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Report on the

# Eastern Mediterranean Drug Regulatory Authorities Conference 2014

Amman, Jordan  
5–8 May 2014



World Health  
Organization

Regional Office for the Eastern Mediterranean

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## EXECUTIVE SUMMARY

The World Health Organization (WHO) Regional Office of the Eastern Mediterranean organized the Eastern Mediterranean Drug Regulatory Authorities Conference (EMDRAC), which took place in Amman, Jordan, from 5 to 8 May 2014. The conference comprised two days of sessions open to national regulatory authorities (NRAs) and partners and two days of closed sessions for NRAs only.

The overall objective of the EMDRAC is to promote effective regulation and control of medical products<sup>1</sup> and the establishment of functional NRAs in the Eastern Mediterranean Region. The specific objectives of EMDRAC 2014 were to:

- review progress made and identify challenges encountered by NRAs in regulation of medical products in the Eastern Mediterranean Region and propose solutions to address them;
- update NRAs about the latest global initiatives in medical product regulation and WHO's role in this area;
- advocate for the creation of common standards for regulatory functions and practices in the Region;
- review and agree on a draft plan of action for strengthening regulatory capacity of medical products in the Eastern Mediterranean Region;
- finalize recommendations of EMDRAC 2014 to be presented in the 16th International Conference of Drug Regulatory Authorities (ICDRA) which will be held in Rio de Janeiro, Brazil, on 24–29 August 2014.

The conference was opened with a video address by Regional Office for the Eastern Mediterranean Regional Director, Dr Ala Alwan, highlighting the importance of EMDRAC and the opportunity it provides to discuss regulatory issues of mutual interest and concern and to promote effective medicines regulation and common priorities. He noted that regulation aims to ensure the quality, safety and efficacy of medical products (medicines, vaccines, diagnostics, medical devices, etc.) through enforcement of legislation, norms and standards and that NRAs with adequate capacity, such as a legal mandate, quality management systems, human and financial resources, infrastructure and enforcement systems, can efficiently play this role. The core functions of NRAs include licensing; health technology assessment and registration of medical products; site inspection; quality control and testing; clinical trials oversight; providing independent information and controlling promotion and advertising of medical products; and monitoring adverse reactions. He outlined the significance of the upcoming WHA resolution for regulatory systems strengthening and how it demonstrates the importance of medical products regulation to ensuring better public health outcomes, and that regulators are an important part of human resources for health and regulation is essential in promoting universal health coverage. The discussion and hopefully the endorsement of this resolution will ensure that NRA will receive increasing global attention.

Conference sessions provided participants information about global and regional initiatives relating to the regulation of medicines, vaccines, biologicals and medical devices, including global health reform at WHO; results of a regional NRA survey; available WHO

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<sup>1</sup> In this report medical products are medicines, vaccines, diagnostics and medical devices.

support for regulatory activities; efforts to establish an African Medicines Agency; an update on the Africa Harmonization of Medicines Regulation initiative; developing medical device regulation and establishing health technology assessment; and progress made on the WHO global system for monitoring and reporting substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products. Countries presented their expertise and experiences of strengthening their regulatory systems and functions for market authorization of medicines, vaccines, blood products, and medical devices; clinical trials; quality control laboratories (QCL) and inspection of good manufacturing practices (GMP).

A draft paper on “Designing and implementing a regulatory programme for medicines and medical devices” was presented by Alan Kent and Sultan Ghani, both Temporary Advisers to EMDRAC. The draft paper was commissioned because there are currently two main challenges for regulators: global harmonization of device regulation and coherence of regulations of medical devices with pharmaceuticals and other health products. A progressive step-by-step approach is recommended for designing and implementing a comprehensive regulatory programme for the Eastern Mediterranean Region. The proposed regulatory models for medicines and medical devices will provide guidance for each regulatory authority to consider where they can place themselves in terms of knowledge, national priorities, human and financial resources and political support over the long-term.

Participants were assigned to three working groups. Groups were asked to identify next steps for NRAs to strengthen their current regulatory system for medicines and medical devices in each of the following areas: assessment and regulation of medicinal products; compliance and enforcement; national medicine control laboratory; and post-marketing surveillance. Groups were then asked to report on their discussion with two or three recommendations per area of what should be done across the Region.

