EDCTP

European & Developing Countries Clinical Trials Partnership

SHARING RESPONSIBILITY

REPORT OF THE POST–REGISTRATION MEDICINAL PRODUCTS SAFETY MONITORING IN AFRICA MEETING

4 NOVEMBER 2012

Towards the second EDCTP programme

The 'Post-Registration Medicinal Products Safety Monitoring in Africa' meeting was held to discuss opportunities to address issues that arise following the approval and deployment of new medicinal products related to both safety and effectiveness in collaboration with other stakeholders. EDCTP supports a 'whole life-cycle' approach and building capacity for post-approval programmes will be within its future remit of phase I-IV studies.

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EDCTP was created in 2003 as a European response to the global health crisis caused by the three main poverty-related diseases (PRDs) of HIV/AIDS, tuberculosis and malaria. Currently EDCTP is a partnership between 16 European countries, the European Union and sub-Saharan African countries. The aim of the programme is to accelerate the development of new and improved drugs, vaccines and microbicides against HIV/AIDS, tuberculosis and malaria through a balanced partnership of European national research programmes on PRDs with their African counterparts in collaboration with the pharmaceutical industry and like-minded organisations.

The second EDCTP programme is expected to start in 2014 as part of the European research framework programme Horizon 2020. Its scope is based on the current objectives and achievements and will be expanded to include: all clinical trial phases I-IV including health services optimisation research; other neglected infectious diseases; closer collaboration with industry, like-minded product development partners and development agencies; and collaborative research with other developing countries outside sub-Saharan Africa when possible and desirable.

Contents

Acronyms and abbreviations

ADR	adverse drug reaction
AEFI	adverse events following immunisation
AMRH	African Medicines Regulatory Harmonisation Programme
AU	African Union
AVAREF	African Vaccines Regulatory Forum
EDCTP	European & Developing Countries Clinical Trials Partnership
EDCTP2	the forthcoming second phase of the EDCTP programme
EPI	Expanded Programme on Immunisation
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
ICSR	individual case safety reports
INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health
NRA	national regulatory authority
NEPAD	New Partnership for Africa's Development
PDP	product development partnership
PRDs	poverty-related diseases
WHO	World Health Organization

1. Executive Summary

As part of the consultative process undertaken in preparation for the second phase of the programme of the European & Developing Countries Clinical Trials Partnership (EDCTP), a meeting – 'Post-registration medicinal products safety monitoring in sub-Saharan Africa' – was held in Cape Town, South Africa, on 4 November 2012. The 60 participants in the meeting heard two addresses, which were followed by an open discussion.

Alex Dodoo – WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, University of Ghana Medical School, Accra, Ghana – gave a detailed account of the current state of drug and vaccine pharmacovigilance in sub-Saharan Africa. Assessments have shown that the functionality of Africa's pharmacovigilance systems is weak. However, a number of new initiatives are now under way, one of which is the 'Pharmacovigilance Toolkit'[1] – a freely available collection of tools and resources. Dr Dodoo argued that, since EDCTP assists in bringing new products into use, it has a duty also to be involved in their post-marketing surveillance and monitoring.

Edith Roset Bahmanyar, Senior Epidemiologist at GlaxoSmithKline Biologicals (GSK) described the post-registration risk management programme that will be introduced when RTS,S/AS – the world's first malaria vaccine – is launched in Africa. Its goals include field evaluation of the benefits and risks of the vaccine, and capacity building for pharmacovigilance and disease surveillance, which will extend beyond the study itself. The core of the risk management programme consists of four studies including a baseline study that will be conducted in advance of the introduction of the vaccine. Dr Bahmanyar stressed the importance of recognising, reporting, analysing and interpreting adverse events following immunisation (AEFIs). GSK hopes that the RTS,S/AS risk management programme will help create a model for other pharmacovigilance sentinel centres and activities, e.g. in Africa.

Contributors from the floor agreed that all available avenues should be pursued to establish whether medicinal products continue to perform as expected in terms of safety and effectiveness in the 'real world'. A collaborative approach will be necessary to achieve this, acknowledging a shared responsibility; the task cannot be left to the pharmaceutical industry alone. EDCTP should find ways to act as a neutral broker with African governments, product developers, academic/research institutions and other stakeholders in order to improve pharmacovigilance, and to create a sustainable system.

