



REGISTERING NEW DRUGS: THE AFRICAN CONTEXT

New tools for new times

HEALTH POLICY DIVISION • THE GEORGE INSTITUTE FOR INTERNATIONAL HEALTH • JANUARY 2010

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REGISTERING NEW DRUGS: THE AFRICAN CONTEXT

New tools for new times

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FOREWORD

What would be the best registration strategy for the approval of a new drug to treat sleeping sickness, a disease which primarily affects neglected patients in Central and West Africa? What would be the best way to support African regulatory authorities in their evaluation of new drugs specifically developed to treat their own populations? How should essential standards for the conduct of clinical trials be defined? For treatment of patients in developing countries, how should the risks and benefits of drugs be assessed in a manner that is appropriate to the needs of the patients, the severity of the disease, and the availability (or not) of alternative treatments, while ensuring that the medicines are safe, effective and of quality?

All these regulatory issues are critical for an organization such as DNDi which aims to develop new drugs and treatments for neglected tropical diseases (NTDs) such as human African trypanosomiasis, visceral leishmaniasis, Chagas' disease or malaria and to ensure equitable access to effective therapeutic options for patients in need in developing countries.

As with any new drug, all individual treatments developed by DNDi must be registered by national drug regulatory authorities as being safe, effective and of quality, before they can be made available to patients in countries affected by NTDs.

Regulatory authorities in most developing countries, particularly in Africa, lack resources to evaluate the safety, efficacy and quality of new medicines, and usually rely on registration by stringent regulatory authorities in developed countries. Conversely, stringent regulatory authorities lack knowledge of NTDs, which only affect very small numbers of people in their territories, to make the appropriate risk-benefit assessment with regard to populations most affected.

Participants of a DNDi regional workshop on this issue in Nairobi in June 2009 acknowledged that the lack of registration capacity in developing countries constituted an obstacle to access to NTD drugs in developing countries.

Although this research project originates from DNDi's own registration issues and needs, these issues are of relevance to most Product Development Partnerships (PDP) working in the field of NTDs, as was discussed during the PDP Forum meeting organized by the Bill & Melinda Gates Foundation in July 2009.

There is a need to think about new mechanisms and pathways, based on international cooperation, to ensure the urgent approval in developing countries of new NTD drugs and treatments, which are safe, effective and of quality.

The WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property adopted by the World Health Assembly in May 2008 required stakeholders to *"develop and/or strengthen the capacity of national regulatory authorities to monitor the quality, safety and efficacy of health products while sustaining ethical review standards"* and *"to initiate programmed actions on regional and sub-regional levels with the ultimate goal of harmonization of processes employed by the regulatory authorities for drug marketing approvals"*.

This report, commissioned from the George Institute for International Health by DNDi, reviews the various mechanisms and strategies available today to support the registration of new drugs for NTDs in developing countries and offers recommendations to further address this issue.

Although the George Institute prepared the report, it is important to emphasise the key role played by others, in particular the international Expert Advisory Group (EAG). The EAG membersⁱ, including both African and Western regulators, played a vital role in reviewing this report and shaping the final analysis and recommendations. The draft report was also work-shopped at a regional meeting in Nairobi, attended by many African regulators, including representatives from Angola, Democratic Republic of Congo, Ethiopia, Uganda, Tanzania and members of the HAT (human African trypanosomiasis) and LEAP (leishmaniasis) platforms (see Annexe 6). These groups provided invaluable feedback that helped shape the final conclusions.

Capacity strengthening is an essential element of DNDi's mission. While using and supporting existing capacity in disease-endemic countries, DNDi is also building additional capacity in a sustainable manner through transfer of knowledge and technology in the field of drug research and development for neglected diseases.

We hope this report and recommendations will further the discussion and catalyze progress on fostering innovation for most neglected diseases and in facilitating access to improved therapeutic options for the most neglected.

Dr Bernard Pécoul

Executive Director

Drugs for Neglected Diseases *Initiative* (DNDi)

ⁱ See Annex 1.

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BACKGROUND

For many years, African medicines regulatory authorities (MRAs) have managed a broad range of responsibilities, often with limited resources. Their focus has generally been on providing their population with access to a wide range of affordable essential medicines, usually multi-source generics, with less emphasis on rapid access to the latest products. As a result, African national MRAs may have experience in managing generics, but many have only limited experience in assessing, approving and registering innovator products, the vast majority of which are for shared 'global' diseases, such as diabetes, hypertension and cancer.

Instead, these innovator products have in virtually all cases been first submitted to Western regulatory authorities - who thus have a great deal of experience in their assessment – and their judgements are, in turn, relied on by many developing country MRAs who may not have the experience or resources to conduct assessments of innovator products themselves.

Recent events have changed this picture, with the result that African MRAs are now being required (sometimes for the first time) to conduct first assessment of novel products that have not previously been reviewed by more experienced regulatory authorities. A key factor behind this shift in regulatory responsibility has been the advent of new products developed specifically for developing world diseases – including new drugs for malaria, sleeping sickness and leishmaniasis; new vaccines targeting malaria, HIV/AIDS, tuberculosis (TB), rotavirus and African strains of pneumonia and meningitis; and new drug combinations from developing country manufacturers. In 2007, over US\$2.5 billion were invested globally in research and development (R&D) of new products for neglected diseases of the developing worldⁱ, and several such products have either recently been registered or are due to be submitted for registration in the next few years.^{2,3}

A further factor driving this regulatory shift was the decision by the US Congress and the European Commission to decrease regulatory

supervision of products that were for export rather than domestic use. For instance, the Food and Drug Administration (FDA) does not require US manufacturers to follow full Investigational New Drug Application (IND)ⁱⁱ procedures if the clinical trials materials are not intended for domestic use and the European Medicines Agency (EMA) adopted a new regulation (726/04) stating that vaccines for exclusive use outside the European Union are not to be licensed in Europe.⁴ Both the FDA and European MRAs may also not review clinical development plans for such products. Some Western regulators are also no longer renewing licences of older vaccines, which are still in wide use in Africa but have been replaced in Western markets by later-generation vaccines.

These changes mean that several new medicines are already sitting in African regulatory in-trays waiting for assessment and registration, or are due to reach those in-trays in the next 12-18 months. These include:

- ▶ Innovator drugs for neglected diseases
- ▶ Novel combinations and formulations of existing drugs for neglected diseases

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WHAT DOES DRUG REGISTRATION INVOLVE?

The role of an MRA is to ensure the quality, safety and efficacy of all medicines in circulation in their country, including regulating and monitoring their clinical development, manufacture, approval for marketing, distribution, procurement, import, export, supply, sale and promotion.

One of the primary challenges facing an MRA is to ensure that the pharmaceutical products they need are registered in their country: this process is called “registration”, “marketing approval”, “marketing authorisation” or “product licensing”, and involves assessment of product information submitted by the manufacturer (the product ‘dossier’) to make sure it is safe and effective for use by local patients.ⁱⁱⁱ The assessment process is technically challenging, with the difficulty increasing from simple generic drugs, to new formulations and fixed-dose combinations (FDCs), while novel drugs and biological products such as vaccines are the most difficult of all to assess.^{iv}

ⁱ An Investigational New Drug Application (IND) is a request for authorization from the US Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans in the United States. Such authorization must be secured prior to shipment and administration of any new drug or biological product in clinical trials that are conducted in the United States

ⁱⁱ A further element that underpins registration is the assessment, approval and registration of in-country clinical trials that will eventually form part of a product dossier (see Annexe 3 for additional information).

ⁱⁱⁱ Biological products (biologics) refer to a wide range of products derived from natural sources such as vaccines, blood and blood components, and recombinant therapeutic proteins among others. These products may be produced by biotechnology and may be used to treat a variety of medical conditions for which no other treatments are available. Biologics in this report refers ONLY to vaccines

Assessment of generic “copy” drugs is relatively simple. This is because the regulator only needs to establish two key points. First, that the generic is bioequivalent to, and thus, therapeutically interchangeable with the comparator product (safety and efficacy therefore do not need to be proven again through clinical trials, because, if the products are bioequivalent, they will be the same for both the generic and the original). Second, that the product meets comparable sustainable quality standards to that of the innovator product. This requires assessment of pharmaceutical development, including Good Manufacturing Practice (GMP) inspections to ensure the manufacturing plant and procedures used will consistently produce the generic to the same quality standards as that authorised for sale by the MRA.

There are several methods to assess generic bioequivalence, including:

- Applying a *biowaiver* based on the Biopharmaceuticals Classification System (BCS), which limits the comparison to laboratory tests of dissolution profiles
- Comparative *pharmacokinetic studies* in humans, which are the commonest method. These measure the concentration of the active ingredients over time in blood and/or plasma
- Pharmacodynamic and comparative *clinical trials* in humans, when bioequivalence cannot be assessed in routine blood or plasma studies (e.g., for topical products or other products that are not absorbed into the blood stream)

The next category of products in terms of regulatory complexity is new formulations and fixed-dose combinations (FDCs). These are previously authorised drugs but in new dosage regimens, new combinations with other drugs, or new formulations e.g. syrup rather than tablet. These products have the potential to bring significant benefits due to increased compliance, improved dosing accuracy, reduced development of resistance, lower manufacturing costs and simpler logistics of distribution. However, depending on the type of FDC or reformulation, they can also present substantial challenges to MRAs. The WHO has outlined four FDC scenarios with different levels of complexity and regulatory requirements⁵:

Simple:
similar to
generic
approval

Type 1: The new product has the same (or bioequivalent) component drugs, dosage regimen, and dosage formulation as existing products

Type 2: The new product includes drugs in the same dosage regimens as an existing regimen of single entity tablets, but combines these ingredients into one tablet

Type 3: The new product combines existing drugs that have *not* previously been used for this disease indication; or in dosages or formulations different to those for which safety and efficacy have been established for this indication e.g. the paediatric syrup of Coartem

Type 4: The new product includes one or more novel drugs that have not been used in humans before

Complex:
similar to
novel
drug
approval

The commonest FDCs presented to African MRAs, and the easiest to deal with, are Type 1 and 2 FDCs, which are handled in much the same manner as generic approvals. However, African regulatory authorities are increasingly being required to assess new Type 3 and 4 FDC products that are being developed by Product Development Partnerships (PDPs), companies and others. For example, new anti-malarial FDCs such as artesunate-amodiaquine (ASAQ) and artesunate-mefloquine (ASMQ) (registered in Morocco in 2007, and in Brazil in 2008, by the Drugs for Neglected Diseases initiative (DNDi)); paediatric reformulations of Combivir and Eпивir for HIV/AIDS (registered in 2007 by GlaxoSmithKline (GSK)^{6,7}; and paediatric Coartem Dispersible (developed by the Medicines for Malaria Venture (MMV) and Novartis and registered in 2009). Each of these included substantial preclinical and clinical data in their regulatory dossiers, requiring assessment similar to that of novel products.

Assessment of regulatory dossiers for novel products is highly complex, even for well-resourced and experienced Western regulators. Dossiers can extend to thousands of pages of data and information that must be sifted through and analysed by MRAs seeking evidence that the product meets their quality, safety and efficacy requirements. In some cases, African MRAs can leverage prior assessments by ‘reference regulators’, that is, by regulatory authorities whose assessments they trust, such as the FDA and EMEA. However, neglected disease dossiers may not be submitted to a reference Western MRA first, and may thus reach the African MRA before any other assessment has been made.

Even when a reliable external assessment has been made, a number of hurdles remain before that assessment can be leveraged by an African regulator. The African MRA must be able to assess the product’s suitability for the local market, as opposed to its suitability for the market served by the Western regulator. This requires a risk/benefit analysis to be conducted at the national level in order to balance the product’s efficacy profile and known side-effects. This requires knowledge of the local risk tolerance situation regarding risk profile of the disease to be treated and the risk profile of the treatment being proposed – a situation that is often unknown in capitals (e.g. Washington or London) outside the local MRA area of concern. It also requires knowledge of how the proposed treatment will act in the local population – an assessment that is often difficult if the clinical trial population is not indicative of or cannot be extrapolated to the local population that is the focus of the African MRA.

The capacity of the local health system to deliver the product may also need to be taken into consideration, as well as, for some MRAs, support for local production or the existence of equivalent products already on the market.

Differences in the structure and requirements of regulatory dossiers between countries can also present hurdles. Most Western regulators follow the Common Technical Document (CTD) structure set out by the 2003 International Conference on Harmonisation (ICH), which was agreed by the MRAs of Europe, Japan and the US and the research-based industry. Many African MRAs structure their dossier requirements along WHO guidelines which, while very close to the CTD format, are according to African regulators better adapted to developing country needs. African regulators are also gradually starting to implement CTD in their national settings as part of the African harmonisation initiative, making it easier for an African MRA to leverage a prior external decision.

AFRICAN MEDICINES REGULATORY AGENCIES

Medicine Regulatory Agencies in Africa face particularly significant challenges in meeting their mandate. African regulatory capacity overall is below that of Europe, Latin America and much of Asia, with a 2004 WHO study reporting that 90% of African MRAs lacked sufficient capacity to guarantee the quality, efficacy and safety of medicines in their country.⁸

A study conducted by WHO in 2006 concluded that South Africa had a fully functional MRA; that the MRAs of Nigeria, Zimbabwe, Senegal, Tunisia, Morocco and Algeria were functional but needed “strengthening in regulation of clinical trials”⁹ amongst other things; and that the MRAs of Ghana, Egypt, Uganda and Ethiopia had “potential” although they were not yet fully functional. Over 40 African MRAs were considered insufficiently functional and needing significant capacity building to perform fundamental regulatory tasks. In 2005, 87% of African MRAs self-reported that they could not evaluate biologics such as vaccines, while some African MRAs did not yet have a vaccine registration system.³⁶

Over 40 African MRAs were considered insufficiently functional and needing significant capacity building to perform fundamental regulatory tasks.

These findings have changed over time, for instance, since the 2006 WHO report there have been substantial investments and progress made by Tanzania and Kenya. WHO is currently preparing an updated report reviewing the regulatory capacity of 26 African MRAs, with results expected to be made public in early 2010.^v This updated WHO report was available too late to be factored into our own work, however we do not expect a major overturn in the 2006 situation i.e. it is still likely that only a minority of African MRAs have the resources to effectively evaluate new medicines de novo.