The meeting reviewed progress and challenges identified in regulation of medical products and presented possible solutions recommended in the Eastern Mediterranean Region; agreed on a plan of action for strengthening regulatory capacity in the Eastern Mediterranean Region; and finalized the following recommendations, which will be presented by Afghanistan during the 16th ICDRA.

#### *To Member States*

1. Begin collaboration across the Region with a step-wise approach beginning with joint on-site good manufacturing practices (GMP) inspections, sharing relevant information and joint training in a way that complements existing initiatives.
2. Actively participate in the new Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products and a functional national monitoring and surveillance system that can report SSFFC medical products to the global WHO monitoring and surveillance system.
3. Take steps towards regulating medical devices and building capacity to apply the health technologies assessment (HTA) as an evidence-informed decision making tool.

4. Undertake a self-assessment using the WHO comprehensive NRA assessment tool.
5. Build capacity of NRA through WHO support and bilateral collaboration between Member States in joint training and orientation visits.
6. Continue to build broad-based pharmacovigilance/post-marketing surveillance systems for all regulated medical products (medicines, vaccines, biopharmaceuticals, diagnostics, herbal and traditional medicines and medical devices).
7. Attend the 16th ICDRA 2014 in Brazil.

*To WHO*

8. Support Member States in strengthening NRA capacity through a step-wise approach to comply with international norms, standards and guidelines by providing guidance, technical assistance, coaching and training.
9. Strengthen regulatory collaboration by mapping the expertise of the NRAs and creating a roster of regulatory experts in various functions.
10. Advocate for Member States support for strengthening and resourcing NRA, including the provision for adequate legislative and regulatory frameworks for medicines, vaccines, biopharmaceuticals, diagnostics, herbal and traditional medicines, and medical devices.
11. Enable a secure web-based platform for regulators to facilitate harmonization and convergence activities and share information including best practices, GMP inspection reports, HTA reports and other assessment reports.
12. Promote effective networking activities for medicines, vaccines and medical devices in all functions of regulation in the Eastern Mediterranean Region.
13. Define terms of reference and identify strengths of national regulatory authorities in specific areas such as assessment and regulation of medical products; compliance and enforcement; national medical control laboratory; post-marketing surveillance, including pharmacovigilance for all medical products.
14. Support Member States in completing NRA assessments and developing institutional development plans.

## 1. INTRODUCTION

The World Health Organization (WHO) Regional Office of the Eastern Mediterranean organized the Eastern Mediterranean Drug Regulatory Authorities Conference (EMDRAC), which took place in Amman, Jordan, from 5 to 8 May 2014. The conference comprised two days of sessions open to partners and two days of closed sessions for national regulatory authorities only.

The overall objective of the EMDRAC is to promote effective regulation and control of medical products, support the establishment of functional national regulatory authorities (NRAs) in the Eastern Mediterranean Region and provide regional input to the International Conference of Drug Regulatory Authorities (ICDRA).

The specific objectives of EMDRAC 2014 are to:

- Review progress made and identify challenges encountered by NRAs in regulation of medical products in the Eastern Mediterranean Region and propose solutions to address them;
- Update NRAs about the latest global initiatives in medical product regulation and WHO's role in this area;
- Advocate for the creation of common standards for regulatory functions and practices in the Region;
- Review and agree on a draft plan of action for strengthening regulatory capacity of medical products in the Eastern Mediterranean Region;
- Finalize recommendations of EMDRAC 2014 to be presented in the 16th ICDRA which will be held in Rio de Janeiro, Brazil, 24–29 August 2014.

EMDRAC is the only forum in the Eastern Mediterranean Region exclusively for NRAs to share information and engage in issues of regional importance. It was recommended by NRAs in the Region that one EMDRAC every two years is appropriate to maintain the functionality of the network and collaboration among NRAs as major stakeholders in the pharmaceutical sector of the Region. The last EMDRAC was held in December 2011.