Capacity building (particularly training and establishment of functional pharmacovigilance monitoring systems) is required to enable efficient handling of spontaneous reporting, coupled with active surveillance systems. However, insufficient capacity is not the only pressing issue.

African governments are not yet fully engaged with pharmacovigilance and a change of mind set is required. Pharmacovigilance programmes should be integrated within health systems and form part of a comprehensive and robust plan for access to health care services. Engaging the public will also be important. If the public lose confidence in the safety of individual drugs, its trust in the entire health care system may be jeopardised.

Amongst the wide range of challenges identified were the complex environments in which new products enter the market in Africa. One of the many complicating factors is the widespread availability of counterfeit products. Not only are risk management plans needed for new products but those already in use should not be neglected. The important issue of pharmacovigilance continues to 'fall through the cracks'. In the context of the issues listed above, EDCTP in the second phase of its programme (EDCTP2) is well placed to play a key brokering role in ending this neglect.

1 WHO updated pharmacovigilance toolkit for developing countries

2. Introduction

The European & Developing Countries Clinical Trials Partnership (EDCTP) aims to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics against HIV/AIDS, tuberculosis and malaria, with a focus on phase II and III clinical trials in sub-Saharan Africa. Preparations are well under way for a proposed second phase of EDCTP (EDCTP2), which is expected to start in 2014 as part of Horizon 2020, the EU Framework Programme for Research and Innovation.

The scientific scope of EDCTP2 will cover all phases of clinical trials on the three major poverty-related diseases (PRDs) and neglected infectious diseases (NIDs)[2]. Although EDCTP2 will retain its focus on phase II and III clinical trials in sub-Saharan Africa, it will also invest in post-registration phase IV studies to ensure that products that have been approved after phase III trials can be effectively and safely implemented as part of national or regional health strategies.

Pharmacovigilance

Pharmacovigilance in resource-limited countries is challenged by a wide range of complex factors such as: potentially unsafe treatment or handling and administration policies; poor access to safe and efficacious essential medicines; counterfeit or substandard medicines; environmental contamination of pharmaceuticals; medication errors; and inappropriate storage, handling, use and disposal of medicinal products. In the majority of African countries pharmacovigilance activities are either non-existent or rudimentary.

Important as it is to develop and introduce new medicinal products, the safety of these products should be assessed during their complete life-cycle. Although the majority of adverse events due to medicinal products may be predictable from what has been learned during product development, many adverse drug reactions (ADRs) are idiosyncratic events that cannot be predicted from knowledge of the parent compound. With increased access to essential drugs and the roll-out of vaccines particularly intended for low- and middle-income countries (e.g. the RTS,S/AS malaria vaccine), there is clearly a greater need to monitor the safety and effectiveness of these medicinal products.

Many of the diverse and multifaceted issues of pharmacovigilance extend beyond the mandate of EDCTP. However, for the second programme EDCTP – supporting the complete life-cycle approach – will seek to define its role in phase IV studies. One aspect of that role is to be a broker, to bring stakeholders together. As part of EDCTP's consultative process in preparation for its second phase, a meeting – '*Post-registration medicinal products safety monitoring in sub-Saharan Africa*' – was therefore held in order to focus on the opportunities, challenges and needs of post-registration programmes that evaluate both safety and effectiveness.

The meeting

The meeting took place in Cape Town, South Africa on 4 November 2012. The purpose of the meeting was to foster collaboration and reinforce partnerships by bringing different stakeholders – the pharmaceutical industry, product development partnerships (PDPs), regulators from regional regulatory agencies and National Regulatory Authorities (NRAs), researchers, policy makers, and funding agencies – together for a discussion on overarching issues concerning post-registration

2 The list of NIDs in EDCTP2 has not yet been defined; for the purpose of this report reference is made to the WHO-TDR list. (source: http://whqlibdoc.who.int/hq/2012/WHO_HTM_NTD_2012.1_eng.pdf)

programmes for medicinal products in sub-Saharan Africa. The discussion focussed on post-registration product safety monitoring. The meeting was chaired by Alex Dodoo – WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, University of Ghana Medical School, Accra, Ghana – and Elly Katabira – College of Health Sciences, Makerere University, Uganda.

Whilst a number of PDPs currently working in Africa are engaged in pharmacovigilance activities during clinical trials, the extent of their involvement tends to vary by factors such as the life cycle stage of the product and the type of clinical trial sponsor. Pharmacovigilance activities during clinical trials are important in preparation for post-registration surveillance and for exploring the possibility of building pharmacovigilance capacity in countries targeted for product uptake.