The main factors behind Africa’s regulatory capacity shortfall are:

- ▶ **Lack of a clear legislative framework** to allow African MRAs to ‘command and control’ their turf by conducting functions ranging from import registration to registration and surveillance of suspected adverse reactions. Despite the centrality of medicines legislation, WHO found it to be “ill-suited or non-existent” in 37% of 38 African countries surveyed¹⁰
- ▶ **Dispersion of regulatory responsibility** among several institutions and ministries in the central government. For instance, some francophone West African countries do not have a unified medicines legislation, with regulatory responsibility being placed in the hands of multiple departments within the Ministry of Health. The situation is compounded by many external interventions and initiatives, which tend to focus on building capacity in specific functions but with limited attention to overarching policy and legislative frameworks

- ▶ **Lack of resources**, with an estimated 63% of African MRAs having insufficient financial resources to evaluate effectively the quality, efficacy and safety of new pharmaceutical products.¹⁰ This is particularly so for MRAs financed from government budgets, rather than from fees
- ▶ **Lack of experienced and qualified staff** in terms of numbers and skills. Some MRAs have only 1 or 2 personnel to conduct all regulatory functions, a situation exacerbated by brain drain. For instance, of the less than 50 pharmacists who graduate in Uganda each year, the majority take up positions with industry and international organisations, leaving the Ugandan National Drug Authority understaffed. In addition, pharmacy schools as a rule do not provide specific training in regulatory affairs, limiting the usefulness of graduates to MRAs and industry
- ▶ **Lack of political support** from many African governments, which in turn results in limited resources being invested into medicines regulation
- ▶ **Lack of appreciation** of the importance of medicine regulation by stakeholders, including researchers, developers, government departments and the general public.

^v Personal communication from Dr Lembit Rägo, WHO

THE CURRENT APPROACH: GAPS AND OBSTACLES

The combination of Africa's long-standing regulatory challenges and new regulatory demands means African MRAs urgently need to be able to assess and make appropriate regulatory decisions regarding new drugs specific to their populations, or to have access to mechanisms to support their assessment and decision-making.

The current mechanisms available to assess new neglected disease drugs are:

- ▶ Standard regulatory review by stringent (usually Western) authorities
 - Routine regulatory review
 - Orphan drug designation and review process
 - Expedited review
- ▶ Neglected disease-specific review by stringent (usually Western) authorities
 - European Union: Article 58
 - US FDA: "Tentative approval"
 - WHO drug prequalification

ROUTINE REGULATORY REVIEW BY (USUALLY WESTERN) AUTHORITIES

The majority of new products for neglected diseases are first submitted to well established Western regulatory authorities such as the US FDA, EU EMEA, UK Medicines and Healthcare Products Regulatory Agency (MHRA) or the Swiss Agency for Therapeutic Products (SwissMedic) for registration. This is the case even for products that are likely to have little or no use in the West but are crucial for developing countries, such as new drugs for sleeping sickness – although we note that travel and immigration mean some of these diseases are increasingly being seen in the West.

This route is typically followed by multinational companies developing products for neglected diseases, and by Product Development Partnerships (PDPs) who may be pressed by their company partners to use this route for drugs they are co-developing. Under this approach, companies wait for FDA or EMEA approval and receipt of a Certificate of a Pharmaceutical Product (CPP)^{vi} before submitting the full or abridged product dossier and CPP to African MRAs.

Application for WHO Prequalification (Prequal) approval (see below) is also generally sought only after FDA or EMEA approval. Occasional instances of early developing country registration occur, for instance some companies submit dossiers to commercially relevant developing countries that do not require CPPs, such as South Africa, while awaiting FDA/ EMEA approval; however these are the exception rather than the rule. The preference shown by multinational companies for first-Western registration is driven by a variety of factors, including familiarity, clear protocols and rules, liability management and access to early commercial returns on products with overlapping rich and poor markets (e.g. vaccines for pneumonia or rotavirus). Pragmatism also plays a role, with firms noting that many African countries will not progress review of a novel product until they have seen an approval by a stringent Western regulatory authority.

This choice of regulatory route has advantages and disadvantages. On the positive side, it brings decades of regulatory experience to bear on assessment of the neglected disease product; however, it is often insufficiently adapted to the specifics of neglected disease products and their end-users in other geographic settings. The fundamental problem is that, while well-resourced Western MRAs have extensive experience in assessing novel products for chronic diseases such as hypertension and diabetes, they are largely unfamiliar with products for malaria or sleeping sickness, or with the circumstances in which they will be used in developing countries. In some cases, such as malaria vaccines, no prior product of this kind has ever existed, thus very few really know how to go about studying, trialling and assessing them.

The fundamental problem is that, while well-resourced Western MRAs have extensive experience in assessing novel products for chronic diseases such as hypertension and diabetes, they are largely unfamiliar with products for malaria or sleeping sickness, or with the circumstances in which they will be used in developing countries.

^{vi} The Certificate of a Pharmaceutical Product (Product Certificate or CPP) is a key certificate within the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce. It is used to exchange information on the safety, efficacy and quality of pharmaceutical products being imported

Examples of problems associated with waiting on a standard Western assessment of a neglected disease product or relying entirely on a standard Western assessment before registering a product in Africa are:

- ▶ **Delayed access** for target patients in Africa, who must wait until Western regulatory review is completed
- ▶ **Inability to provide clear guidance** on the clinical trial design and the data required for marketing approval, sometimes despite recruitment of expert opinions in areas where Western MRAs have less experience (e.g. paediatric toxicity of malaria drugs)
- ▶ **Lack of sufficient safety and efficacy data** requirements for wider use. In approving a new drug, no MRA has the obligation to request clinical data that is relevant *outside* their own markets, even though it may be crucial for safe use in those settings. For instance, African AIDS patients are far more likely to be co-infected with TB or malaria than Western patients, therefore local trial data is crucial to assess safe interaction of HIV and malaria drugs, or use in patients with TB co-infection. However, these issues are often raised only long after clinical development is completed and drugs have been registered and marketed in the US and Europe – if they are raised at all.¹¹ The specific needs of African patients are sometimes taken into account but this is ad-hoc rather than systematic, depending on the decision of the developer not the mandate of the regulator. For instance, in the case of rotavirus vaccines, additional phase III clinical trials are currently planned or ongoing in Africa and Asia for Rotarix (GSK) and RotaTeq (Merck). These are designed to provide locally relevant safety and efficacy data; in particular, to take into account factors uniquely present in Africa such as widespread malnutrition, diversity of strains in the region, and the high incidence of malaria, HIV infection and diarrheal pathogens, which may inhibit the efficacy of these second generation rotavirus vaccines or affect their safety profile^{12,13}
- ▶ **Inappropriate data requirements.** Western regulatory rules may require product trials in their own jurisdictions, even for tropical diseases that do not occur there, adding expense and delay to the development process for little or no benefit
- ▶ **Inappropriate risk-benefit assessment for wider use.** The relative risk/benefit of neglected disease drugs may be dramatically different in Africa and the West – indeed, it is likely to be one of the major determinants of the registration outcome, as seen in the example of first generation rotavirus vaccines. The first rotavirus vaccine, RotaShield, developed by Wyeth-Ayerst and licensed by the FDA in August 1998, was later found to have a 1 in 10,000 risk of intussusception in children and was therefore withdrawn by the company from the US market in October 1999, precluding its subsequent introduction in the developing world.^{14,15} Although this risk/benefit analysis was perfectly valid for the US, where rotavirus causes less than 60 deaths per year, the *same* analysis could lead to a completely different outcome in developing countries, where rotavirus is responsible for approximately 5% of deaths in children under the age of five (a mortality rate of 183/100,000).¹⁶ However, the benefit of the vaccine to Africa could not be realized as the product's withdrawal from the US market signaled its death knell.

ORPHAN DRUG APPROVAL

Orphan Drug Legislation (ODL) in the US, European Union (EU), Japan and Australia provides incentives to manufacturers to develop and register drugs for diseases that have too few patients to constitute a profitable market within each of those jurisdictions.^{vii} It is primarily designed for Western diseases such as rare cancers or endocrine disorders and, indeed, the vast majority of orphan applications and approvals are treatments for Western disorders. However, small numbers of neglected disease treatments have been and continue to be submitted through the orphan designation and assessment route:

- ▶ As of May 2008, FDA has approved 325 products that had been designated as orphan products, of which 10 were for neglected diseases (four for malaria, four for tuberculosis and two for kinetoplastid diseases)
- ▶ Australia's orphan drug programme shows a broadly similar result with 156 approvals, of which one was for malaria
- ▶ Of the 50 EMEA approved orphan drugs, none were for neglected diseases

Several PDPs or their industry partners are planning to submit neglected disease products for assessment under these orphan programmes. Several have already received Orphan Drug designations for example, paromomycin intramuscular (IM) injection for visceral leishmaniasis, and Eurartesim (dihydroartemisinin and piperaquine) for malaria received Orphan Drug designations from the FDA and the EMEA in 2005 and 2007 respectively. This growing trend of applying for orphan designation in the West may have implications for African MRAs who may rely on approvals by Western regulators as a sign that the product is also safe and suitable for their population.

ODL has features that may make it unsuitable as the *primary* vehicle to approve neglected disease products for use in the developing world, although it may be highly valuable for specific categories of product. Western ODL programmes are based on the assumption that so few patients have a given orphan disease that it would be unreasonable to require the large-scale trials normally needed to generate sufficient data to substantiate the quality, safety and efficacy of a new product before it is authorised for marketing and use. Although entirely reasonable in the situation of a rare cancer, with perhaps a few hundred sufferers, it is potentially dangerous in our view to allow an abbreviated product registration in the case of products for a disease that may have few patients in the West, but may have literally hundreds of thousands of patients in other countries where registration may occur based on prior Western approval through the ODL route.

ODL also may have the perverse effect of incentivising *less over more* valuable health innovations related to African markets, because the Western neglected disease market conferred by orphan status is generally so small that only the feeblest of research efforts can be funded if the company is still to make a profit. These small profits in turn generally attract small firms with limited knowledge of developing country markets or diseases; and with their eyes firmly fixed on the needs of consumers in the home market where the ODL monopoly rights apply.

As a result, orphan neglected disease products registered to date have been of very limited value in developing countries. An internal review shows that half of the 10 neglected disease products approved by the FDA under Orphan legislation until May 2008 had little or no innovative value. The majority – even those with innovative value -

^{vii} Several countries have instituted Orphan Drug laws, including the US (1984), Japan (1993), Australia (1998) and the European Union (2000). Though all slightly different, in general each legislative package provides a mix of measures to cut development costs (such as tax credits, research grants) and increases the monopoly sales period to allow the pharmaceutical company to reap greater rewards (market extensions, more rapid regulatory review)

were also unsuited to developing country use, for example due to inappropriate formulation and/or price. A typical example is rifapentine, a novel TB drug registered under US Orphan Drug provisions. Although rifapentine was trialled in Africa as well as the US, it cannot be used in African TB patients. This is because the trial design excluded HIV-positive patients, because HIV is less commonly associated with TB in the US although it represents up to 75 percent of TB patients in some sub-Saharan Africa countries.¹⁷ Since rifapentin's safety and efficacy have not been proven in HIV-positive TB patients, the efficacy data's relevance to the African population is unknown – a highly unfortunate situation as a large proportion of TB deaths occur there.

These provisos aside, it is important to note that ODL can offer useful benefits, in particular for cases where a product developer is already developing a full regulatory package with the goal of providing a safe, effective product for developing world markets, for instance neglected disease PDPs. For these groups, ODL research grants, tax breaks, regulatory benefits such as free scientific advice, and monopoly rights in the admittedly small Western market are valuable supports to an *existing* R&D programme targeting the larger but less lucrative developing world market. For them, ODL benefits are the “icing on the cake” rather than the goal or guide to their product development design and efforts.

The key takeaway message with ODL, however, is that neglected disease product approvals that use small data sets should not automatically be relied on by African regulatory authorities as indicating that a product is safe, effective and suitable for use in their own countries, where large populations with the disease exist and where other unique factors may play a role in overall safety and efficacy of the product. Rather they will need to review the extent and thoroughness of the development programme, which will depend to a great extent on the sponsoring product developer's motivations, approach and target market; or, to consider other approaches.^{viii}

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EXPEDITED APPROVAL PROCEDURES

Both the US FDA and the EU EMEA have special regulatory procedures that expedite the progress of products through the development and marketing application review process. These procedures are essentially the same in concept and practice between the US FDA and EMEA although their names differ. They include:

- ▶ “Accelerated approval” (US FDA) / “conditional approval” (EU EMEA)
- ▶ “Priority review” (US FDA) / “fast track” (EU EMEA)
- ▶ “Fast track” (US FDA) / no comparable EU EMEA programme at present

These pathways are not primarily designed for neglected disease drugs but have been and can be used for that purpose. They are therefore discussed only briefly here to highlight points of relevance to African regulators.

In each program, the manufacturer and regulatory authority work closely together during the product development and review process to ensure the development scheme is designed in the most scientifically appropriate manner to answer critical safety and efficacy questions. This includes advice on appropriate trial design, comparators, statistical approaches, safety monitoring functions, etc. The three processes are also non-exclusive, that is, product developers can apply for and use two or more of these processes simultaneously in each jurisdiction.

Accelerated approval (US FDA) / Conditional approval (EU EMEA): This procedure applies to products for serious and life-threatening diseases for which there are few, if any, effective products, allowing them to be registered based on studies using unvalidated surrogate endpoints.

We note that validated surrogate markers or endpoints are commonly used as predictors of clinical benefit, for example, anti-hypertensive drugs are generally assessed on their ability to lower blood pressure, and products for hypercholesterolaemia are assessed based on their ability to lower cholesterol (with blood pressure and cholesterol both being validated surrogate endpoints). The difference between Accelerated/ Conditional approval and routine approval is that, in the former, the surrogate endpoint has not yet been validated as predictive of clinical benefit although data shows it is reasonably predictive. Accelerated/ Conditional approval is used when the urgency of medical need is so great that the regulatory authority, patients and medical practitioners are willing to accept product authorisation based on an unvalidated surrogate while they await results of further clinical trials. If the trials fail to demonstrate ultimate clinical benefit, the product is removed from the market. An example of the Accelerated approval mechanism at work is the first anti-HIV drugs, which were authorised in the US using the, at that time, unvalidated surrogate endpoint of a positive effect on CD4 counts. Although evidence at the time strongly suggested CD4s were a valid predictor of clinical benefit, this was only proven subsequently.