Of the 22 NRAs invited from countries of the Eastern Mediterranean Region, 17 sent two representatives each to participate in the meeting. The Secretariat comprised staff members from the WHO Regional Office for the Eastern Mediterranean and headquarters. Qualified experts from related agencies and international and regional organizations working in the field of strengthening regulatory systems attended, including the following:

- WHO Collaborating Centre for Pharmacovigilance – Morocco
- Regional pharmaceutical industry association: Arab Union of the Manufacturers of Pharmaceuticals and Medical Appliances (AUPAM)
- Gulf Cooperation Council (GCC) partners: European Medicines Agency (EMA) (by Skype) and U.S. Pharmacopoeial Convention (USP)
- Essential Medicines and Policies country advisers and WHO temporary advisers.

The Conference had two parts, open sessions from 5 to 6 May and closed sessions from 7 to 8 May 2014. The open sessions were attended by ministry of health/NRA officials, related agencies and partners, whereas the closed sessions were for ministry of health/NRA officials only.

The conference opened with remarks by Dr Marthe Everard, Coordinator Essential Medicines and Health Technologies, WHO Regional Office for the Eastern Mediterranean, who welcomed participants and outlined the conference agenda, describing that it would provide during day one and two an overview of how WHO's Essential Medicines and Health Products department has reorganized itself bringing together medicines, vaccines and medical products; a global and regional overview of the regulatory environment and current initiatives; as well as a discussion of other challenges such as substandard/spurious/false-labelled/falsified/counterfeit (SSFFC) medical products and pharmacovigilance. Days three and four would focus on country experiences in regulatory functions, the contents of a draft NRA paper and a demonstration of a WHO comprehensive national regulatory authority assessment tool to help identify weaknesses in regulatory core functions that may need to be improved.

A video address by the WHO Regional Director for the Eastern Mediterranean, Dr Ala Alwan, noted that EMDRAC was created to strengthen regulatory collaboration between Member States in the Region, exchange information among national regulatory authorities and discuss issues of global and regional importance in the area of quality, safety and efficacy of medical products. He introduced the theme of EMDRAC 2014 as being "Towards regulatory cooperation" and stressed how this is the direction that countries, regions and continents are moving. He identified increased collaboration within the Region as a solution for many of the challenges faced by the 22 national regulatory authorities – insufficient investment, inadequate infrastructure and organization, limited trained human resources – that contribute to delays in dossier assessment and registration procedures. He suggested that collective action on regional monitoring, surveillance and reporting for quality compromised products in the Region would help minimize the consequences these products can have on the health and wellbeing of patients and citizens of the Region. He raised the importance of the role of regulatory authorities and the upcoming draft resolution for discussion at the World Health Assembly that recognizes that, "...effective regulatory systems are an essential component of health systems strengthening and contribute to better public health outcomes, that regulators are an essential part of the health workforce and that inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products," and that "effective regulatory systems are necessary for implementing universal health coverage...by promoting access to essential medical products."

Jordan Food and Drug Administration – Dr Ikhlas Hadidi noted that the EMDRAC provides a valuable opportunity to exchange ideas to develop the regulatory sector and address challenges faced by the sector across the Region. She highlighted the importance of the pharmaceutical sector to Jordan, with its high rate of exports to other countries and the importance of strengthening local industry.

Dr Lembit Rägo, Head, Regulation of Medicines and Other Health Technologies, WHO headquarters, noted that the Regional Director presented the big picture and the role of regulatory systems in delivering universal health coverage. He commented, “if we talk about health care, we must talk about regulated products, medicines, medical devices, vaccines – we must be able to rely on the quality and effectiveness of these products.” Strengthening regulatory systems is gaining profile internationally with many regions encouraging governments to build up credible regulatory systems. Ideally national regulatory authorities should be able to administer the full spectrum of regulatory activities, including at least the following functions:

- Marketing authorization for new products and variation of existing authorizations;
- GMP, GCP, GLP inspections;
- Licensing and post-license control of manufacturers, wholesalers and other distribution channels;
- Quality control laboratory testing;
- Adverse drug reaction monitoring;
- Provision of drug information and promotion of rational drug use;
- Enforcement operations;
- Monitoring of drug utilization, etc.

Dr Rägo noted that the draft resolution on strengthening national regulatory systems (EB134.R17) will be discussed at the upcoming WHA and that the regulatory focus is also embedded in other resolutions, such as the resolution on biotherapeutics, traditional medicine and anti-microbial resistance. He noted that the complex global situation impacts all regions, including EM and provided an overview of the many international initiatives that bring together medicine regulators to ensure safety, effectiveness of medicines and medical products including ICDRA, the International Conference of Drug Regulatory Authorities, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). He stressed the importance of regional collaboration to not just discuss challenges, but to work together to achieve common results. He suggested that the pressure on limited resources could be mitigated by working collectively to leverage and strengthen existing human, infrastructure and financial resources and minimize duplication, ensuring that they are providing added value to improving health of populations.