As part of the product registration process, product developers (the pharmaceutical industry and PDPs) in high-income countries are obliged to develop risk management plans and studies for collecting safety data as both regulators and product developers are responsible for the safety of a product. However, in Africa most of the product developers focus on pre-approval safety monitoring and leave the post-registration surveillance activities to the NRAs, hereby creating an asymmetric accountability.

The capacity of the NRAs in Africa to oversee, guide and enforce pharmacovigilance activities varies greatly and is limited in the majority of African countries. In order to assess the safety of products during all stages of product development, the capacity of African NRAs to establish robust pharmacovigilance and risk management[3] systems needs to be strengthened. This should encompass a broader capacity to assess all medical products including medicines, diagnostics and medicinal devises.

3 Risk management applies to scientifically based methodologies to identify, assess, communicate and minimise risk throughout a medicinal product's life cycle in order to establish and maintain a favourable benefit-risk profile in patients.

3. Proceedings

EDCTP's Executive Director, **Prof. Charles Mgone**, explained that the meeting was being held in context of the broadening of EDCTP's remit (in the forthcoming EDCTP2 programme) to include phase I and phase IV clinical trials. This will offer new opportunities to develop synergies with EDCTP's partners to address issues that arise following the approval of new medicinal products, regarding both safety and effectiveness. This is an area that currently 'falls through the cracks'. Building capacity is part of EDCTP's remit and capacity for post-approval programmes should be part of this.

Different stakeholders – such as funding and development agencies, product developers and regulators – can work together to develop a common strategy to fill in existent gaps.

In their opening comments, the Chairs of the meeting stressed the importance of a whole life-cycle approach in the development of new healthcare products intended for use in the battle against poverty-related diseases (PRDs). EDCTP's partnership approach, with its search for synergies is also highly relevant in efforts to improve pharmacovigilance.

Current vaccine and drug pharmacovigilance activities in sub-Saharan Africa

In his discussion of current drug and vaccine pharmacovigilance activities in Africa, **Dr Dodoo** argued that, since EDCTP assists in bringing new products into use, it has a duty also to be involved in post-marketing surveillance and monitoring. He explained that clear terminology for pharmacovigilance is important; any definition not clearly specified can bring difficulties, for example in relation to industry compliance. The World Health Organization (WHO) and national authorities have to be very precise in their communications or reporting to regulatory authorities. It is also important to separate problems that are related to rumours – especially those associated with mass drug or vaccine administration – from those due to the actual medicine, and this is one area where EDCTP can play a role. He reminded the meeting of the WHO definition of pharmacovigilance: "*The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems*". Pharmacovigilance extends beyond drugs, to include vaccines and herbal medications.

Pharmacovigilance is globally monitored through the WHO International Drug Monitoring Programme, which has to date 110 full member nations; 32 further countries are associated members. In Africa the respective figures are 29 and 8, leaving 17 countries that are not part of the programme. Individual case safety reports (ICSRs) submitted by member nations to the programme are stored on VigiBase – a centralised database maintained and developed on behalf of WHO by the Uppsala Monitoring Centre in Uppsala, Sweden. As part of its International Drug Monitoring Programme, WHO recommends one pharmacovigilance system and one database to include ADR reports on all three types of products (i.e. drugs, vaccines and herbal medications). Of the total of over seven million reports included in VigiBase since the launch of the programme in 1968, only 0.43% originated from Africa, most of these emanating from just three countries – Kenya, Nigeria and South Africa. Many African countries have become more involved in the programme only recently, i.e. since 2004.

Assessments have shown that the functionality of pharmacovigilance systems in sub-Saharan Africa is weak. Researchers have suggested innovative ways of reporting information, in addition to maintaining and developing passive