In the context of Accelerated/ Conditional approval, African regulators may need to consider the option of African validation studies to ensure the unvalidated surrogate is indeed predictive in the African context. In reality, however, Accelerated/ Conditional approval is not an option for most neglected disease products in the African context, since appropriate surrogate endpoints do not exist for many of these diseases.

^{viii} WHO notes the option of “controlled release”, with broader product rollout based on local pharmacovigilance data. (Personal communication from Dr Lembit Rägo, WHO)

Priority Review (US FDA) / “Fast track” (EU EMEA) reduces the time taken by the regulator to review the final product dossier but does not allow short-cuts in the development process. In the US, for example, a marketing application that is given “priority” review is allotted 6 months for review and decision, rather than the 10 months allotted to a “standard” review. Similar time frames are seen for the equivalent EU EMEA review process.

Most neglected diseases dossiers would routinely be given “priority review” in the USA and “fast track” in Europe. A product authorised under this mechanism should not cause any particular concern for African regulators, since it simply demonstrates that the US FDA and/or EU EMEA thought the product of sufficient public health importance that they conducted a full standard review, albeit in a shorter time by prioritizing the review and allocating the necessary resources to do so.


FDA priority review voucher for tropical medicines

The chief application of priority review in the neglected disease field is courtesy of the 2007 Brownback legislation in the US, which offers Priority Review of a commercial product as a reward for the development and US registration of a product for one of 16 listed neglected “tropical” diseases. This mechanism is called the Priority Review Voucher or PRV.

The priority review and consequent four months of earlier market access in the West have significant value for companies, with this value intended to incentivise firms to develop new products for tropical diseases. A possible cause for concern, however, is that the PRV may impact on how and where new neglected disease products are registered in future. This is because companies developing new neglected disease products are likely to preferentially seek FDA registration over other approval routes that are better tailored to developing country needs (see below), in order to get the lucrative associated Priority Review Voucher, estimated by its authors to be around US\$300 million.

Fast Track approval (US FDA) / no equivalent process at present in the EU EMEA: This process needs to be differentiated from the EMEA “fast track” process (see above). Contrary to its name, the US Fast Track programme offers very rigorous development and review. It is called Fast-Track not because it allows short-cuts, but because the manufacturer is allowed to submit their product dossier in sections as each element of the pre-clinical, clinical and manufacturing are completed rather than waiting to conclude the whole development programme before submitting the dossier. This “rolling review” saves the manufacturer’s time (since they can move on to other development stages while the regulator reviews the first dossier sections) and provides invaluable feedback as the product is being developed. Fast-track involves very intensive interaction with the regulator, and is reserved for products for serious and life-threatening diseases for which there are few or no treatment alternatives – it is likely that products for many neglected diseases would be eligible. Although it is a very robust scientific review process, the relevance of the data and the risk- benefit analysis for the African versus the American context is nevertheless still something an African regulator would need to assess before simply relying on this, or any other, “external” assessment.

In summary, neglected disease products approved through the Accelerated (FDA) / Conditional (EMEA) approval processes should be treated with caution by African regulators, however approvals through the Priority Review (FDA) / Fast track (EMEA) or Fast-Track (FDA) processes can be relied on for regulatory guidance to the same extent as standard FDA and EMEA regulatory approvals.



FORMAL ALTERNATIVES FOR NEGLECTED DISEASE PRODUCT REVIEW

It is clear from the above discussion that simple reliance on Western regulatory decisions, which are quite appropriate for the jurisdictions for which they are responsible, may nevertheless have drawbacks in terms of relevance of clinical trials design and risk-benefit analysis and profile when it comes to deciding if the product is safe and effective when used in the African context. As a result, several new regulatory mechanisms have been formalised over the past few years to more specifically address some of these “relevance” issues and to create more incentives for the development of neglected disease products. All are in their infancy, however their performance to date, and the pros and cons of each, are discussed below.

ARTICLE 58

The Article 58 mechanism was established by the European Commission in 2004 to facilitate developing country registration of medicines to prevent or treat diseases of major public health interest, including neglected infectious diseases. It was designed to assist developing country regulators by providing a scientific assessment of a dossier for a medicinal product for use outside the European Union. This assessment is intended to provide developing country MRAs with analysis and information to support their own registration decisions, rather than making this decision for them.

Under Article 58, EMEA staff conduct a regulatory review that is identical in all aspects to standard EMEA regulatory review and requires submission of a full regulatory dossier as for any other product submitted to the EMEA. Article 58 then adds an additional level of review in the form of technical disease input from WHO-recommended experts, many from developing countries. This includes advice on risk-benefit in developing country settings, and on whether the drug is needed and appropriate for these settings. Additionally, when a factory inspection is scheduled, EMEA informs and invites developing country MRAs to join. Observers from WHO and developing country MRAs recommended by WHO may attend plenary discussions on products, provided that they sign a Public Declaration of Interests

and Confidentiality Undertaking, but these experts and observers have no voting rights in the plenary.

The basic fee for a marketing authorisation application under Article 58 is €251,600, although total or partial fee exemptions may be granted in exceptional circumstances for imperative reasons of public or animal health.^{18, 19} EMEA also offers scientific advice during the development process which can be invaluable in guiding developers as to the best clinical trial plan, inclusion of the right comparators in studies, and other aspects that improve the product development plan and the chances of successful registration. However, we note that developers are charged a basic fee of €75,500 for this advice.

An important point to note is that the Art.58 process does NOT culminate in a regulatory approval. At the end of an Art.58 review, the EMEA's Committee for Medicinal Products for Human Use (CHMP) instead reaches a scientific opinion on the product, with positive opinions published on their website.

Article 58 has several strengths, particularly from the patient perspective:

- ▶ It is very quick, averaging 2.5 months from submission to publication of a positive assessment (perhaps because so few products are submitted, as seen below)
- ▶ It offers a superior standard to most regulatory alternatives since it not only provides a regulatory assessment to the same level afforded to any product for use in the EU, but also incorporates an informed risk/benefit assessment from endemic country experts. This differentiates it from the approval mechanisms discussed above, which do not have significant structured developing country input
- ▶ Being able to omit European data from the regulatory dossier can offer real advantages to product developers and African patients
- ▶ WHO involvement in the review process may help to facilitate National Regulatory Approval at country level, although too few drugs have been approved to know if this is the case in practice.

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¹⁸ For comparison, FDA fees for FY2009⁽⁶⁾ (see paragraph 2 of ref 6) are US\$623,600 for applications not requiring clinical data, or supplements requiring clinical data; and US\$1.2 million for applications requiring clinical data review. The FDA also several mechanisms to waive or reduced these fees for neglected disease products. Also, FDA has a comprehensive fee system, rather than the more a la carte system used by the EMEA. For example, FDA has no fees for scientific advice, whereas the EMEA charges €90,000 for each scientific advice session.

However, Article 58 also has drawbacks. It has been poorly understood, poorly positioned, and has lacked good advocates and, as a result, has barely been used. Only four product applications have been submitted to the Art.58 process since 2004, all from multinational pharmaceutical companies. Of the submitted products, one was withdrawn and the remaining three, all label extensions or new formulations of existing HIV drugs, received a positive scientific opinion from the EMEA. These included paediatric reformulations of Combivir and Efavir, which improved HIV treatment for children in developing countries. We note, though, that several PDPs, including MMV, are now planning to submit products through the Article 58 process.

Article 58's underuse stems from two causes. The requirement that Article 58 only be used for products to be marketed outside Europe has led to African distrust of it as a "double standard", although the EMEA and WHO have recently held sessions with seven African countries to improve understanding and use of Article 58.

However, by far the greatest obstacle to Art. 58's success is its lack of incentives for companies, who by and large continue to choose other regulatory routes. Article 58 does not offer the benefits of Orphan Drug approval (e.g. tax breaks, research grants, free scientific advice, marketing exclusivity). It also has the major disadvantage of disallowing access to the European market since the regulations require that developers choose between Article 58 and the more beneficial (at least to developers) EU orphan drug status, unlike the US situation where developers can benefit from several incentives simultaneously e.g. Orphan status and Priority Review Voucher. Finally, there is a lack of clarity over which applications are eligible for partial or total fee waivers (an important factor if the end market is very low in value), which greatly reduces the attractiveness of the waiver to product developers.

By far the greatest obstacle to Article 58's success is its lack of incentives for companies, who by and large continue to choose other regulatory routes.

We also note that, despite a PDP preference for using the Art. 58 route because of its inclusion of endemic country expertise and exclusion of the need for European trials, this was sometimes rejected by the manufacturing partner, who preferred to secure the financial benefits associated with Orphan approvals and to register through the FDA in order to gain the lucrative associated PRV.

The only advantage offered to developers by Article 58 (i.e. non-requirement for European trial data) may also shortly disappear as a pharmaceutical company is now interested in making a test submission through regular EMEA channels of a dossier without European trial data. If accepted, this precedent would effectively eliminate the only substantial incentive offered by Article 58.

FDA "TENTATIVE APPROVAL" FOR PRODUCTS SUBMITTED IN ASSOCIATION WITH THE PEPFAR PROGRAMME

As part of the US President's Emergency Plan for AIDS Relief programme (PEPFAR), the US FDA announced in May 2004 the use of its tentative approval process to help assure the safety and quality of the HIV drugs purchased with PEPFAR funds for use outside the US. (We note that WHO had already begun to assess HIV treatments as part of their Prequalification programme at this time, and this may have helped to catalyse the FDA programme.)

While called a "tentative approval" in the US FDA regulations, a product must meet all of the safety, efficacy, and manufacturing quality standards of any product that would be allowed on the US market. The only reason the approval is called "tentative" and a full approval is not given is that patent or other market protection exists in the United States. Once this expires, the product is given a full approval and may be marketed in the USA.

The initiative includes five components:

1. FDA regulatory review (product meets all safety, efficacy and manufacturing quality standards for marketing in the US)
2. FDA works closely with manufacturers who have not interacted with them before to help them prepare the FDA application and inspection
3. FDA prioritizes review of these submissions (with a commitment to complete review in as little as two to six weeks after submission)
4. Engagement with WHO prequalification (PQ) to facilitate essentially automatic incorporation of these products into the WHO PQ lists, and closely working with regulatory authorities in endemic countries to assist rapid national assessment there
5. There are no registration fees associated with products submitted under this programme if they are generic products, or the fees are waived if they are new products

To date, around 100 products have been assessed by the US FDA and have been fully or tentatively approved in association with the PEPFAR program. Of these, 71 have been generic copies of products previously authorised in the USA and 29 have been new products. Twenty-two of these new products are new combinations or complete regimens that had not previously been authorised in the USA. In addition, there are 7 new paediatric products considered innovative for patients in emerging economies because they are small tablet formulations that are logistically easier to store, ship, distribute and administer than currently authorised formulations in the USA, which are typically solutions or powders for solution. Additionally, for children who are not able to swallow small tablets, these tablets may be dispersed in water and taken orally.

US FDA and the WHO PQ unit have a confidentiality arrangement that allows the exchange of reviews and inspection reports, so that these products can be quickly added to the prequal list. As a result, over one-third of WHO prequalified products are now PEPFAR products (113 or 41%), with the majority (66 products, or 58%) receiving automatic WHO approval. This contributed to the number of WHO prequalification approvals in 2008, and has accelerated African access to many HIV products.

WHO DRUG PREQUALIFICATION

The final route to expedite African access to quality drugs for neglected diseases is the WHO drug prequalification program, which started in 2001 as a means to assure the quality of drugs procured through the UN system. WHO prequalification provides a “surrogate” regulatory approval on which developing countries can rely, and seeks to build developing world capacity for dossier preparation and evaluation. The programme is focussed on drugs for HIV/AIDS, malaria and tuberculosis, but has recently invited companies to submit products for reproductive health, influenza and zinc supplements for use in managing acute diarrhoea. WHO prequalification or stringent regulatory approval is also a precondition (with limited exceptions) for procurement through several multilateral initiatives, e.g. the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and the Affordable Medicines Facility - malaria (AMFm). Many African MRAs rely heavily on the WHO drug pre-qualification system as a proxy dossier assessment and, in some cases, decision making entity and will quickly approve products that receive WHO prequalification.

allow PEPFAR-approved drugs to receive automatic WHO pre-qualification approval and listing. Around one-third of WHO prequal approvals (95 of 280) were new fixed-dose combinations: 72 for HIV, 12 for TB, and 10 for malaria (see Fig. 5). WHO drug prequal also approved 22 paediatric syrups (including two FDCs), nine of which had been previously approved under the PEPFAR scheme.

The majority of products given pre-qualification approval (77%) were generics manufactured by developing country firms, with two-thirds coming from India. This included 156 generic drugs (56% of all prequalified drugs) and 60 new FDCs or formulations of existing drugs (21% of the total). Some innovator products were also prequalified (64 drugs; 23%), however WHO Prequal normally requires these to have been previously approved by a stringent regulatory authority. For instance, emtricitabine+Tenofovir (Truvada) developed by Gilead Sciences, Inc. (FDA approval August 2004; prequalification May 2006); and efavirenz (Stocrin), (EMEA1999; prequalification 2006).

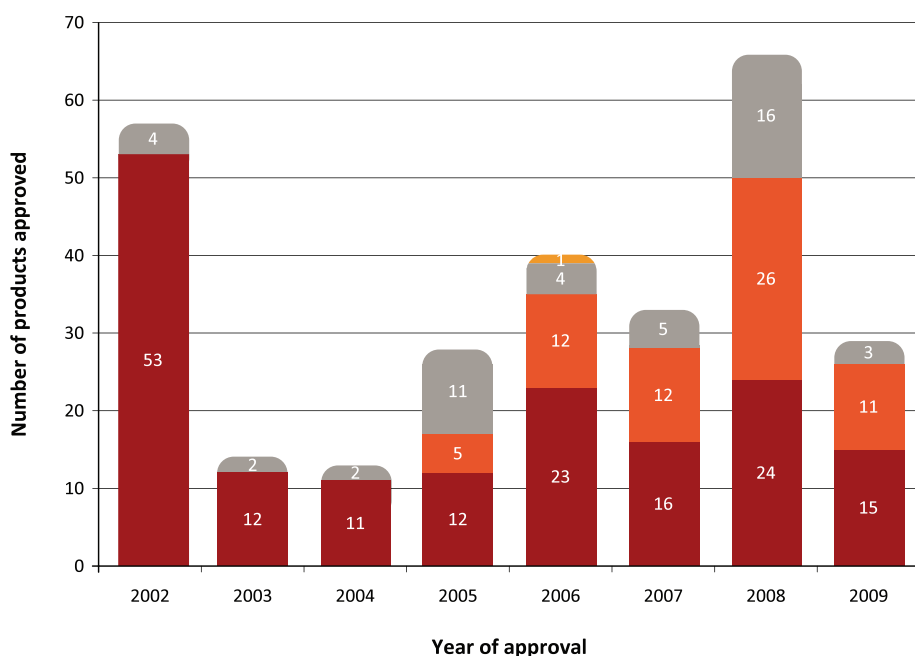


Figure 1:
WHO pre-qualified drugs per year by regulatory agency¹⁹

WHO Prequal conducts evaluation of medicinal products based on information submitted by the manufacturers, and inspection of the corresponding manufacturing and clinical sites. The scientific dossier for WHO Prequal is very close to the CTD described above. Evaluations are conducted approximately 6-9 times per year, generally lasting one week each, with the assessment teams typically being a mix of around 20 developed and developing country experts pulled together from around the world. Around one-third of reviewers are from Africa.