The session was joined by Acting WHO Representative Jordan, Dr Ahmad Basel Al-Yousfi, who brought greetings on behalf of WHO Jordan and wished EMDRAC successful deliberations.

The conference programme is provided in Annex 1 and the list of participants is attached in Annex 2.

## **2. GLOBAL AND REGIONAL OVERVIEW OF MEDICINES REGULATION**

### **2.1 WHO reform and how medicines regulation is key to universal health coverage**

*Dr Clive Ondari, WHO headquarters*

WHO's Member States-driven reform aims to ensure that WHO is better equipped and able to address the increasingly complex health challenges in the 21st century. From persisting problems to new and emerging public health threats, WHO needs to be flexible enough to respond to the evolving global health environment. The three objectives of the reform as defined by the Sixty-fourth World Health Assembly to address these challenges, are: improved health outcomes, greater coherence in global health and pursuit of excellence.

The six leadership priorities give focus and direction to WHO's work – advancing universal health coverage, achieving the health related Millennium Development Goals (MDGs), addressing the challenge of noncommunicable diseases, implementing the international health regulations, increasing access to essential, quality-assured and affordable medical products, and reducing health inequalities.

Governance reform aims to increase coherence in global health by addressing the way the World Health Assembly, the Executive Board and its subcommittees operate – to strengthen oversight, strengthen engagement with partners and stakeholders – such as UN agencies, nongovernmental organizations, civil society, foundations, academia and industry – and better align actions to promote health and well-being.

Management reforms are revitalizing managerial processes and organizational structures to build an organization that is more effective, efficient, responsive, objective, transparent and accountable.

The restructuring of the Department of Essential Medicines and Health Products has been centred on access to essential, quality-assured and affordable health products as one of the six leadership priorities articulated by the WHO Director-General. It has a focus on improved access to medicines, vaccines, diagnostics and medical devices as a key element to the achievement of universal health coverage, the acceleration of achievement of the MDGs and the reduction of deaths from noncommunicable diseases.

The WHO General Programme of Work 2014-2019 and Programme Budget for 2014-2015 organize the work of WHO towards increased access to medicines and other health technologies in three broad areas, which correspond to the new Department of Essential Medicines and Health Products structure and areas of focus: medicines policies and access to medicines, regulation of medical products and innovation.

Regulation of health technologies unit is composed of four teams: Norms and Standards Team; Regulatory Systems Strengthening Team; Prequalification Team; and Safety and Vigilance Team, which brings together post marketing surveillance, pharmacovigilance, safe use of medical products and SSFFC medical products.

Going forward it is anticipated that this restructuring will lead to four outcomes. First, streamlined and merged functions for all medical products. Second, a renewed emphasis on policies and actions on innovation. Third, reinforced capacity of WHO in the area of medicines and health products policies and implementation. Finally, optimized technical guidance and support to countries in implementing national policies that enhance the access to medical products of assured quality.

## **2.2 Medicines regulation in the Eastern Mediterranean Region: Results from survey**

*Dr Marthe Everard, WHO Regional Office for the Eastern Mediterranean*

Prior to EMDRAC a survey was sent to participants from 17 NRAs. The results from this survey showed that NRAs in the Region are on the right track. More details are provided in Annex 3.

The survey was meant to provide a “snap shot” of the current situation. It will not be used in developing strategies and global reports. It was meant to highlight some of the achievements in the Region in the area of regulatory strengthening in relation to one of the recommendations of EMDRAC 2011. In 2015, it is planned that the Department of Essential Medicines and Health Products at WHO headquarters and in the regions will initiate a pharmaceutical sector profile survey, a more formal process for providing documented evidence and information to WHO, which includes, among others, sections on NRAs and the local pharmaceutical industry.