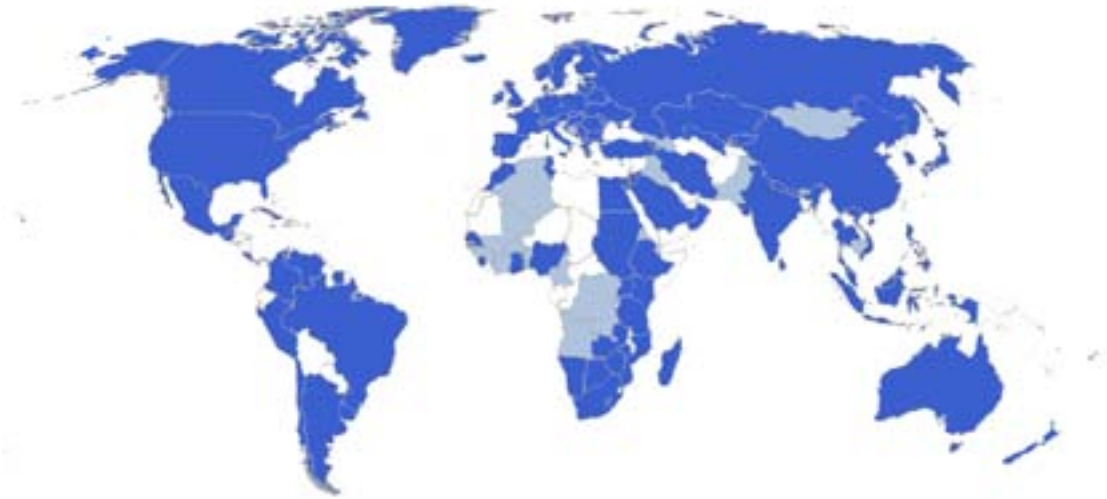

Figure 1. The WHO PV Programme:
110 Full members **32 Associate members**

reporting systems. Dr Dodoo quoted from one such study (Olsson et al. 2010): "*A pharmacovigilance strategy in these settings needs to help build health systems that can serve the purpose of multiple health conditions. It needs to identify and implement feasible systems, governance, infrastructures, human resource, training and capacity building, sustainable methodologies and innovations in pharmacovigilance*"[4].

National pharmacovigilance centres in Africa are new and have so far contributed little to the global database, even for medicines for diseases with high burden in Africa, such as HIV/AIDS, TB and malaria. However, there has recently been published a signal of drug safety emanating solely due to data from Africa. This signal of extrapyramidal ADRs to amodiaquine–artesunate combination treatment for malaria on Vigibase, was picked up due to 49 reports from Africa[5].

One key issue to be addressed is industry reporting of ADRs, which is not mandatory in most African countries, though in some (e.g. South Africa, Tunisia and Morocco) it is quite well enforced. It is widely recognised that there is a need to establish systems of patient reporting, and to ensure that pharmacovigilance informs decision-making and becomes a recognised part of public health programmes and activities. With regard to post-marketing surveillance and monitoring of vaccines, there is not as yet a global collaborative system for the collection of information on adverse events following immunisation (AEFI). WHO is encouraging countries to ensure vaccines and drugs are regulated in the same way and that the details are kept in the same database. Some countries maintain separate spontaneous reporting systems for drugs and vaccines, while others have one system covering both types of product. Vigibase contains individual case safety reports (ICSRs) related to vaccines, but this constitutes less than 10% of reports on the database.

In Africa the safety capacity system for vaccines is probably even weaker than that for drugs. Clinical trials of new vaccines provide most of

4 Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries: a questionnaire-based analysis. Drug Saf. 2010: 1;33(8):689-703.

5 McEwen J. Artesunate- and amodiaquine-associated extrapyramidal reactions: a series of 49 cases in VigiBase™. Drug Saf. 2012:1;35(8):667-675.

the available information on vaccine safety, but these data are not publicly available. Better integration of pharmacovigilance for vaccines into the Expanded Programme of Immunization (EPI) would be a positive step, as would be increased collaboration between pharmacovigilance centres and EPI programmes, and organisations collecting information on AEFIs globally.

There are, however, some vaccine pharmacovigilance initiatives under way in certain Africa countries, for example the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) is assessing the impact of vaccinations on child survival at selected centres; the INDEPTH Effectiveness and Safety Studies of Antimalarial Drugs in Africa (INESS) programme may also be expanded to include vaccines.

There is a pharmacovigilance component in the deployment of the MenAfriVac® vaccine in the African meningitis belt. Safety monitoring is also taking place of the Rotarix® and Prevnar 13® vaccines (respectively, for the prevention of rotavirus diarrhoea and IPD [invasive pneumococcal disease, such as pneumococcal meningitis]) following their nationwide deployment in Ghana's EPI. Vaccine Adverse Events In Kenya (VAIEK) – a collaborative programme between the Kenya Medical Research Institute (KEMRI) and the US Centers for Disease Control (CDC) – is assessing the safety of the Synflorex PCV10® pneumococcal conjugate vaccine. Médecins sans Frontières (MSF) or Doctors without Borders is also collaborating in pharmacovigilance for NID treatments in East Africa. In collaboration with the University of Maputo, EDCTP funded a project to measure the incidence of ADRs and to determine risk factors that may contribute to the development of ADRs to antiretroviral and antimalarial drugs in pregnant women.