Average time to pre-qualification of 156 products up to 2007 was 24 months. As of June 2009, the programme had pre-qualified 280 drugs, the vast majority for HIV (241 or 86%), 20 for TB (7%) and 16 for malaria (6%). The 2002 peak in approvals reflects recognition of Western-approved products at the inception of the WHO programme; while the second peak partly reflects the agreement to

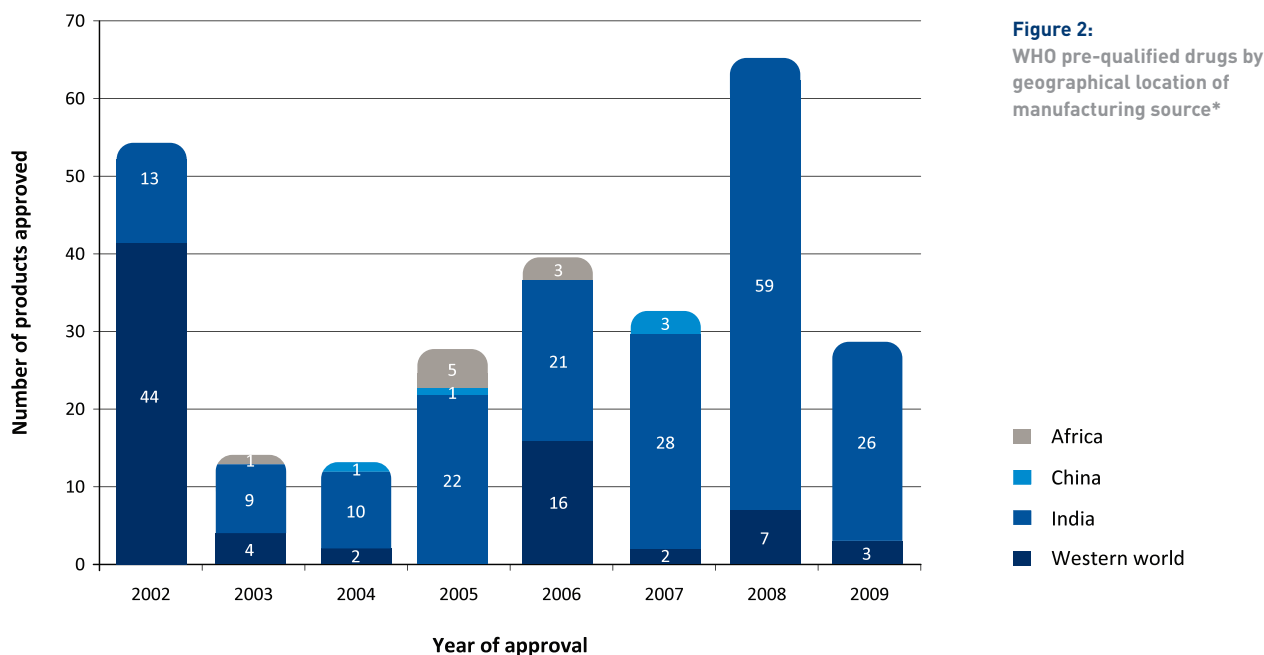


Figure 2:
WHO pre-qualified drugs by
geographical location of
manufacturing source*

Unlike routine MRA regulatory approval, WHO Prequal provides generic manufacturers with support to help them secure approval e.g. by providing assistance with dossier preparation such as advice on which bio-studies and comparators to use.^x There is also no application fee, which compares favourably to Western, but also African, MRAs - for instance, Ghanaian fees for registration of a new product manufactured locally are US\$500, while local registration for a repackaged imported product is US\$1,500. The prequal process also has no fixed deadline, with WHO working with manufacturers to get their product and dossier right for as long as they are willing. The Prequal team additionally conducts a wide range of capacity building activities, including:

- ▶ Training staff from MRAs, quality control laboratories and manufacturers to ensure medicines quality (10 people trained by 2008)
- ▶ A “rotational post” for assessors from less resourced countries, who join the WHO Prequal programme for three months before going back to their home agencies
- ▶ Training courses in standards and evaluation skills (over 500 participants to date)
- ▶ Joint plant inspections with developed and developing country MRAs

The WHO Drug Prequal program is viewed as having been generally successful. Developers welcome WHO’s training and assistance, and the programme is perceived as having quality standards similar to those of the FDA or EMEA. For instance, a Lancet editorial noted that:

*“... the latest news of the withdrawal of much-needed antiretrovirals from the prequalification list ... shows that this little known part of WHO is effective and has teeth that can bite rapidly...and prequalification status means that some of the most important drugs are being made safely available in parts of the world where they are most needed.”*²⁰

However, the program has also drawn criticism. It has mostly only approved drugs for HIV, malaria and tuberculosis, with the vast majority being generic HIV drugs.^{xi} This focus is based on recommendations from the International Conference of Drug Regulatory Authorities (ICDRA)^{12xii,21}, however, some argue that it fast-tracks HIV drugs at the expense of other products.

The problem seems to be that African authorities do not have the resources to conduct these assessments in a timely manner rather than that they have chosen to abdicate responsibility to WHO Prequalification.

^x PEPFAR offers similar support

^{xi} The openness to other products including reproductive health products is not evident in the list of drugs pre-qualified so far.

^{xii} The International Conference of Drug Regulatory Authorities (ICDRA) is made up of more than 100 national medicines regulatory authorities

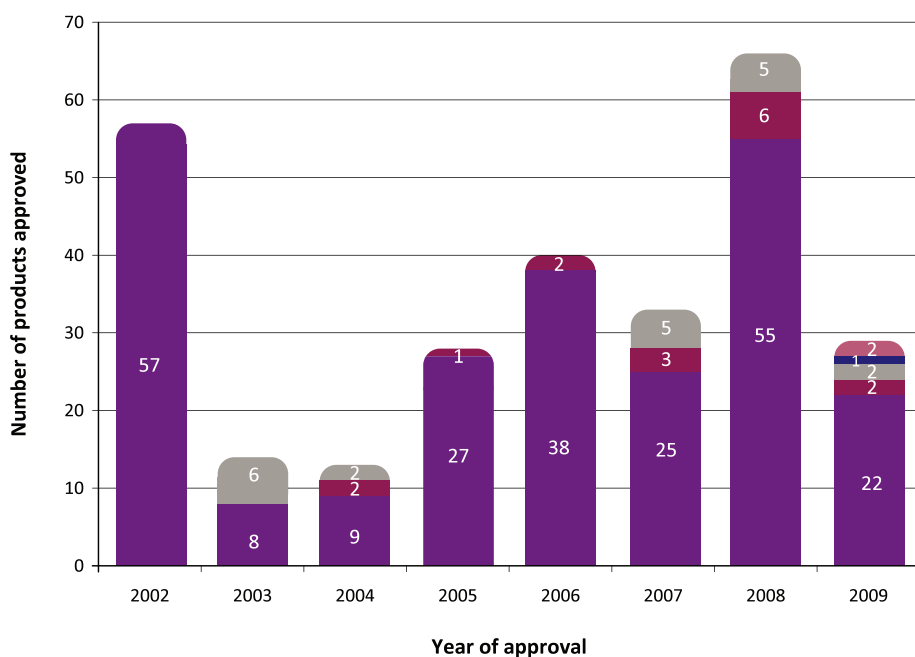


Figure 3:
WHO prequalified drugs
by disease

- Reproductive health
- Influenza
- Tuberculosis
- Malaria
- HIV/AIDS

Prequalification is also very slow, averaging two years. This reflects its voluntary, no-fee, capacity building approach, as well as the inexperience of many developing country manufacturers in preparing dossiers, with some requiring a great deal of work with WHO Prequal before they meet international standards. Initially, lack of resources also contributed to delays, but substantial funding from UNITAID (US\$6 million in 2007)²² and the Bill & Melinda Gates Foundation (US\$28.5 million over 5 years starting in 2007)²³ has since allowed recruitment of additional qualified staff.

Some interviewees felt the practice of pulling together teams from five continents to do each prequalification review was inefficient, expensive, slow and led to decision-makers being divorced from responsibility for the products they were approving. While several interviewees also queried the programmes' practice of drawing repeatedly on a small handful of African experts, many of whom are sorely needed in their home agencies.

Finally, some interviewees were concerned about over-reliance on the WHO Prequal programme, particularly given the constraints described above, with one interviewee asserting that, "the whole [African regulatory system] cannot rely on a single mechanism". In practice, however, the problem seems to be that African authorities do not have the resources to conduct these assessments in a timely manner rather than that they have chosen to abdicate responsibility to WHO Prequalification.

OTHER APPROACHES THAT OFFER LESSONS

It is clear that the formal neglected disease regulatory approaches outlined above offer benefits over standard Western regulatory review but it is equally clear that none are perfect and that more could be done to improve African access to new quality medicines.

Therefore, we also examine a number of informal alternatives that have been tried by product developers over the past few years, as well as routes used for vaccines, to see if these can offer lessons for drug registration in Africa.

PARALLEL WESTERN AND DEVELOPING COUNTRY APPROVALS

Under the parallel approval route, product developers simultaneously submit full dossiers to a Western regulator and developing country MRAs, who conduct their regulatory reviews simultaneously but independently. This approach aims to speed delivery of the neglected disease product to endemic countries.

The parallel route is more typically used by PDPs (whose mission is rapid access to patients) than by companies (who also focus on rapid access to commercial markets). For instance, one major PDP said they typically submitted dossiers simultaneously to African MRAs in the target countries, WHO Prequal and to a top-tier regulatory authority

(nominating EMEA Article 58 as their ideal route). They would not seek first registration in a developing country, as they believed review of dossiers by a top-tier Western regulator was the minimum baseline, however they saw parallel registration as an acceptable solution to maintaining standards while still expediting African registration.

In practice, the time gains offered by parallel approval may be illusory. Even if a dossier is submitted to them, many African MRAs wait on WHO prequalification or approval by a respected Western regulator before registering products, while some African MRAs will not even accept an application without prior external regulatory approval. The WHO also seeks prior approval of novel products by a respected regulatory authority before giving WHO prequalification. The troubling exception is in the case of weaker MRAs, some of whom have approved products before any external review and without a CPP even though it seemed unlikely they had in-house capacity to conduct a thorough safety, efficacy and quality review of the dossier themselves.

Two further drawbacks of parallel approval are that it neither assists African MRAs to review and approve complex dossiers, nor builds African regulatory capacity.

TWINNED WESTERN AND DEVELOPING COUNTRY APPROVALS

Twinned review refers to a process whereby a developing country regulator would assess a pharmaceutical dossier in consultation with, or alongside, a reviewer from a well-resourced regulatory agency.

In practice, there has NOT yet been a twinned review of a product dossier, although steps have been taken in this direction since 2006, including joint assessment of clinical trial applications and twinned review of 'training' dossiers. These initiatives have been facilitated by Product Development Partnerships who have an interest in capacity building as well as product registration.

As with Article 58, twinned reviews offer a potentially superior outcome by virtue of combining Western experience in product assessment with developing country experience in the specifics of the disease in their country and the risk tolerance from the perspective of that country. Twinned reviews have the additional merits of expediting African regulatory approval from the product developer's perspective; and building capacity for African MRAs themselves. We note though, that progress has been slow, with no actual twinned reviews conducted.

EXAMPLES OF TWINNED REVIEWS (BUT NOT FINAL APPROVALS)

ASAQ training dossier

In 2008, the WHO organised a regulatory training session that involved joint review and assessment of a full regulatory dossier by regulators from African MRAs, the EMEA and WHO. The ASAQ dossier developed by the Drugs for Neglected Diseases initiative (DNDi) was used as the case study (see Annexe 4).

RTS,S malaria vaccine trials

The World Health Organization (WHO), GlaxoSmithKline (GSK) and the Program for Appropriate Technology in Health-Malaria Vaccine Initiative (PATH-MVI) worked with seven African MRAs and the Belgian MRA (the country where the vaccine was manufactured) to jointly review and approve the clinical development plan for RTS,S.

Conjugate meningitis A vaccine trials

The WHO assisted in joint review and approval by four African countries (The Gambia, Mali, Ghana and Senegal) of the clinical trial application for a meningitis A conjugate vaccine by the PATH Meningitis Vaccine Program (MVP).

FIRST APPROVAL BY A DEVELOPING COUNTRY MRA

Under this approach, the product developer does not seek prior, parallel or twinned approval by WHO prequalification or by a stringent Western regulator, but instead submits the dossier first to a developing country regulator, usually their home regulator.

First registration in developing countries has typically been used by either developing country manufacturers or PDPs, with typical approaches noted below:

- ▶ An Indian pharmaceutical company, which focuses on generics and novel FDCs, routinely seeks first registration with their home regulatory authority in India. However, in order to maximise their market (an important consideration for low-margin, high-volume products), they then submit the dossier very widely, including to WHO Prequal, prominent Western authorities (usually the EMEA and FDA) and regulators in ‘tens of other countries’, including developing countries. Although first submission is in India, the firm works closely with both the Indian regulator and the FDA/EMEA from the beginning of the development process to ensure the final dossier matches regulatory requirements in all settings
- ▶ An African pharmaceutical company with an Indian joint venture partner seeks first registration with their home regulatory authority in Africa, while the partner company simultaneously registers in India. Registrations in Africa and India are followed by dossier submission to WHO Prequalification and to Western authorities such as the FDA and EMEA
- ▶ A vaccine PDP, which has a developing country manufacturing partner, seeks first registration in the developing country of production. In order to build capacity, clinical development oversight is conducted by African MRAs working in conjunction with WHO Vaccine Prequalification. Inclusion of WHO Prequal facilitates United Nations (UN) purchase and subsequent African regulatory approval

We note that first-line developing country approval and registration is routine for first-generation vaccine products procured for UNICEF, although in this case it is backed up by second line review by WHO Vaccine Prequalification, as discussed below.