## **2.3 Good Governance for Medicines: Transparency and accountability framework**

*Dr Mohamed Ramzy, Regional Office for the Eastern Mediterranean*

The WHO Good governance for medicines programme (GGM) started in the Eastern Mediterranean Region in 2007. Sixteen countries in the Eastern Mediterranean Region currently participate in the programme, supported by WHO senior management. The pharmaceutical sector is a great target for corruption and unethical practices. Governments invest a lot of resources in trying to curb corruption and limit opportunities for its entry in the medicines chain. Each year US\$ 6.5 trillion is spent on health services. The global pharmaceutical market comprises more than US\$ 930 billion. While there is no global estimate on financial losses, 10% to 25% of procurement spending is lost to corruption. Some countries report losses of up to two-thirds of medicines supplies in hospitals and 10% of national expenditures on health care. Medicines are prone to corruption due to their high market value. Therefore, there is a need for control/regulation and correcting the information imbalance that exists between various players (e.g. health professionals and patients). Technical guidelines already exist. The challenge is in balancing these with ethical practices such as accountability, transparency and rule of law.

In the WHO GGM programme, good governance refers to the formulation and implementation of appropriate policies and procedures that ensure the effective, efficient and ethical management of pharmaceutical systems, in particular medicine regulatory systems and medicine supply systems, in a manner that is transparent, accountable, follows the rule of

law and minimizes corruption. The programme is based on the assumption that the more transparent any system is, the less vulnerable it will be to corruption and unethical practices.

The WHO GGM programme applies a two-track approach: a discipline-based approach and a values-based approach. These two approaches are applied in the three-phase GGM process: national transparency assessment by using the WHO assessment tool, national GGM framework development based on the WHO model framework and examples from Member States, and implementation of national GGM programme with support from WHO as needed. The GGM programme works on five regulatory functions and three supply functions and should be integrated into existing structures and supported by an implementing team. The Member States that have been most successful are those that have institutionalized it within their Ministry of Health. National GGM programmes engage all actors in the pharmaceutical sector in countries when performing the assessments and developing their national GGM frameworks.

National GGM frameworks should include ten key components from both the values-based and discipline-based approaches such as a code of conduct, promotion of moral leadership, truth, service to a common good, established legislation, transparent and accountable regulation and administrative procedure, and whistle-blowing mechanism. These components should be supported by collaboration with other good governance and anti-corruption initiatives as well as management, coordination and evaluation of the GGM programme by a steering committee and task force.

The WHO GGM programme started in 2004, and is financially supported by the governments of the Federal Republic of Germany and Kuwait. The process has made an impact in governance overall and in the regulatory system by identifying vulnerabilities in pharmaceutical systems and suggesting ways to address them.

#### **2.4 Good Governance for Medicines: A model for evidence-based selection of medical products**

*Professor Ibrahim Alabbadi, University of Jordan*

Jordan has introduced and begun implementing an evidence-based medicines selection method for formulary inclusion, which was adapted from the System of Objectified Judgment Analysis (SOJA). It is a method designed specifically for hospitals that helps to ensure patients receive medicines that provide the best value for money and increase drug availability and adherence. This evidence- and science-based selection approach uses a structure and process that are transparent and robust and is based on four elements or STEPS: 1) clinical evaluation phase, 2) safety and risk assessment phase, 3) budget impact analysis, and 4) final product selection based on scoring system.

The methodology follows four phases adapted to Jordan: safety, clinical evaluation, product selection and cost analysis prior to final selection of drug and medical products. Every three years a tendering process for accepted products is conducted based on calculating costs using WHO defined daily dose (DDD). This has led to a cost savings of nearly 42%.

The benefits of the STEPS model include optimized patient care, fully integrated product use in all sectors, selection of products based on safety, therapeutic efficiency and quality as the prime determinant. The model can be used for any formulary developed for ministry of health health facilities, private hospitals, or civil society health facilities.

Additional information can be found in the article “Impact of Modified System of Objectified Judgment Analysis (SOJA) methodology on prescribing costs of ACE inhibitors”.<sup>2</sup>

## 2.5 Panel Discussion

*Moderators: Dr Abdillahi Youssouf Nour, Ministry of Health Djibouti and Dr Marthe Everard, Regional Office for the Eastern Mediterranean*

Member States expressed a need for a strong recommendation from WHO for countries to have an “independent” national regulatory authority. It was noted that it is important for NRAs that they have clear, independent managerial decision-making ability and be able to retain the necessary financial and human resources. Some NRA commented that it is easier for parent ministries to allow for flexibility rather than full autonomy.

