan2010.pdf
2. MMV (2012) **Press release: Pyramax®, a new antimalarial combination, receives positive opinion from European Medicines Agency**: 1–6.
3. Karita E, Ketter N, Price M a, Kayitenkore K, Kaleebu P, et al. (2009) **CLSI-derived hematology and biochemistry reference intervals for healthy adults in eastern and southern Africa**. PLoS one 4: e4401. doi:10.1371/journal.pone.0004401.
4. Zeh C, Amornkul PN, Inzaule S, Ondoa P, Oyaro B, et al. (2011) **Population-based biochemistry, immunologic and hematological reference values for adolescents and young adults in a rural population in Western Kenya**. PLoS one 6: e21040. doi:10.1371/journal.pone.0021040.
5. NEPAD, WHO (2009) **African Medicines Registration Harmonisation (AMRH) Initiative: Summary , Status and Future Plans**.

APPENDICES

APPENDIX 1 AFRICAN VACCINE REGULATORY FORUM

The African Vaccine Regulatory Forum (AVAREF) of the WHO, established in September 2006, acts as a resource of expert scientific advice to national regulators, in order to arrive at informed decisions when reviewing clinical trial applications and registration dossiers concerning vaccine development. Meetings are held annually. There are 22 member countries across in Africa, with the possibility of expanding to a total of 46, with the network consisting of one representative of the NMRA and of the National Ethics Committee of each country. Vaccine developers, clinical trial sponsors, vaccine manufacturers and experts in relevant areas of expertise are invited by WHO to make presentations at information sessions, providing a non-threatening environment for regulators to discuss with experts and colleague regulators.

AVAREF has undertaken joint reviews of the Phase II trial of conjugate Meningitis A vaccine (MenAfrivac A) and the Phase III trial of RTS,S/AS01 (Malaria Vaccine Initiative – Glaxo SmithKline) malaria vaccine in infants. In addition, a candidate Phase II tuberculosis vaccine trial (M72/AS01E; GSK) has been discussed.



APPENDIX 2

MEMBER INVOLVEMENT IN JOINT REVIEW PROCESSES

| TREATMENT | Protocol or Product (Sponsor / Developer) | JOINT ETHICS REVIEW | | | | | REGULATORY MECHANISM FOR FINAL PRODUCT | | | |
|------------|--|---------------------|-------------------------------|--------------------------------------|---------|-------------------------|---|-----------------------------|-------------------------|--------------------|
| | | NMRA | ECs of member countries | International (non-African) EC | WHO | Other | NMRA | EMA's Article 58 | WHO Prequalification | Other |
| HAT | Fexinidazole Phase II/III protocol (DNDi) | | ✓ | ✓ | Support | Investigators | | For scientific advice | | |
| MALARIA | Eurartesim® (piperazine tetraphosphate / dihydroartemisinin) Phase III protocols (MMV/Sigma Tau) | ✓ | ✓ | ✓ | | | ✓ | | | EMA Orphan Drug |
| | Pyramax® (pyronaridine tetraphosphate / artesunate) Phase III protocols (MMV/Shin Poong) | ✓ | ✓ | | | | ✓ | ✓ | ✓ | |
| HIV | Abacavir (WHO-EAC joint pilot project) | ✓ | | | | | ✓ | | ✓ | |
| | Dapivirine Ring-004 Phase III protocol (International Partnership for Microbicides – IPM) | ✓ | ✓ | | ✓ | EDCTP; Investigators | ✓ | | | |
| ANTIBIOTIC | Amikacin (WHO-EAC joint pilot project) | ✓ | | | | | ✓ | | ✓ | |
| VACCINES | MenAfriVac Phase II protocol – conjugate Meningitis A vaccine (Millenium Villages Partnership – MVP) | ✓ | | | | AVAREF | ✓ | | ✓ | |

APPENDIX 3

ADVANCES IN DRUG REGULATION SINCE PUBLICATION OF THE GEORGE INSTITUTE REPORT (2010)¹

| | RECOMMENDATIONS 2010 | CURRENT STATUS (2013) |
|---|---|---|
| 1 | All regulatory reviews of novel neglected disease products by stringent MRAs – including Article 58 reviews and WHO prequalification assessments – should formally include regulators from endemic countries that will be targeted for that product (i.e. formal twinned review in all cases) | Needs to happen in all cases – one DRC expert invited to the EMA Article 58/FDA joint scientific advice for fexinidazole |
| 2 | On condition that Recommendation 1 is implemented, to provide automatic WHO prequalification for novel neglected disease products approved by stringent MRAs and that meet WHO treatment recommendations (with the exception of approvals under the accelerated approval (FDA) / conditional approval (EMA) mechanisms. Approvals under Orphan Drug legislation to be reviewed on a case-by-case basis | |
| 3 | <p>Improve Article 58's attractiveness to product developers by allowing:</p> <ul style="list-style-type: none"> ■ Automatic WHO drug prequalification of products given a positive opinion under Article 58 ■ A positive Article 58 opinion to be converted to EMA approval with a single European bridging study OR ■ A positive Article 58 opinion to provide automatic EU Orphan Drug approval | No automatic process as yet, but Pyramax® granted a positive scientific approval by EMA under Article 58 (Feb 2012) and subsequently prequalified by WHO (May 2012) |
| 4 | <p>Selected experienced Western MRAs to conduct prequalifications on behalf of, and in addition to, WHO. Individual reference MRAs could either specialize in a single disease area (cf. the FDA and PEPFAR drugs), or could nominate to review a fixed number of dossiers per year. Eight experienced MRAs each conducting six relatively simple generic dossier reviews per year would more than double WHO's current in-house drug prequalification capacity:</p> <ul style="list-style-type: none"> ■ The Western MRA would be responsible for the dossier assessment; and overall management of the process ■ WHO would liaise with manufacturers to improve dossiers as needed (supported by the Western MRA) | |

| | | |
|---|---|--|
| 5 | <p>WHO to conduct a strategic review of WHO drug prequalification priorities, along the lines of SAGE reviews for vaccines, including working with African MRAs and Ministries of Health to identify priority diseases or areas to be included in prequalification (and/or outsourced to reference MRAs)</p> | |
| 6 | <p>Fund Centres of Regulatory Excellence in each of Africa's main subregions: West, South, East, Central and North Africa. The Centres would provide regulatory skills and efficiencies to support African MRAs in meeting their immediate regulatory challenges, as well as providing an institutional pathway for professional training to build and retain African regulatory capacity in the mid-to-long term. They would additionally provide a forum for networking and sharing of expertise, and a natural hub to coordinate donor funding and activities. The Centre's activities could include:</p> <ul style="list-style-type: none"> ■ Joint regional review of product dossiers (with external support as necessary) ■ Joint GMP plant inspections at the regional level ■ "Twinning", i.e. formal participation in external regulatory reviews such as FDA PEPFAR-linked reviews, EMEA Article 58 assessments, WHO prequalification, etc. ■ Clinical trial regulation, including joint review and approval ■ Training and Regulatory Fellowships. | <p>AMRH provides funding for review processes and personnel training and has launched a call for Regional Centres of Regulatory Excellence (RCoREs) in Africa, see http://www.amrh.org/news/request-expressions-interest-regional-centres-regulatory-excellence-rcores-africa</p> <p>Need to ensure harmonization so funding resources not drained from elsewhere.</p> |



We would like to thank the speakers for their valuable contributions.