In practice, the time gains offered by parallel approval may be illusory. Even if a dossier is submitted to them, many African MRA’s wait on WHO prequalification or approval by a respected Western regulator before registering products, while some African MRAs will not even accept an application without prior external regulatory approval.

EXAMPLES OF DEVELOPING COUNTRY (DC)-FIRST REGISTRATION

Conjugate meningitis A vaccine (India)

The PATH-Meningitis Vaccine Project (PATH-MVP) is developing a meningitis A conjugate vaccine with Netherland’s BioPartners BV, the Serum Institute of India and the US Center for Biologics Evaluation and Research (CBER). Clearance to start Phase I studies in India was given by the Drugs Controller General of India in early 2005, where registration is also expected to take place.^{24, 25} No Western regulator has been involved to date.

Paromomycin (India)

The Institute for One World Health (iOWH), a Product Development Partnership (PDP) based in the US, developed paromomycin, an intramuscular drug for the treatment of visceral leishmaniasis (VL). Phase III paromomycin trials were approved by the Drugs Controller General of India and conducted in India. In August 2006, India approved paromomycin for the treatment of VL.²⁶ Paromomycin dossiers will next be submitted to the MRAs of Bangladesh and Nepal, relying on Indian approval and information in the Indian dossier, as well as safety information from post-registration trials; and for inclusion in the WHO Essential Medicines List. We note that the iOWH also applied for and received Orphan Drug Designation from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for paromomycin intramuscular injection in early 2005, but did not submit final dossiers to either regulator.

Artesunate-mefloquine (Brazil)

The Drugs for Neglected Diseases initiative (DNDi) and Brazil’s Farminguihos/ Fiocruz partnered to develop the fixed-dose antimalarial combination, artesunate mefloquine (ASMQ), and the product was registered in Brazil in April 2008 through the Agencia Nacional de Vigilância Sanitária (ANVISA).²⁷ No Western regulator was involved apart from an initial scientific consultation with the UK MHRA to guide development of the dossier.

Artesunate-amodiaquine (Morocco)

DNDi partnered with sanofi-aventis and the WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) to develop a new fixed-dose antimalarial, combining artesunate and amodiaquine (ASAQ), which had already been used together in co-blisters for the treatment of uncomplicated malaria. The UK MHRA was approached first for scientific guidance in developing the dossier, however the product was first licensed by the Moroccan regulatory authority in Feb 2007. Morocco was chosen for first registration for a number of reasons, including that it was the product’s manufacturing site and in order to bring product to patients more quickly. ASAQ received WHO prequalification approval in October 2008, after the sanofi-aventis industrial site in Morocco received WHO Good Manufacturing Practice (GMP) certification in January 2008. While the prequalification process was underway, sanofi-aventis registered the product in 24 African disease endemic countries (see Annex 4 for more details).

WHO VACCINE PREQUALIFICATION

The WHO Vaccine Prequalification programme was set up in 1987 as a service to UNICEF and other UN vaccine procurement agencies, to determine that products bought by these agencies and used in national immunization services were safe, effective and met operational and quality standards. This system predominantly deals with vaccines used by Expanded Program on Immunization (EPI) (e.g. vaccines for diphtheria, tetanus, pertussis, measles and TB)²⁸, while the Global Alliance for Vaccines and Immunisation (GAVI) has offered a similar facility since 2000 for newer products such as Haemophilus influenzae type b (Hib) and Hepatitis B vaccines.²⁹

The programme's chief function is to identify suitable vaccines for countries that either:

- a) Source their vaccines through UN agencies. As of 2006, 57% of African countries used WHO prequalified vaccines sourced through the UN system³⁰
- b) Import directly from manufacturers. In 2006, 33% of African countries procured their vaccines from countries with a functioning MRA, as assessed against WHO guidelines.³⁰

Initial evaluation and approval of vaccines is conducted by the MRA in the country of manufacture (often a developing country). The WHO prequal programme then re-evaluates the vaccine dossier to determine safety, efficacy and suitability for UN procurement and developing country use; including analysis of local risk-benefit, which takes vaccine cost and the logistics of vaccine delivery into account. Developing country experts are routinely included in these WHO evaluations.

The vaccine prequalification programme offers a number of other services to support developing country vaccine regulators, including:

- ▶ Conducting regulatory services (e.g. laboratory services, GMP site inspections) for countries with minimal regulatory capacity who procure vaccines directly from the UN system
- ▶ Reviewing MRAs, with more than 80 having been assessed^{xiii}
- ▶ Capacity building, with over 1,000 technical personnel trained in vaccine regulation, surveillance of adverse events and vaccine quality
- ▶ Identification of regulatory experts to conduct vaccine evaluations, with over 400 experts identified globally^{31,32,33}

Since its inception just over 20 years ago, the programme has prequalified 82 vaccines produced by 21 manufacturers from 18 countries (12 industrialized country manufacturers and 6 developing country manufacturers) for the prevention of 14 infectious diseases.

WHO vaccine pre-qualification is strongly supported by African governments, and is often seen as being preferred over FDA and EMEA vaccine approvals. This is due to the associated training opportunities, and to the fact that WHO pre-qualification is linked to procurement of lower-cost vaccines from the UN.

However, there were also perceived downsides. Vaccine pre-qualification has significant costs - around US\$25,000 per application for a conventional vaccine and US\$66,500 for a novel vaccine.³⁴ The process is also relatively slow, typically taking 31 months for a vaccine produced in the EU to be registered for use in Africa: 13 months for European approval; 18 months for WHO pre-qualification; and 12 months for registration with an African MRA. This is partly ameliorated by the WHO's recommendation that African MRAs develop a 'fast-

track' review mechanism to expedite local approval of WHO pre-qualified vaccines, but not all MRAs have done so.

Despite the programme's energetic efforts to include and train developing country regulators, some commentators also felt WHO vaccine prequalification had delayed growth of indigenous African capacity to independently review vaccines, with under-resourced MRAs readily transferring this responsibility to WHO.

WHO vaccine pre-qualification is strongly supported by African governments, and is often seen as being preferred over FDA and EMEA vaccine approvals. However, there were also perceived downsides. Vaccine pre-qualification has significant costs ... and the process is also relatively slow.

^{xiii} The WHO MRA assessment tool evaluates country MRAs based on several criteria, including legislative and enforcement power, sufficient financial and human resources, appropriate expertise and quality of staff, independence in decision making, adequate mechanisms for recalling products, and transparency and public accountability. WHO requires that a vaccine producing country has an assessed and functional MRA before prequalification can begin.

AFRICAN REGULATORY ADVANCES

As noted above, divergent regulatory and dossier requirements between countries introduce costly inefficiencies and time-delays into the process of approving new products, be it for the EU or Africa. African regulatory 'dis-harmony' not only creates difficulties for African MRAs seeking to maximise use of scarce regulatory resources by sharing information, but also places unnecessary burdens on the low-cost manufacturers on whom Africa relies.

Therefore, a great deal of effort has been put into African regulatory harmonisation initiatives for many years, including by multilateral organisations such as the World Health Organisation and its regional offices in Africa, the Americas and South East-Asia; as well as by donors such as the Department for International Development (DFID) in the UK, the European Commission through its EDCTP (the European & Developing Countries Clinical Trials Partnership) initiative, and more recently the Gates Foundation and Clinton Foundation. In recent months, these efforts have been matched by African initiatives led by the African Union through its economic development program, the New Partnership for Africa's Development (NEPAD), and by Regional Economic Communities (REC) on the continent. RECs such as the Economic Community of West African States (ECOWAS), the Southern African Development Community (SADC), and the East African Community (EAC), have made some progress, as described below.

SADC

Although loosely in existence since 1980, the SADC was formally established by Treaty in Namibia on 17th August 1992. It consists of 15 Member States: Angola, Botswana, Democratic Republic of the Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe, and covers an estimated total population of 200 million people.

The SADC health agenda is driven by an overarching Protocol of Health signed by the SADC Heads of States, which came into force in August 2004. This gives regional cooperation a legally enforceable framework. An example of this in action is the pharmaceutical business plan for the period of 2007-2013, which includes:

- ▶ Leveraging the strength of several member state MRAs to build the capacity of weaker members through training, capacity assessments and information exchanges
- ▶ Regional pooled procurement
- ▶ Harmonisation of Essential Medicines Lists
- ▶ Implementation of guidelines already developed and approved, including Licensing for Export/Import of Medicines, Validation (Analytical and Process), and Clinical Trials for HIV Vaccines. Other guidelines will address registration of medicines, stability, biostudies (Bio Availability/Bio Equivalence), GMP and clinical trials for human participants
- ▶ Development of new guidelines on crucial issues such as registration of vaccines and African traditional medicines
- ▶ Harmonisation of clinical trial regulatory evaluation, review and monitoring
- ▶ Harmonisation of regional dossier requirements

ECOWAS

The West African Drugs Regulatory Authority Network (WADRAN) was born in the wake of the crack-down by Nigeria's National Agency for Food and Drug Administration and Control (NAFDAC) on drug counterfeiting; being designed as a pre-emptive strike against counterfeiting activities in neighbouring countries with weaker regulation.

Championed by the Director-General of NAFDAC, Dr Dora Akunyili, WADRAN is a forum where heads of drug regulatory authorities in anglophone and francophone West Africa can share strategies, experience and capacity in the fight against counterfeiting. Activities include:

- ▶ Regional sharing of information on blacklisted companies
- ▶ Advocating for collaboration between customs and regulatory agencies
- ▶ Intensifying post-registration surveillance and effective GMP inspections
- ▶ Development of regional "centres of excellence" including quality control labs to serve the region:
 - Burkina Faso has been suggested to host a vaccine quality control lab
 - The Kumasi University of Science and Technology, Ghana, is developing a drug bioequivalence centre
- ▶ Developing expert committees to conduct dossier evaluations for some products on behalf of the region, in collaboration with ECOWAS and the West Africa Health Organisation (WAHO).
- ▶ Acknowledging the value of a harmonised regulatory dossier

EAC

The Treaty for Establishment of the East African Community (which entered into force in 2000) explicitly notes harmonisation of drug registration procedures as an objective to achieve good pharmaceutical standards without posing an obstacle to the free movement of pharmaceutical products. So far the EAC has made progress in the following:

- ▶ Country-level assessments, using the WHO Standard Technical Assessment Tool, to assess existing capacities across the region
- ▶ Initial steps towards harmonization of standards and practices for Quality Assurance
- ▶ Evaluation and feasibility studies of regional pooled procurement
- ▶ Development of a 2009-2013 Strategic Plan, under which the EAC plans to utilise existing regional regulatory infrastructure and to centralise registration evaluation, inspection and testing functions to Kenya, Uganda and Tanzania according to the comparative advantage of each MRA.

Despite these advances, overall progress towards greater harmonisation has been slow. Disparate legislative frameworks based on national level regulatory functioning rather than regional harmonisation add substantial practical obstacles to progress. Some African MRAs also cite lack of trust, for example, distrust of data generated in neighbouring countries, or of bioequivalence studies performed elsewhere even where the comparator is the same. The “national sovereignty imperative” also presents hurdles, with some countries offering a lukewarm response to suggestions of regional harmonisation, emphasising that they wanted to build their own capacity and conduct regulatory functions themselves; loss of income from regulatory fees can also pose difficulties. We note, however, that reluctance to harmonise is a universal problem – for instance, Europe’s regional EMEA regulatory mechanism was only developed after 40 years of trust-building.

The role of external donors in driving harmonisation also received a mixed response. It was acknowledged that external efforts were often the main catalyst to harmonisation but they were also seen as unreliable and patchy, tending to die off when donor funds or political will waned. Donors were also seen as prescriptive, “rather than allowing MRAs to own the process and decide the harmonization model they feel is feasible to meet their need.” One approach that received a warmer welcome was the bottom-up approach, such as that of the African Drug Registration Harmonisation consortium led by NEPAD, the Pan African Parliament (PAP), the Bill & Melinda Gates Foundation, DFID, the Clinton Foundation and the WHO. Under this initiative, started in February 2009, African policy makers set the agenda and drive progress. For instance, African RECs and organisations are in charge of developing high-level plans that will be used to attract donors, who will then be asked to review these and to consider funding full project proposals to build and harmonise African regulatory capacity, with a first focus on regulation of generic medicines.³⁵

A last critical consideration for harmonisation activities is striking the right balance between regional rationalisation and national level capacity building. As one African expert noted: “While efforts are made to harmonise medicines regulation in the region, they should at the same time be geared towards assisting countries with limited resources to build their regulatory capacity as this will be the foundation for building trust among different MRAs and eventually lead to mutual recognition of regulatory decisions.” Harmonisation without strengthening will be short-lived and ineffective. At the end of the day, initiatives must continue to seek to build national African MRAs to a high level of competence.

“While efforts are made to harmonise medicines regulation in the region, they should at the same time be geared towards assisting countries with limited resources to build their regulatory capacity as this will be the foundation for building trust among different MRAs and eventually lead to mutual recognition of regulatory decisions.”

DISCUSSION

New times require new tools. A reduction in Western regulatory checks on medicines commonly used in Africa, combined with the advent of new products developed for tropical diseases, means that standard approaches to registration of novel drugs need to be rethought or augmented for the African context.

Indeed, there are currently no regulatory approaches that satisfy all components of optimal drug registration for Africa:

1 Reliably assesses safety, efficacy and quality for African use

The most reliable mechanisms for assessing the safety, efficacy and quality of novel neglected disease products for use in Africa are those that include:

- ▶ Expertise in assessing novel products
- ▶ Expertise in developing country disease presentations, products and risk-benefit factors
- ▶ Trials and data relevant to developing world settings

For this reason, Article 58, WHO prequalification and twinned review are superior from the neglected disease perspective to standard or fast-track Western regulatory approval, accelerated review, Orphan drug, or first registration by a developing country MRA. Unlike Article 58, WHO prequalification and twinned review, an approval or rejection by these other regulatory routes does not automatically mean a product is safe or unsafe for use in Africa. This is particularly the case for accelerated review, orphan approval and first registration by a developing country MRA, whose judgments need to be reviewed on a case-by-case basis for applicability to Africa.