Discussion on the NRA survey highlighted that the results will help identify areas for improvement for each country and suggested that bench-marking and sharing lessons learnt and best practices among NRAs could help regulatory authorities in the Region. Participants suggested that if this is communicated by WHO it helps NRAs bring change in their countries and that there is a role for WHO to promote collaboration between countries. Regional Office for the Eastern Mediterranean is working on an NRA paper that will be presented at the Regional Committee meeting in 2015. It is important to be sensitive to existing NRA capacities. There are good things happening. The issue is how the Region can work together.

Discussion noted that surveys are most informative if they are within a closed environment. A safe environment is needed to respond honestly to the questions, without ramifications. Participants were informed that WHO has a self-assessment tool that would be presented in the closed session part of EMDRAC to aid NRAs in reviewing functions and procedures that they have in place. The self-assessment highlights the needs for NRAs in terms of competency but also brings best practices to functions that may present conflict of interest and areas that may require guidance to protect safety, procurement, etc.

During the discussion, participants raised the challenge of getting medicines registered and on the market. The issue of access is a challenge for all regulatory agencies – particularly smaller countries. The question is what they can do. There is a role for industry, but regulators must say what products are needed on their registry. There needs to be a network among regulators to identify where the products have been registered. A medical justification for products can help to speed up this process.

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<sup>2</sup> Alabbadi I et al. Impact of Modified System of Objectified Judgment Analysis (SOJA) methodology on prescribing costs of ACE inhibitors. *Clinical Drug Investigation*. 2006;26(9):485–94.

The role of physicians in the supply chain between NRAs, manufacturers, suppliers and the patient was discussed. It was noted that physicians and other health practitioners are key to ensuring that the supply chain remains functional and that persons using the medicine/technology remain safe. Two components of how this is addressed in countries are advocacy, information sharing and awareness; and continuous feedback to NRAs in countries. WHO has guidance of how to manage this relationship through training for prescribers. Some universities have adopted WHO training materials into their curriculum. A manual for prescribers in handling drug promotion is also available. It was noted that physicians and pharmacists also need to be involved in providing feedback for pharmacovigilance – all adverse events, irrational use, antimicrobial resistance should be reported by physicians.

Interest in applying the STEPS method across the Region was expressed. The medicine selection criteria are objective and evidence-based and also consider cost implications after the first three phases have been completed. It was noted that STEPS can be applied at any health care level, including hospitals, and by any country. It was noted that the STEPS method has been broadly applied and used in the UK for eight years.

## **2.6 Information on the forthcoming 16th ICDRA**

*Dr Samvel Azatyan, WHO headquarters*

The International Conference of Drug Regulatory Authorities (ICDRA) was established to develop international consensus on regulatory matters and is an important platform for WHO and national regulatory authorities in their efforts to harmonize regulation and improve the safety, efficacy and quality of medicines.

The main objectives of the ICDRA meetings are to promote collaboration between national medicines regulatory authorities; to reach a consensus on the matters of interest; to facilitate timely and adequate exchange of information and to discuss issues of international relevance.

While ICDRA meetings are for regulators only, pre-ICDRA meetings are open to all interested parties including academia, industry, and civil society. The ICDRA programme includes plenary discussions and thematic workshops. ICDRA produces recommendations to NRAs, national authorities, manufacturers, member states and WHO, which are sent to all participants and published in WHO Drug Information and on the WHO website. The 15<sup>th</sup> ICDRA included recommendations for NRAs, manufacturers and WHO on ensuring the quality of active pharmaceutical ingredients; regulatory collaboration and networking; assessing and responding to the needs of regulators and the application of a risk-based approach for managing NRA activities with limited financial and human resources. ICDRA recommendations provide a good mandate for proposing activities for NRAs and can be used by NRAs to justify their actions and requests. It is the highest forum of NRAs worldwide. The issues discussed at ICDRA are covered over the course of every meeting, allowing issues that require long-term responses have time to implement, learn and report on progress.