In 2008 WHO established the Global Network for Post-marketing Surveillance of Newly Prequalified Vaccines[6] to provide support to countries deploying newly pre-qualified vaccines; three African countries are already actively involved and the programme is likely to be extended.

Dr Dodoo went on to describe the Global Vaccine Safety Blueprint Initiative, which has three main goals:

- Assisting low and middle-income countries to have at least minimal capacity for vaccine safety activities
- Enhancing capacity for vaccine safety assessment in countries that introduce newly developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines
- Establishing a global vaccine safety support structure.

A 'landscape assessment' was undertaken in 2010 to find out the true state of pharmacovigilance in Africa. The relevant authorities in 54 countries were contacted through a questionnaire survey complemented by telephone calls; 35 responded. The main finding from the assessment was that support (including training in both pharmacovigilance and information technology) is needed by most African countries before progress can be made. Countries need to collect data, develop capacity to analyse the data and use the results to guide policy decisions. Exchange programmes and attachments to established centres were also seen as desirable by several responding countries.

From 2002 onwards WHO has been undertaking several capacity building initiatives. At the funding level, Dr Dodoo gave the example of the Global Fund to Fight AIDS, Tuberculosis

6 More information at http://www.who.int/vaccine_safety/committee/topics/global_AEFI_monitoring/Dec_2011/en/

and Malaria, which has in its Round 10 indicated the availability of funds for pharmacovigilance. However, an assessment of applications received found that less than 20% contained a component for safety monitoring.

Looking ahead, several interventions are planned by WHO and other partners. One important initiative is the Pharmacovigilance Toolkit, managed by the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance in Accra, Ghana – a collection of tools and resources to assist in the proper conduct of pharmacovigilance. It provides countries with the freely available technical information and resources required for a functional system. It also assists countries in putting together proposals for funding pharmacovigilance to donors, and offers many other resources. Dr Dodoo described it as a 'one-stop shop for pharmacovigilance'.

Dr Dodoo also noted that in some areas populations have become 'quite militant' as a result of their concerns regarding vaccine and drug safety. Issues with even just one drug can easily lead to a lack of confidence in healthcare services as a whole.

Malaria vaccine: the RTS,S/AS post-registration programme

Dr Edith Roset Bahmanyar, Senior Epidemiologist at GlaxoSmithKline Biologicals (GSK) mentioned that RTS,S/AS – the world's first malaria vaccine – will be implemented in sub-Saharan Africa accompanied by a comprehensive risk-management programme. This is necessary because GSK experience shows there is a low likelihood of signal detection based on spontaneous reports; an additional concern is Africa's limited disease surveillance systems, which might pose limitations in terms of assessing the impact of this new intervention.

A risk-management programme for vaccines should plan for both pharmacovigilance and risk minimisation, and this will be the case in the RTS,S/AS post-approval programme. There will be four large studies within the programme – in which some 50,000 children will be vaccinated – and a model will be developed for pharmacovigilance and disease surveillance in sentinel centres. The goals of the programme include both field evaluation of the benefits and risks of the vaccine, and capacity building for pharmacovigilance and disease surveillance that will extend beyond the study itself.

Dr Bahmanyar went on to provide an outline of the four studies, the first of which is a baseline study that will be conducted in advance of the registration of the vaccine. GSK hopes that experience gained in this study will make it possible to establish a model that can be used in the establishment of sentinel surveillance centres elsewhere. Dr Bahmanyar stressed the importance of recognising, reporting, analysing and interpreting AEFIs. She described AEFIs as 'rare diseases or events' but said that they could be serious.

Pharmacovigilance requires a number of activities occurring at different levels, and the ability to detect and diagnose rare and severe reactions. Reports of adverse reactions must be made using a common terminology based on standard case definitions. With this in mind, GSK has developed a pharmacovigilance and disease surveillance training package, and will collaborate with health ministries and external organisations in the training of health care workers in specific study areas. Also involved in this process will be the RAFT Network and Agence de Médecine Preventive. (Dr Bahmanyar gave a brief account of the work of both these organisations.)