2 Assesses suitability for African use with formal DC input

Likewise, the only way to guarantee that safe, effective products are also *suitable* for African use (e.g. address all key patient groups; are affordable etc) is to include African expertise in the product review process. Mechanisms that mandate or require involvement of developing country experts or regulators, such as twinned review, Article 58 and WHO prequalification, are superior to mechanisms that either do not include such input or do so only on an ad-hoc basis, such as standard Western regulatory review pathways.

3 Expedites access for African patients

Sequential product reviews by different regulators extend the time from first registration to African access by months or years. The quickest way to get products to African patients is to conduct African product review either before, or simultaneously with, Western regulatory review but, as we have seen, this is easier said than done. Many African MRAs prefer to wait on a prior Western approval; others go ahead, but may not have sufficient experience to fully assess the product in question. The most reliable way to secure early African registration is to conduct joint African-Western assessments of neglected disease products.

4 Uses resources efficiently (avoids duplication of regulatory reviews)

Most of the regulatory pathways outlined in this report are inefficient – some extremely so. Several require double or triple reviews by Western regulators, WHO and African MRAs, often conducted sequentially, as noted above. Others, such as WHO prequalification reviews, repeatedly convene new groups of reviewers; while Western regulators may also pull in experts in an ad-hoc manner to advise on situations where the regulator does not have the local perspective needed e.g. standard Western review and Article 58. The most efficient use of resources is achieved by joint review that includes those parties who will need to approve a product, including the Western MRA, African MRAs and WHO. Further efficiencies are reaped if this process is formalised rather than ad-hoc, with a mechanism that builds in African regulatory participation in a predictable and structured way.

5 Builds African capacity (a desirable positive externality of any mechanism)

The priority in drug registration is the delivery of safe, effective, suitable, quality products to populations in need. However, mechanisms that additionally build African capacity to regulate products must be valued above those that do not. Thus, twinned reviews, Article 58 opinions and WHO prequalification offer greater benefits for registration of a product than parallel review or standard Western review of that same product.

Mechanisms that include capacity-building elements also do so to differing degrees. Thus, WHO vaccine prequalification offers broad regulatory training but is seen by some as undermining the ability (or will) of African MRAs to take over vaccine regulation themselves. Likewise, WHO drug prequalification includes training elements and involves African regulators in assessments, but there is also a view that it drains off African experts to conduct repeated prequalification reviews.

Table 1: Relative performance of neglected disease regulatory approaches

	Safety, efficacy, quality assessment	Assesses suitability for Africa	Systematic DC input	Expedites access	Resource-efficient	Builds African capacity
Twinned approval	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
Article 58	✓✓	✓✓	✓	✓		✓
WHO drug and vaccine prequalification	✓✓	✓✓	✓			✓
Parallel approval	✓✓	✓✓	✓		?	✓
Routine and expedited Western approval <i>(Fast-track, priority review, standard review)</i>	✓	?				
Orphan approval	✓	?				
First approval by DC regulator	?	✓	✓✓	✓✓	✓	
Accelerated review	?	?		✓		

? Signifies that the mechanism's delivery against that criterion must be assessed on a case-by-case basis

A summary of the performance of each regulatory approach against these criteria is shown above. This analysis throws up some interesting points. Twinned review is the most promising approach from the African perspective but is the only approach that is currently not used, since no regulatory authority or pathway currently endorses or practices twinned reviews of regulatory dossiers. Article 58, the next most promising approach (from the African if not the industry perspective), has also barely been used. Ironically, those approaches that incorporate fewest of the desirable elements of neglected disease drug review are those that are most commonly used, in particular Western review mechanisms that were never designed to assess neglected disease drugs.

There are several possible explanations. The choice of regulatory route is up to product developers, most of whom choose the route with which they are most familiar or that offers them the greatest benefits. Thus, the pull of commercial markets encourages many developers and PDP development partners to submit neglected disease products through standard FDA or EMEA routes rather than Article 58 or WHO prequalification. This tendency has been unwittingly exacerbated by regulators and policy-makers who have put neglected disease incentives in place, sometimes without reference to events elsewhere. Thus, Priority Review Vouchers and Orphan Drug legislation draw product developers away from mechanisms that include developing country input or expedite developing country access, and towards regulatory pathways that do not offer these advantages.

A further factor seems to be that neglected disease product registration has been forced to accommodate to existing national regulations and approaches, rather than the other way around. This is understandable given that all regulators (Western and African) are responsible for their own populations. It also produces challenges for Western regulators whose systems were never constructed to accommodate a handful of drugs that may rarely if ever be used within their borders. However, given the might, experience and

resources of large Western regulators, it is also not unreasonable to believe that more could be done to incorporate practices that assist African patients and regulators.

This does not have to mean costly impositions on either developers or regulators. The field of regulation has plenty of room for efficiency gains and is a policy area where all parties share the same goal of reaching the maximum number of patients as quickly, cheaply and effectively as possible. Several proposals to achieve these aims are set out below.

RECOMMENDATIONS

Below we set out a series of proposals to optimise neglected disease drug registration for Africa according to the five principles set out above. These proposals are based on the views and suggestions of stakeholders, and on our analysis of the findings, and were designed with the twin objectives of:

- ▶ Managing scarce regulatory resources in the short term to fill the capacity gap while African MRAs move through their growth period
- ▶ Strengthening African MRAs in the medium to long-term so they can conduct their own regulatory reviews of novel neglected disease drugs.

We also provide an action map that prioritises and locates these recommendations.

RECOMMENDATION → 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)

RECOMMENDATION → 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

RECOMMENDATION → 3

Improve Article 58's attractiveness to product developers by allowing:

- ▶ Automatic WHO drug prequalification of products given a positive opinion under Article 58
- ▶ A positive Art.58 opinion to be converted to EMA approval with a single European bridging study *OR*
- ▶ A positive Art.58 opinion to provide automatic EU Orphan approval

RECOMMENDATION → 4

Selected experienced Western MRAs to conduct prequalifications on behalf of, and in addition to, WHO. Individual reference MRAs could either specialise in a single disease area (cf. the FDA and PEPFAR drugs), or could nominate to review a fixed number of dossiers a 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:

- ▶ 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)

RECOMMENDATION → 5

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)

RECOMMENDATION → 6

Fund Centres of Regulatory Excellence in each of Africa's main sub-regions: West, South, East, Central and North Africa. (See Annexe 2 for more detail)

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^{xiv}:

- ▶ 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, EMA Article 58 assessments, WHO prequalification etc
- ▶ Clinical trial regulation, including joint review and approval
- ▶ Training and Regulatory Fellowships

^{xiv} Other functions which might be at the Centre, or could be conducted elsewhere, include bioequivalence testing; hosting of sub-regional trial registers; hosting of regulatory conferences and workshops; and centralization of regional adverse events reports. Unlike training, trial assessment and joint authorizations, which are best centralized in one location to maximize free exchange of information, these other functions do not necessarily benefit from being integrated into a larger centre, although there may be a case in some circumstances.

The Action Map is not only a guide to current capacity-building, but is intended as a map to the future ... the goal is to work towards a system where national, regional and global regulatory organisations work efficiently together to deal with the regulatory challenges of a globalized world.

ACTION MAP

The action map (see Figure 4) is designed to assist funders and national governments to prioritise regulatory capacity-building investments and activities to achieve the goals identified above. Each proposal on the map has been assessed against three criteria:

1. **Urgency / criticality** i.e. which functions pose a major public health risk if not performed
2. **Complexity.** Some MRA functions are fundamentally more complex than others and strengthening them to the point of competency in Africa will require greater efforts, resources and time. For example, conducting quality, safety and efficacy analysis of novel neglected disease drugs is complex even for well-resourced Western MRAs. Other functions e.g. bioequivalence testing are easier to achieve
3. **Efficiency of resource use** i.e. the level at which a specific regulatory task can be most efficiently and cost-effectively performed - nationally, regionally or internationally? This applies to existing regulatory resources as well as to new resources that may be invested

Based on these criteria, regulatory proposals and recommendations are assigned to national, regional or global level. Within each level, activities are then assigned to one of four quadrants of the map:

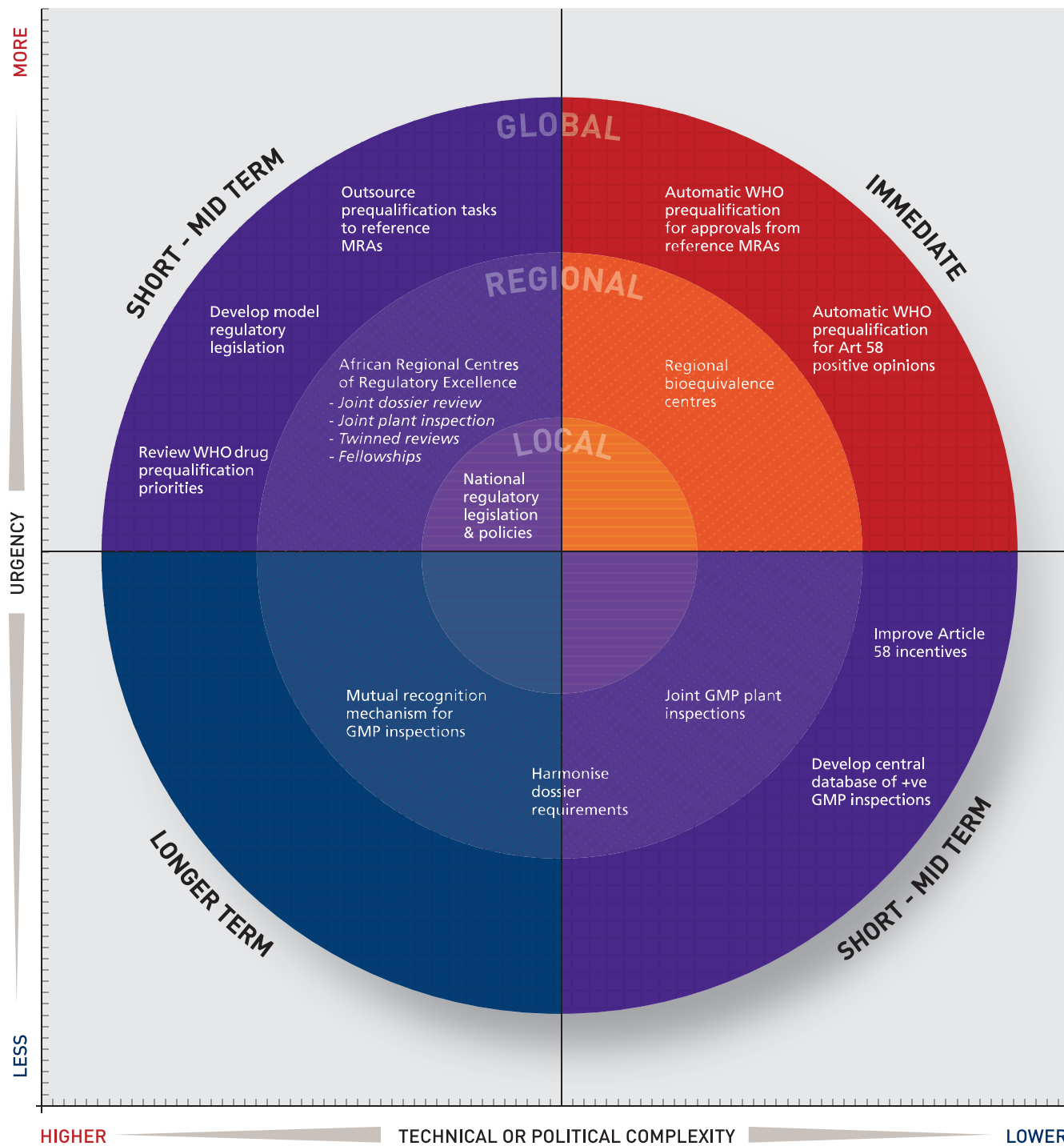
- ▶ Activities that fall into the top right "*Immediate*" quadrant are both urgently needed and relatively cheap and simple to implement i.e. quick wins
- ▶ Activities in the two "*Short to mid-term*" quadrants are those that are either urgent (albeit more difficult to implement) or relatively cheap and simple to implement (albeit less urgent) i.e. results should be seen in 1-3 years
- ▶ Activities in the lower left "*Longer term*" quadrant are both less urgent, as there are currently stopgap alternatives; and are more difficult to implement either due to cost, or to the difficulty of aligning the interests of multiple stakeholders

Using this tool, stakeholders can see which regulatory tasks are the highest priority and which are the lowest hanging fruit. Or they can approach the analysis from a geographic perspective, identifying which tasks should be prioritised and conducted at the national, regional or global level, in order to deliver both the best short-term outcomes and a solid platform for longer-term capacity growth.

Two points of over-riding importance needs to be made with regard to the map. It is not only a guide to current capacity-building, but is intended as a map to the future. In other words, as African MRAs grow in capacity, more regulatory functions will move into the central "local" level of the map. Of course, it is both unrealistic and inefficient to expect any regulatory authority, developed or developing, to perform all functions alone. Therefore the goal is not to have all functions performed nationally, but rather to work towards a system where national, regional and global regulatory organisations work efficiently together to deal with the regulatory challenges of a globalized world.

Finally, the map works best as a shared enterprise. If there is joint agreement as to what is needed and who will do it; and greater harmonisation between European and American led initiatives, top down and bottom up approaches, and funder-driven versus African-driven capacity building efforts, the efficiency and effectiveness of the many global efforts to support African medicines regulation will be greatly improved.