The 16th International Conference of Drug Regulatory Authorities, including pre-meeting, will be taking place in Rio de Janeiro, Brazil from 24 to 29 August 2014. This year's pre-ICDRA meeting will focus on "ensuring quality and safety of biosimilars for patients worldwide". The meeting will be co-organized and hosted by the Brazilian Health Surveillance Agency, ANVISA.

## **2.7 WHO regulatory support to Member States**

*Dr Samvel Azatyan, WHO headquarters*

In the context of WHO reform and with the view to improve alignment between the prequalification programmes for medicines, vaccines and biologicals the two streams have been brought together, in the new Regulatory Systems Strengthening (RSS) team. And, as was outlined earlier, the Essential Medicines and Health Products at WHO headquarters department was completely restructured to better reflect the objectives of WHO.

The RSS team is responsible for one of the six strategic priorities of the department - supporting WHO Member States to achieve optimal regulatory capacity and promoting regulatory harmonization between countries. The RSS vision is that all Members States have regulatory systems to ensure that all medical products and other health technologies meet internationally recognized standards of quality, safety and efficacy.

The mission of RSS is to strengthen capacity of regional/sub-regional and/or national regulatory systems in order to contribute to improved access to medical products and other health technologies of assured quality, safety and efficacy. It aims to do this by delivering on three strategic objectives: functional national regulatory systems developed and sustained; regulatory networks developed and sustained; and seek convergence and alignment of regulatory requirements. To achieve these objectives WHO provides support through capacity building and NRA assessments. An example is the five step strategic approach to strengthening NRA applied to vaccines that includes bench-marking and development of NRA assessment tool; assessment of NRA; development of institutional development plan (IDP); providing technical support/training/learning/networking and monitoring progress and impact. WHO is working towards developing a similar approach to medicines but it will take time.

Planned regulatory support activities for 2014 include completing the development of a harmonized tool to be used in the joint assessment of NRAs for all medical products, including medicines, vaccines, traditional medicines and medical devices; revision/update of the NRA assessment process; development of a comprehensive policy on WHO's role in strengthening regulatory capacity at the global level, by establishing working groups at the global level and convening an international consultation of experts to finalize and approve the tool. The next step will also be to pilot the prototype tool for vaccines and medicines through joint assessment of priority countries on voluntary basis.

Other RSS activities for 2014, include delivering in-country training in priority countries according to IDPs; providing technical support to selected African countries' NRAs in the framework of European Commission (EC)/African, Caribbean and Pacific Island

countries (ACP)/WHO; renewed partnership on access to quality medicines; supporting regulators' networks such as the African Medicines Registration Harmonization Initiative (AMRH), African Vaccine Regulatory Forum (AVAREF), Developing Country Vaccine Regulators' Network (DCVRN), International Regulatory Cooperation for Herbal Medicines (IRCH), and others; and supporting efforts on strengthening the global regulatory workforce by launching a global regulatory curriculum.

Drawing on the support available from WHO, this Region has a lot of potential and could benefit from taking advantage of what WHO has to offer.

## **2.8 Establishing an African medicine agency: challenges and future prospects**

*Dr Clive Ondari, WHO headquarters on behalf of Dr Ossy Kasilo, WHO Regional Office for Africa*

This presentation provided an overview of the situation of national medicines regulatory systems, the rationale for establishing the African Medicine Agency (AMA) and the opportunities it will offer.

Effective regulation is key to protecting public health through ensuring safe, quality-assured and effective medicines and other health technologies. Robust regulatory systems are crucial to support an enabling environment for the implementation of the African Union Commission's (AUC) Pharmaceutical Manufacturing Plan for Africa (PMPA). Laying the foundation for a single African medicines regulatory agency will strengthen regional cooperation. Lessons learnt from other regions have shown that various regulation and control tasks can be shared between national level and centralized mechanism e.g. EMA.

Currently there are various levels of economic development, resources, legislative and regulatory tools in place across the continent. While there is disparity in regulatory capacity across the African continent and continued challenges in meeting benchmark targets due to lack of resources, there are many initiatives to harmonize regulatory tools and activities and a willingness among countries to cooperate.

Many medicines, new vaccines and medical products are being made available through initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GF), GAVI Alliance, and Neglected Tropical Diseases (NTD) partnerships, all of which require functional regulatory systems to ensure quality and safety. Networks of regulators (AVAREF and AMRC), institutional reforms across the continent provide an opportunity for regional convergence and harmonization of regulatory systems.