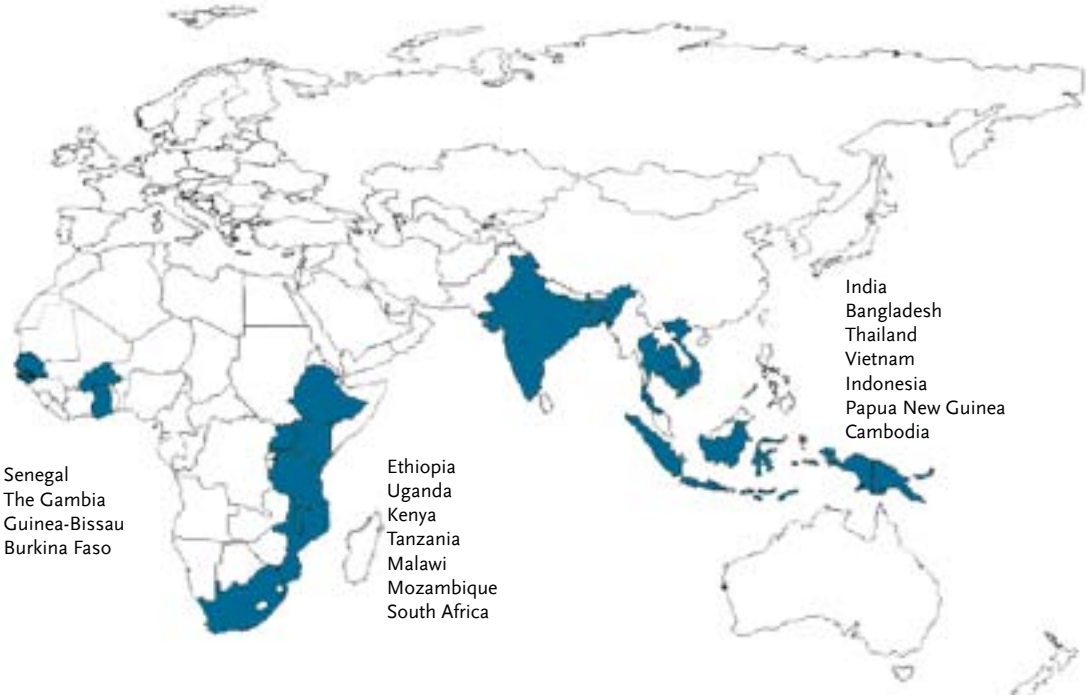

Figure 2. Low- and midle-income countries with INDEPTH member centres running health and demographic surveillance systems

Summing up Dr Bahmanyar said the post-approval studies will allow evaluation in real-life settings of the benefit and risks of the RTS,S/AS malaria vaccine. Nevertheless, although the conclusions drawn from these studies can be extrapolated to large populations, it will still be important to monitor the impact and safety in countries where pharmacovigilance does not yet exist. She hoped that the post-approval studies tools (and collaboration with AMP, RAFT and INDEPTH) would lead to a model for the development of new sentinel centres in African countries that have no surveillance in place. Such new health and demographic surveillance systems (HDSS) could be used to monitor other interventions or address epidemiological questions.

- Answering questions from the floor, Dr Bahmanyar said the baseline study had been submitted to receive ethical approval. All planned studies will be submitted for ethical approval and post-approval studies may require clearance from NRAs. Two of the four studies will be conducted before registration and two after.
The fourth study is a cross-sectional study that will follow malaria transmission intensity across baseline and safety studies to allow for vaccine impact measures. The mitigation for the risks identified in the risk management plan is based on a study protocol in which a cohort is monitored for events and during which children will be actively surveyed. The data collected during the study will build a health and safety database on 40,000 children.
In this sense, the risk management plan will not only include spontaneous reporting but also active surveillance of events of special interest. It will operate in parallel to the national system, but because of the capacity building on pharmacovigilance that will take place for all health care workers, it is expected that incidents recorded will be reported as AEFIs to the respective ministry

of health and sustained beyond study end. In parallel, national systems should also be strengthened.

Discussion

Contributors from the floor raised a wide range of issues. It was agreed that the first challenge faced by EDCTP is to determine *how* it can act as a neutral broker with African governments, product developers, academic/research institutions and other stakeholders in order to improve pharmacovigilance, and to create a sustainable system.