Figure 5: Action map of regulatory capacity-building investments and activities



ANNEXE 1: LIST OF INTERVIEWEES

EXPERT ADVISORY GROUP

ADVISORY GROUP MEMBER	ORGANISATION	TITLE
Benjamin Kwame Botwe	Ghana Food and Drugs Board	Deputy Chief Executive
Peter Folb	South African Medicines Control Council	Chief Specialist Scientist
Patrick Le Courtois	European Medicines Agency (EMA)	Head of Unit, Pre-Authorisation Evaluation of Medicines for Human Use
Murray Lumpkin	US Food and Drug Administration	Deputy Commissioner for International Programs
Precious Matsoso	World Health Organization	Director: Public Health, Innovation and Intellectual Property
Margareth Ndomondo-Sigonda	Tanzanian Food and Drug Authority	Director-General
Shirley Vincent Ramesh	ASEAN Pharmaceutical Product Working Group (PPWG)	Senior Officer, Bureau for Economic Integration and Finance

ADDITIONAL EXPERTS

ADDITIONAL EXPERT	ORGANISATION	TITLE
Omotayo Akanji	LaGray Chemical	QC Supervisor
Lahouari Belgharbi	World Health Organization	Department of Immunization, Vaccines and Biologicals (IVB)
Shing Chang	Drugs for Neglected Diseases initiative (DNDi)	Director of Research and Development
Liliana Chocarro	Developing Countries' Vaccine Regulators Network (DCVRN) and World Health Organization	Scientist, Regulatory Pathways, Quality, Safety and Standards (IVB/QSS), WHO
Max Ciarlet	Merck & Co	Associate Director, Vaccine & Biologics
Mary Couper	World Health Organization	Medical Officer, Safety Efficacy and Pharmacovigilance
Grahame Dickson	Therapeutic Goods Administration of Australia	Head, Clinical Evaluation Section
Robert Don	Drugs for Neglected Diseases initiative (DNDi)	Senior Project Manager
Stephan Duparc	Medicines for Malaria Venture (MMV)	Medical Director
Chris Hentschel	Medicines for Malaria Venture (MMV)	President and Chief Executive Officer
Emmanuel Katongole	Quality Chemicals Ltd	Managing Director and Chief Executive Officer
Raul Kiiwet	World Health Organization	Former manager, Prequalification Programme
Sabine Kopp	World Health Organization	Scientist, Quality Assurance and Safety: Medicines
Marc LaForce	PATH	Global Program Leader, Meningitis Vaccine Project (MVP)
John Lim	Singapore Health Sciences Authority	Chief Executive Officer
Charles Mgone	European & Developing Countries Clinical Trials Partnership (EDCTP)	Executive Director
Bernice Mwale	Pharmaceutical Regulatory Authority of Zambia	Director, Product Registration
Alain Prat	World Health Organization	Technical Officer, Medicines Regulatory Support; Technical Cooperation for Essential Drugs and Traditional Medicine
Lembit Rāgo	World Health Organization	Coordinator, Quality Assurance and Safety: Medicines; Essential Medicines and Pharmaceutical Policies
S D Ravetkar	Serum Institute of India	Senior Director
Els Torreelle	Drugs for Neglected Diseases initiative (DNDi)	Senior Project Manager
Gina Weston	GlaxoSmithKline	Head Strategic Registration Unit, International Regulatory Affairs
Morteza Zaim	WHO Pesticide Evaluation Scheme (WHOPES)	Coordinator, Vector and Ecology Management; Department of Control of Neglected Tropical Diseases

ANNEXE 2: PROPOSED CENTRES OF REGULATORY EXCELLENCE

There are four to five proposed Centres of Regulatory Excellence, one in each of Africa's main sub-regions: West, South, East, Central and North Africa.

Each Centre would have a small permanent trained staff. These would be supplemented by visiting regulatory staff from regional member governments (either on task-related visits, or on longer attachments where resources allowed); by staff from member-state MRAs who would rotate through the centre for training purposes; and/ or by visiting professionals from external regulatory authorities, either on task-related visits (e.g. twinned reviews) or on longer-term secondments or sabbaticals.

The Centre's activities could include:

► Product review

- Regional review of dossiers for novel FDCs and reformulations
- Joint GMP plant inspections at the regional level
- "Twinning", via formal participation in:
 - Western regulatory reviews of neglected disease dossiers
 - EMEA Article 58 assessments
 - FDA PEPFAR-linked assessments
 - WHO prequalification assessments (also reducing the burden of pulling together new prequal teams each time)
- Joint regional review of dossiers for novel drugs, with external expert input as necessary
- Eventual full independent joint review of innovator products

► Clinical trial regulation

- Joint review of clinical trial proposals and protocols
- Joint inspections of clinical trials
- Maintaining regional clinical trial registers
- Joint regional approval of multicentre clinical trials (currently included in the SADC business plan); also a major benefit to product developers

► Training

- Regulatory training
- Regulatory Fellowships

Other functions which might be at the Centre, or could be conducted elsewhere, include bioequivalence testing; hosting of sub-regional trial registers; hosting of regulatory conferences and workshops; and centralization of regional adverse events reports. Unlike training, trial assessment and joint authorizations, which are best centralized in one location to maximize free exchange of information, these other functions do not necessarily benefit from being integrated into a larger centre, although there may be a case in some circumstances.

The proposed *regulatory fellowships* are absolutely central to the purpose of each Centre. These are envisioned as including (times to be decided in consultation):

- Attachment with WHO or a reference Western regulator for 1 year
- Attachment with the Centre of Regulatory Excellence for 1 year
- Attachment with a pharmaceutical company for 6 months
- Funded position with their home regulator for 2.5 years, including participating in regional assessments conducted through the Centre

The Centres are envisioned as bricks-and-mortar institutions, not disseminated networks. Where possible, they could be linked to existing initiatives, for example:

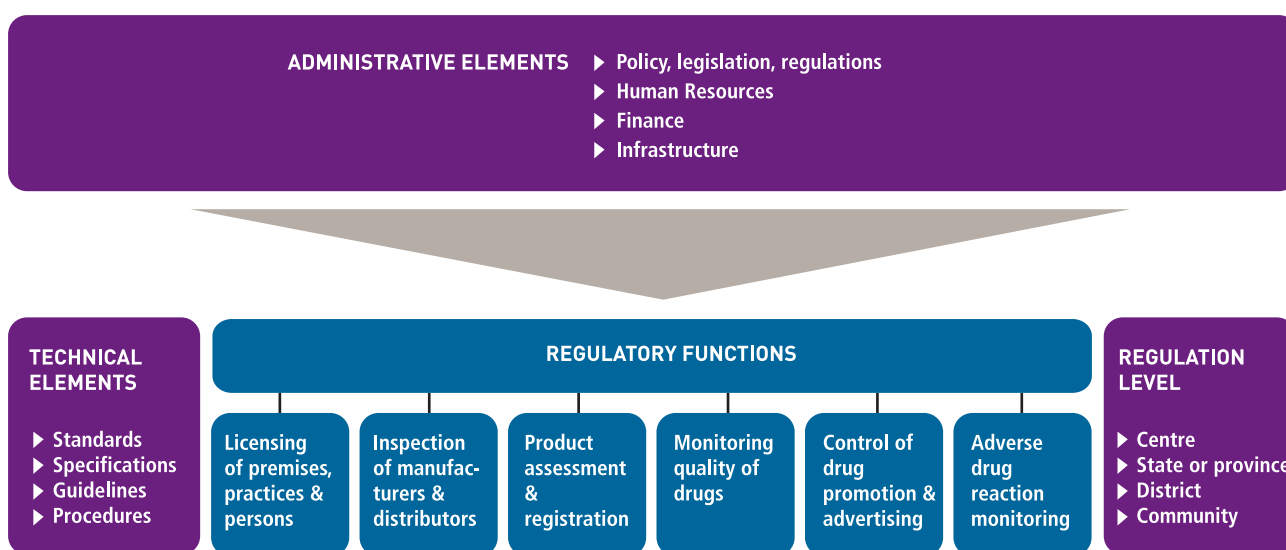
- Clinical trial regulatory initiatives e.g. African Vaccine Regulatory Forum (AVAREF)
- Regulatory harmonisation efforts e.g. SADC, WADRAN
- Existing Centres of Excellence for clinical trial capacity building e.g. the EDCTP "Regional Network of Excellence for Conducting Clinical Trials" and/or the Wellcome Trust "Capacity Strengthening in African Institutions for Endemic Diseases Research Initiative"
- African academic centres of excellence in pharmacology

The Centres would require sufficiently attractive salaried positions to attract a small permanent trained staff. We also envision a minimum of two Fellowships offered annually at each of the four to five Centres, resulting in a minimum of 20-25 fully trained and experienced African regulatory staff and 20-25 partially-trained staff in five years i.e. 40-50 regulatory staff in total.

ANNEXE 3: FUNCTIONS OF MEDICINES REGULATORY AGENCIES (MRAs)

Regulatory functions and elements have been classified into three groups - administrative, technical and functional – with the location of these functions being a further consideration (see Figure 5). As noted in the introduction, this report focuses on product assessment and registration, with discussion of other elements only as needed to support this.

Figure 5: Functions of MRAs



Source: Modified from Ratanawijitrasin/Wondemagegnehu 2002, 12.

Regulatory needs and approaches differ from country to country for a variety of reasons including the resource base, size of industry, research capacity and political commitment. However, no matter the approach, delivery of regulatory functions requires a broad range of skills from toxicology and statistics to pharmaceutical chemistry and clinical science, as well as the ability to effectively manage and integrate legislation, customs, inspections and monitoring. The skill and resources involved present a challenge to all MRAs but particularly those in low income countries.

ANNEXE 4: REGULATING CLINICAL TRIALS OF NEW PRODUCTS

Over the last 5-10 years, the increased interest in and funding for neglected disease research and development (R&D) has led to a plethora of applications to African governments for clinical trials of novel drugs, FDCs and vaccine candidates for malaria, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis (TB), sleeping sickness, leishmaniasis, rotavirus, pneumonia, meningitis and a host of other tropical diseases.

Clinical trial evaluation includes:

- ▶ reviewing and approving clinical trial applications
- ▶ authorising importation of trial batches (the product that will be trialled in local patients)
- ▶ monitoring all product trials within the national borders, including through development or use of clinical trial registers and trial site inspections¹⁰

However, in 2005 the World Health Organization (WHO) assessed that 84% of African countries were unable to carry out clinical trial authorisation to a satisfactory level,⁸ while some did not have a clinical trial authorisation system.³⁶

Identified problems related to clinical trial evaluation and approval included:

- ▶ **Lack of a clear legislative framework covering clinical trial conduct and regulation** and/or lack of national guidelines on trial registration and ethics approval. Most African countries do not have legislation to make clinical trial registration compulsory. South Africa is an exception, as their 2004 National Health Act makes ethics clearance and clinical trial registration of any clinical research in the country compulsory. Other countries keep a register of trials (e.g. Malawi registers all trials with their Pharmacy, Medicines and Poisons Board) but do not have the legislative mandate or resources to review or approve trials
- ▶ **Unclear delineation of authority and responsibility between ethical review boards and Medicines Regulatory Authorities (MRAs).** Many countries only require local ethics approval for a clinical trial to proceed, although MRA participation in the regulatory oversight of clinical trials, especially product licensure trials, is widely agreed and recommended³⁷
- ▶ **Lack of skills to review and approve clinical trial applications efficiently.** Some experts believed that MRA involvement (while improving the chances that problems would be detected early), was also “leading to delays as MRAs do not have the resources” to approve trial applications quickly and competently
- ▶ **Requests for additional trials, sometimes without sufficient cause or sufficient ability to act on the results.** This partly reflects a global trend, with WHO and industry interviewees in India and Europe noting that the “very cautious approach now globally” is leading to a situation where “every day, more data is required – especially safety data”.

Increased demand for *localised* clinical trial data – a trend that originated in Asia based on ethno-sensitivity arguments – is also driving pressure for more trials. This demand is partly scientific in

basis; and African data may also be required by WHO to support global pre-qualification, as was the case with the rotavirus vaccine.^{xv} However, interviewees also suggested that politics and issues of national pride were playing a role. They cited, for instance, requests for local trials despite the presence of trials in a neighbouring country that would generate reliable data for both settings; or requests for local trials too small to support a meaningful analysis e.g. a local Phase III trial of 30 people compared to the hundreds or thousands normally needed to generate a meaningful Phase III result.

Compounding the problem, the MRA requesting these additional local studies may not have the resources to review the trial design once submitted; or to assess the additional data generated by the trial. This represents a waste of resource for stretched MRAs and for product developers, and leads to unnecessary delays and higher prices for patients needing these products.

Initiatives to build and supplement clinical trial regulatory capacity

Isolated examples of capacity building in clinical trial regulation occur, often funded, promoted or coordinated by WHO. For example, WHO, the Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative and GlaxoSmithKline (GSK) worked together on the phase III clinical trial application for RTS,S, a malaria vaccine candidate, including working with MRAs in Senegal and Mali on inspection of trials sites. The Belgian MRA (the country where the product was manufactured), then worked jointly with 7 African MRAs, where each conducted an independent review, with the final trial design then jointly agreed and approved. In another example, four African countries (The Gambia, Mali, Ghana and Senegal) were involved in a joint review, funded by WHO, of the clinical trial application for the new conjugate Meningitis A vaccine being developed by PATH/ Meningitis Vaccine Project (MVP).

A number of formal initiatives have also commenced, aimed at building developing country capacity to manage and regulate clinical trials, including the Developing Country Vaccine Regulator Network (DCVRN) (a global initiative with one African member, South Africa); and the African Vaccine Regulatory Forum (AVAREF), which is specifically focused on African regulatory issues.

The DCVRN, launched in 2004, is a group of nine developing or transitional countries with vaccine production capability (Cuba, Brazil, India, China, South Korea, Indonesia, Thailand, Russia and South Africa). It is coordinated by the WHO, with the aim of improving regulation of vaccine trials and review of vaccine trial data by both DCVRN members and other developing countries. Key activities include:

- ▶ Sharing technical information among participating vaccine regulators
- ▶ Exchanging information with vaccine developers and producers on upcoming trials, products and on WHO guidelines
- ▶ Developing a training module in clinical trial Good Clinical Practice (GCP) inspection (since transferred to the WHO's Global Training Network (GTN))

^{xv} The original pre-qualification of GSK's rotavirus vaccine was based on data generated in Latin America and Western Europe, however results from ongoing studies in high-child mortality settings in Asia and Africa - Bangladesh, South Africa, Malawi - will be used to inform the decision to extend the indication for use to Asia and Africa

- ▶ This group helped to secure agreement on regulatory harmonisation among Association of Southeast Asian Nations (ASEAN)^{xvi} countries, with a resulting Common Technical Requirements and Dossier in the region (we note though, that some companies suggest this occurs more in theory than practice, with some member states still requesting additional data for domestic registration)

Of more relevance to Africa is the AVAREF network, set up in late 2006 to support MRAs and Ethics Committees in African countries that were targeted for clinical trials of innovator vaccines, for example vaccines now in development for malaria, HIV, meningitis and rotavirus. AVAREF has 19 African country members^{xvii} and experts from WHO, DCVRN, FDA and EMEA, as well as product developers, also participate.

Key activities include:

- ▶ Conducting an inventory of MRA clinical trial regulatory capacity
- ▶ Helping to clarify the respective roles and responsibilities of ethics committees and MRAs
- ▶ Developing tools and guidelines to improve the vaccine review process
- ▶ Preparing common technical documents such as harmonised dossiers to facilitate joint review of clinical trial applications
- ▶ Providing training and capacity building in clinical trial monitoring, review, registration and authorisation
- ▶ Conducting joint reviews of clinical trial applications/ protocols
- ▶ Conducting joint inspections of clinical trials

AVAREF has been active and successful in providing timely support to African MRAs who are in the frontline of new product regulation.

^{xvi} ASEAN is the Association of Southeast Asian Nations and includes 10 country members (Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam)

^{xvii} Ghana, Gambia, Mali, Burkina Faso, Senegal, Nigeria, Malawi, Botswana, Zimbabwe, Kenya, Uganda, Ethiopia, Gabon, Cameroon, South Africa, Rwanda, Zambia, Tanzania and Mozambique

ANNEXE 5: DNDi DOCUMENT ON THEIR ASAQ REGISTRATION STRATEGY



ANTI-MALARIAL "ASQA" REGULATORY STRATEGY

ASQA, a fixed-dose combination of artesunate and amodiaquine, is a DNDi-managed drug development project which started in 2002 by the FACT (fixed-dose artesunate combination therapy) Consortium comprising experts in malaria and in drug development. In 2005, DNDi partnered with sanofi-aventis to move forward with the project.

FACT rationale of ASQA regulatory strategy

Due to widespread drug resistance and the limited access to artemisinin-based fixed-dose combinations (FDCs) now available, there was an urgent need to make the new FDC, ASQA, available to patients. ASQA provides a true innovation in patient treatment by being simple to use, adapted to all ages, affordable, and state-of-the-art galenical formulation. To facilitate its implementation in malaria-endemic countries, the registration strategy was discussed in the early stages of its development within the team. Ultimately, ASQA would become a tool for malaria reduction and resistance prevention.

The guiding principles for the regulatory strategy were:

- ▶ To build off of the knowledge and work already done on the separate active pharmaceutical ingredients for the programme and the registration. Both active ingredients artesunate (AS) and amodiaquine (AQ) were well-established products and well-documented as loose dose combination. Co-blister packs of the loose-dose combination treatment had already been developed and were widely available.
- ▶ To identify ways to minimize delays. No registration plan in countries not affected by malaria.
- ▶ To minimise the programme of development to make the new FDC available to patients as soon as possible.
- ▶ To constitute a file of international quality in accordance with good working principles through the use by the FACT Consortium of an international contract research organization (CRO) knowledgeable in international registration and in conformity with International Conference on Harmonization (ICH) standards
- ▶ To involve and consult regulatory authorities.
- ▶ To inform WHO malaria experts on progress and content of the file

Building of the FACT registration dossier

At the beginning of the programme, both France and the United Kingdom (UK) stood as options for planned ASQA filings for first

regulatory approval. Germany was also a potential registration country due to the scale up manufacture of ASQA in the country. A consultation of the UK Medicines and Healthcare products Regulatory Agency (MHRA) took place in March 2005 in view of preparing a registration file. Through this review, DNDi discovered that amodiaquine was no longer listed in the UK Pharmacopoeia and that there was a risk that artesunate would be considered a new chemical entity which would entail significant delay in the regulatory process. Most importantly, the UK MHRA gave extremely valuable advice to DNDi which led DNDi to increase the number of patients for the pivotal clinical study and to support performance of a multi centre study comparing ASQA with the co-formulation considered at the time as reference, artemether+lumefantrine. In addition, a requested food interaction study was planned by DNDi industrial partner sanofi-aventis. Finally, the UK MHRA informed DNDi of the sunset clause which meant that DNDi would not be allowed UK registration status unless ASQA would be developed for use by tourists. This option was not one DNDi was ready to consider. DNDi also considered obtaining consultation from the European Medicines Agency (EMA) under the new Article 58 consultation but decided not to pursue this as it risked delaying the project.

ASQA international registration process

The registration plan changed with the signing of the partnership with sanofi-aventis, who developed both a quality and pre-clinical programme of international standard.

Considering the background of the AS+AQ combination and the urgent need of patients in malaria endemic countries, sanofi-aventis, with the support of DNDi, chose to register in Morocco and in endemic countries as well as to apply for WHO prequalification to allow qualified assessment experts to evaluate the quality, safety and efficacy of the medicine.

Morocco is the country where sanofi-aventis manufactures ASQA, in line with its commitment to maintain its industrial assets in "Southern" countries. To register a medicinal product in Africa, it is customary to register the drug first in the country of manufacture. The registration file was submitted for approval by the drug regulatory authority of Morocco in November 2006. Co-blisters of AS and AQ were already registered and manufactured in Morocco and thus known by the authorities. Marketing approval was granted by the Moroccan authorities on February 1, 2007.

Because regulatory assessments of risk and benefit apply primarily to the population of the regulatory authority's country and because ASQA was not intended for use in American or European travellers,

filing for registration in the US or in Europe was not considered as a priority, and focus was on malaria-endemic countries, based on the Moroccan marketing authorisation. Today, ASAQ is registered and available in 24 countries.

Artesunate is the most widely used artemisinin derivative in the world, yet for the US FDA and the EMEA, it is still a New Chemical Entity, whereas it is not for the WHO. Amodiaquine is registered in many European countries (eg. France). The WHO prequalification process was chosen over the EMEA "Article 58" procedure because at that time the later was really new and never used for a combination of compounds which were not already licensed in Europe. Moreover, this choice was also supported by WHO's ample regulatory documentation on artesunate and on amodiaquine: Arsumax® (the sanofi-aventis artesunate) was already WHO prequalified and Arsucam® (the sanofi-aventis artesunate-amodiaquine co-blisters) was submitted for WHO prequalification; work on this file was suspended to focus on ASAQ in line with WHO recommendations to develop co-formulations.

A full "Quality package" (former CMC file) in ICH format and in accordance with ICH standards was submitted including extensive work on stability and packaging and also on potential degradation products. A pre-clinical safety package testing of the drug substances used for the new FDC was also submitted. DNDi's approach was "the well-established" use argument for presenting the minimal package based mainly on genotoxicity, in accordance with the "well-established use" strategy. However, as the combination was never registered as such by a stringent authority, sanofi-aventis performed a series of 47 additional studies (including safety pharmacology, repeat-dose toxicity, genotoxicity, reproductive and development toxicity on artesunate on amodiaquine and on the combination).

The clinical package included:

- (i) the initial multi-centre study performed by TDR in Africa demonstrating the therapeutic benefit of using the combination of artesunate (AS) with amodiaquine (AQ) versus AQ alone,
- (ii) a pharmacokinetic study performed by TDR (with supplies of artesunate by Sanofi) comparing the kinetics of AS, AQ, and AS+AQ in volunteers, showing the absence of clinically significant Pharmacokinetic interactions between the two drugs,
- (iii) a Pharmacokinetic/Tolerance/ECG study in 24 healthy volunteers comparing the new fixed dose formulation and the separate drugs administered at the recommended dose,
- (iv) a food interaction study,
- (v) the field study in 750 patients in Burkina Faso,
- (vi) a multi-centre study comparing Coartem (considered by the MHRA as the "gold standard") and ASAQ in about 1000 patients including adults.

The file was assessed according to the 'Procedure for Assessing the Acceptability, in principle, of Pharmaceutical Products for purchase by United Nations Agencies' by the team of WHO assessors. The assessors were senior experts, mainly from national authorities, invited by WHO to participate in the prequalification assessment process. The countries of origin for the assessors involved were Canada, Germany, The Netherlands, South Africa, Spain, Switzerland, and Uganda.

The sanofi-aventis industrial site in Morocco received WHO GMP certification in January 2008. Prequalification status was granted by the WHO in October 2008, following a thorough assessment of ASAQ.

The regulatory dossiers that were submitted to Morocco, African malaria-endemic countries, and the WHO prequalification process, strictly comply with these institutions' respective regulatory requirements based on the regulatory status of the ASAQ combination.

ASAQ was launched in 2007 as an innovative fixed-dose formulation of artesunate and amodiaquine, easy-to-use and therefore ensuring better compliance. The combination of AS and AQ is one of the four ACTs recommended by the WHO since 2001^{xviii} but did not exist as a co-formulation, nor was under such development.

The strategy for the registration of ASAQ was therefore designed with the objective to render the treatment available to patients fast, while, at the same time, demonstrating adherence to international quality standards and contributing to building regulatory capacity in the South.

Other developments

DNDi intends to make sure that the new treatments, drugs, and combinations it develops benefits patients in the countries affected by neglected tropical diseases and that the treatment is indeed used in those countries. To achieve this aim, DNDi is involved in capacity building and was very interested in participating in a WHO regulatory training in Africa in 2008. In line with this commitment to support and contribute to capacity building, DNDi offered its ASAQ file – not the one of sanofi-aventis submitted to the pre-qualification - for use as a case study in the WHO training. The ASAQ dossier was made available to a group of regulatory experts from Africa, EMEA, and WHO. DNDi project manager formally presented the file, which was then discussed and reviewed for a "virtual approval" by developing countries participants, with support from WHO and EMEA experts. The experience, which was the first of this kind, received very positive feedback.

ANNEXE 6: DNDi REGULATORY WORKSHOP, 24 JUNE 2009, NAIROBI, KENYA

A regional workshop on **“Strengthening regulatory capacities in Africa for the registration of new drugs for neglected diseases”** was organized on 24 June 2009 in Nairobi, Kenya, on the occasion of DNDi stakeholder meeting. About 100 people participated in the workshop including representatives from African regulatory authorities in Angola, Democratic Republic of Congo, Ethiopia, Uganda, Tanzania and members of the HAT (human African trypanosomiasis) and LEAP (leishmaniasis) platforms.

The objective of the workshop was to present and discuss findings of a draft version of this report on new challenges related to the registration in Africa of new treatments for neglected diseases, commissioned from the George Institute for International Health by DNDi.

The report was presented by one of its authors, and commented on by regulatory experts from Tanzania and Europe. This was followed by presentations of case studies illustrating various regulatory strategies including the registration of artesunate+amodiaquine fixed dose combination in Morocco followed by WHO prequalification, the registration of paromomycin for the treatment of visceral leishmaniasis in India, and challenges related to the registration of a new drug such as fexinidazole for the treatment of human African trypanosomiasis.

The report, which offers an overview of the various international mechanisms available to support the registration of new drugs for neglected diseases, stimulated much interest and discussion. It was acknowledged that lack of capacity of most African regulatory authorities constituted an obstacle to access to drugs for neglected diseases. Several participants commented that WHO should play a major role in strengthening the capacity of African regulatory authorities.

ANNEXE 7. ACRONYMS

- ACTs** Artemisinin-based combination therapies
- AMFm** Affordable Medicines Facility - malaria
- ANVISA** Brazilian Agencia Nacional de Vigilancia Sanitaria
- API** Active Pharmaceutical Ingredient
- ASAQ** Artesunate Amodiaquine fixed-dose combination
- ASEAN** Association of Southeast Asian Nations
- ASMQ** Artesunate Mefloquine fixed-dose combination
- AVAREF** African Vaccine Regulatory Forum
- BCG** Bacillus Calmette-Guérin vaccine
- CBER** US Center for Biologics Evaluation and Research
- CHMP** Committee for Medicinal Products for Human Use
- CPP** Certificate of a Pharmaceutical Product
- CTD** Common Technical Document
- DCs** Developing Countries
- DCVRN** Developing Countries' Vaccine Regulators Network
- DFID** UK Department for International Development
- DNDi** Drugs for Neglected Diseases initiative
- DTP** Diphtheria Tetanus Pertussis vaccine
- EAC** East African Community
- ECOWAS** Economic Community of West African States
- EDCTP** European & Developing Countries Clinical Trials Partnership
- EMA** European Medicines Agency
- EPI** Expanded Program on Immunisation
- EU** European Union
- FDA** US Food and Drug Administration
- FDC** Fixed-Dose Combination
- GAVI** The Global Alliance for Vaccines and Immunisation
- GCP** Good Clinical Practice
- GFATM** Global Fund to Fight AIDS, Tuberculosis and Malaria
- GMP** Good Manufacturing Practice
- GSK** GlaxoSmithKline
- GTN** WHO's Global Training Network
- Hib** Haemophilus influenzae type b
- HIV/AIDS** Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
- ICDRA** International Conference of Drug Regulatory Authorities
- ICH** International Conference on Harmonisation
- IM** Intramuscular
- IND** Investigational New Drug Application
- iOWH** Institute for One World Health
- IVB** WHO Department of Immunization, Vaccines and Biologicals
- MHRA** UK Medicines and Healthcare Products Regulatory Agency
- MMV** Medicines for Malaria Venture
- MRA**s Medicines Regulatory Authorities
- MVP** PATH Meningitis Vaccine Project
- NAFDAC** Nigeria's National Agency for Food and Drug Administration and Control
- NDs** Neglected Diseases
- NEPAD** The New Partnership for Africa's Development
- NRA** National Regulatory Authority
- ODL** Orphan Drug Legislation
- PAP** Pan African Parliament
- PATH** Program for Appropriate Technology in Health
- PDP** Product Development Partnership
- PEPFAR** US President's Emergency Plan for AIDS Relief
- PPWG** ASEAN Pharmaceutical Product Working Group
- Prequal** WHO Prequalification
- PRV** Priority Review Voucher
- R&D** Research and Development
- REC** Regional Economic Communities
- SADC** Southern African Development Community
- SAGE** WHO's Strategic Advisory Group of Experts
- SwissMedic** Swiss Agency for Therapeutic Products
- TB** Tuberculosis
- UK** United Kingdom
- UN** United Nations
- UNICEF** United Nations Children's Fund
- US** United States of America
- VL** Visceral Leishmaniasis
- WADRAN** West African Drugs Regulatory Authority Network
- WAHO** West Africa Health Organisation
- WHO** World Health Organization
- WHO/TCM** WHO Department of Technical Cooperation for Essential Drugs and Traditional Medicine
- WHO/TDR** WHO-based Special Programme for Research and Training in Tropical Diseases
- WHOPES** WHO Pesticide Evaluation Scheme

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