Capacity issues in health systems are one reason for the current lack of effective pharmacovigilance in Africa. Training needs were seen as of particular importance. The capacity must be developed to conduct active surveillance and to collect, analyse, and interpret data. Other priorities for capacity building efforts will also need to be defined.

Capacity issues are, however, only part of the problem. A point made by several speakers was that African governments, through disease control programmes and NRAs, must engage more fully with the issue of pharmacovigilance; they were said to be 'the real stakeholders' in this area and to hold the primary responsibility for establishing and maintaining systems. When registering a new product a risk management plan should be mandatory, as is the case in Europe, USA or Japan. It was also strongly recommended that risk management plans should be developed before product launch – i.e. they should be designed at phase II–III stage. Ministries of health should also have effective systems for handling spontaneous reports. Some data on ADRs is already collected but national health systems 'seem not to be interested'. Pharmaceutical companies are now more willing to share ADR data but health ministries are not yet taking advantage of this development. Policy makers generally fail to make changes in the light of new data sent to them. It is often difficult even to discuss issues such as post-registration programmes with government; a solution to overcome this barrier could be to formulate the discussion with governments around access issues. EDCTP could help as a broker here.

It was agreed that good governance was a key issue. Part of the problem is inefficient bureaucracy – the pressures of too much paperwork mean that pharmacovigilance data collected on the frontline of healthcare may not reach health ministry headquarters for many months. More training and resources in IT are required, but a complete change of mind-set is also necessary. Pharmacovigilance should be integrated with efforts to strengthen health systems. Plans to establish sentinel centres to facilitate safety data collection were welcomed, but it was regarded as essential that these should become part of health care delivery systems. National centres for pharmacovigilance should also provide information on AEFIs to health care delivery centres, following a clearly defined process.

A large proportion of Africa's drug supply consists of counterfeit products. Reports of ADRs may indicate toxicity due to a fake medication and not to the genuine substance. Co-infections and common use of traditional medicines also complicate the challenge of pharmacovigilance in Africa.

Participants were reminded that clinical trials are conducted in a relatively controlled environment. Once a product comes into widespread use, it enters a far less controlled world. It is vital that EDCTP should support post-registration studies, as it would not be right to rely completely on industry partners to be responsible for this stage of a product's life cycle.

It was noted that the discussion seemed to be focusing on pharmacovigilance for new products. While a full risk management plan is needed for all new products, existing products already on the market, such as the yellow fever vaccine, should also be the subject of pharmacovigilance. Many of these products were developed and registered in high-income countries and have come into use in low-income countries without previously being tested there.

Post-registration studies focus on specific drugs and vaccines in specific locations and time periods. What is also needed, however, is a platform on which data can be shared across diseases and populations. There could be a role for EDCTP here; it could establish a framework for managing data. As pharmacovigilance relies on collaboration with several partners, EDCTP could take on the role of ensuring that they are making their required contributions. It is good news that industry is now more willing to share data, but do people know how to access and use these data? Again EDCTP might be able to assist.

Countries should also share their product safety data. For example, South Africa has considerable experience with pharmacovigilance for stavudine for HIV treatment; the data arising could be shared more widely. For EDCTP, Prof. Mgone said that sharing data is already agreed to be desirable and has indeed often been discussed. The challenge was to determine how it should be done. EDCTP, however, was the 'glue' that could make such collaboration possible.

Contributors welcomed the new initiatives described by Dr Dodoo, particularly the Pharmacovigilance Toolkit. Collaboration with relevant organisations – including the African Union, The New Partnership for Africa's Development (NEPAD) and African universities and research centres – will be necessary to improve pharmacovigilance in Africa. Clearly WHO will also play a central role. EDCTP is already actively engaged in what was termed 'pharmaco-diplomacy'. Regional economic bodies are also part of the picture. Existing initiatives such as the Pharmacovigilance Department and Drug Safety Repository at the Liverpool School of Tropical Medicine[7] should be taken into consideration, rather than attempting to start pharmacovigilance from the beginning. International harmonisation is needed, particularly with regard to training and case definitions. (The work of the Brighton Collaboration in the latter area might be helpful.)

The importance of baseline data was frequently referred to. For the collection of such data, research grants were unlikely to be awarded. With creative thinking, however, it could be drawn from many sources; baseline and control group data from the RTS,S/AS trial could for example be useful in other vaccine studies. Some participants cautioned that the 'right sort' of baseline data was needed – thus data from a vaccine trial were unlikely to be relevant to pharmacovigilance for drugs. A wide range of types of data on drugs in current use is needed; pharmacovigilance needs to be linked to broader pharmaco-epidemiological studies to better inform future policy decisions.

The issue of how pharmacovigilance activities might be financed also received the meeting's attention. Some participants in the meeting argued that agencies such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and the GAVI Alliance were prepared to fund pharmacovigilance. Others were more sceptical, saying that in the absence of existing programmes there was nothing taking place that could be funded, and no one to apply for the funds. It was also noted that it is hard for PDPs to get funding for post-registration studies from their industrial partners. However, it seems to be

7 Information about the Pharmacovigilance Department and Drug Safety Repository at the Liverpool School of Tropical Medicine was sent to the EDCTP Secretariat after the meeting.

that, for once, the problem is not the money – it is the capacity to apply for it. What is needed is to raise awareness of the funds available and address the lack of capacity in Africa to apply for them.

Dr Dodoo's comment about the importance of maintaining the trust of the African general public in drugs, vaccines and healthcare services as a whole was emphatically endorsed by the meeting – their concerns and demands must be recognised and their engagement should be part of the pharmacovigilance process.

Other comments made included the following:

- Pharmacovigilance must extend to drugs sold in the private health care system
- Safety activities can have unexpected benefits – new benefits from drugs can come to light, as has been the case with the antibiotic moxifloxacin
- In designing systems for pharmacovigilance, one size will not fit all. In other words a single new vaccine may be introduced in one country but elsewhere there may be programmes involving two or more new vaccines; different pharmacovigilance activities will be needed and the focus should be on the priorities rather than attempting to cover all needs
- Who the key players are in a pharmacovigilance system will depend on the intended beneficiaries of the treatment or prevention interventions. For example vaccination products for children may involve stakeholders in the EPI, while those for pregnant mothers involve those involved in the effective implementation of antenatal care services.

4. Conclusions and recommendations

In its background paper for the meeting EDCTP recommended that:

- Future post-registration programme activities should be undertaken in partnership with product developers (industry and PDPs) NRAs, African Vaccines Regulatory Forum (AVAREF), the African Medicines Regulatory Harmonisation Programme (AMRH), and the Ministries of Health
- These activities should be embedded in an overarching programme to strengthen institutional capacity and foster sustainability
- Involvement of AVAREF, which is currently active in the initial regulatory joint reviews of clinical trial applications, will also encourage ownership and continuity
- Post-registration pharmacovigilance programmes must be aligned to national programmes including the EPI and other existing surveillance activities focusing on product safety
- However, these programmes should not overburden existing systems or draw human resources away from core activities.

The main issues which arose from the discussions are summarised below:

- All available avenues should be pursued and existing partners and initiatives should collaborate, to establish whether medicinal products continue to perform as expected in terms of effectiveness and safety in the 'real world'
- Capacity building (particularly training and establishment of functional pharmacovigilance monitoring systems) will be required to enable efficient handling of spontaneous reporting, coupled with active surveillance systems. For countries where funding is available from organisations like the Global Fund and other agencies, training is required to facilitate funding applications
- Increased engagement with the issue of pharmacovigilance on the part of African governments will be essential. Pharmacovigilance programmes should be integrated within health systems and form part of a comprehensive and robust plan for access to health care services
- Collaborative efforts are needed in a spirit of partnership, including a harmonisation of procedures and the sharing of pharmacovigilance data through an appropriate platform. EDCTP will continue its role as a broker to make possible such a collaborative approach
- Engaging the public is a key element in the establishment of good pharmacovigilance systems. Confidence in drugs and vaccines and the healthcare delivery system as a whole must be maintained
- Overarching issues could be tackled if EDCTP could consider funding projects that ensure manufacturers contribute to implementing programmes on pharmacovigilance
- Other issues: risk management plans are needed for new products but those already in use should not be neglected; baseline and pharmaco-epidemiological data are both necessary; the environment which new products enter in Africa is complicated by many factors including the widespread prevalence of counterfeit products.

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EDCTP emphasised that pharmacovigilance is the responsibility of all involved in product development together with national regulatory authorities and those responsible for national health systems. EDCTP is willing to play the role of a broker to bring together all pertinent partners and also participate in the required capacity development relevant to improve post-registration safety monitoring of medicinal products in sub-Saharan Africa.

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