The proposed AMA through its mandate from the African Union will provide a mechanism for coordination and strengthening of ongoing initiatives to harmonize medicine regulation; map and pool expertise, capabilities and strengthen networks optimizing the use of resources; and provide guidance and complement the efforts of the Regional Economic Communities towards harmonization of regulation of medical products.

The mission and vision of the AMA are based on the guiding principles of good governance, transparency and accountability in decision-making, commitment to sound, quality management, partnerships and effective collaboration, support for innovation of medicines and health technologies.

The AMA will perform regulatory functions including inspections, post-market surveillance, safety monitoring, clinical trial oversight, and quality assurance. Work will be supported by expert committees for each function. The primary source of funding for the AMA will be from AMA Member states. In kind contributions from member states in the form of seconding human resources will be looked at.

The responsibilities of Member States, Regional Economic Communities (RECs), AUC and WHO, have been outlined in planning documents. Member States are expected to delegate decentralized functions to the AMA, allocate and mobilize required resources, identify a host institution, and commit themselves to the decisions of AMA. The role of RECs is to ensure participation of Member States in the regulatory harmonization initiative and the inclusion of regulatory issues in the health protocols of trade treaties. The AUC will ensure the application of the AU model law on medicines regulation and harmonization; ensure the administrative, technical, legal procedures to establish the AMA. WHO will provide technical support to the AMA, regional bodies and NRAs.

The next step in the process is for the WHO Regional Office for Africa and AUC to establish the task force team with the resources necessary to implement the agreed plan. Progress will be reported every two years by AUC. The roadmap for AMA up to its planned launch in 2018 is linked to regional harmonization and the AMRH initiative. The WHO Regional Office for Africa will work with the Regional Office for the Eastern Mediterranean to help with the implementation of this initiative, as a number of Eastern Mediterranean Region countries are part of the African continent.

## **2.9 WHO prequalification team (PQT): medicines/vaccines/diagnostics**

*Dr Lembit Rägo, WHO headquarters*

Advances in science technology create new increasingly sophisticated medical products. Medicines need to be carefully regulated for quality and safety. Modern health systems rely heavily on availability of and access to safe, effective quality medical products. WHO uses the same scientific principles to assess product safety, quality and efficacy/performance as well-resourced national regulators. Other technical work areas support and link to the work of prequalification are norms and standards, safety and vigilance and disease programmes. The restructuring at the WHO Department of Essential Medicines and Health Products has brought together the programmes for prequalification of medicines, vaccines, diagnostics and devices, and active pharmaceutical ingredients.

The new prequalification (PQ) team has five functional groups, with cross-cutting and product-specific responsibilities for Good Manufacturing Practices (GMP) inspection and technical assistance to laboratory services for all products such as medicines, vaccines,

medical devices, and active pharmaceutical ingredients (APIs). This new approach allows for “one structure, one entry” for all products and partners and promotes learning from best practices between product streams to increase efficiency.

The PQ programme uses the same scientific principles used by well-resourced national regulators to assess product safety, quality and efficacy/performance: scientific assessment of documented evidence for quality, safety and efficacy; site inspections for GMP, Good Laboratory Practices (GLP) and Good Clinical Practices (GCP); control of variations to products and their manufacturing processes; post-approval monitoring of quality and safety. Where possible, the programme cooperates and relies on other regulators decisions to avoid duplication.

The PQ programme has prequalified around 500 medicines, 56 APIs, QC laboratories (29, and 38 in the pipeline). More than 2000 regulators, manufacturers, quality control laboratory staff and others are trained every year. All products that have been prequalified are listed on the WHO PQ website. If a problem with a previously PQ product is found WHO issues a “notice of concern” to the manufacturer that is posted publicly on the WHO PQ website. This has been very effective to date.

The PQ programme offers regulators capacity building opportunities to improve technical knowledge and skills including rotational fellows from NRAs; practice and experience for collaboration and cooperation; practical tools and guidelines; building more credible regulatory systems; savings of resources. Together these opportunities leverage greater advantage for regulators.

The PQ programme plans to continue to reduce duplication and increase collaboration with NRAs for better access to safe and effective quality products through shorter timelines for approvals. It will also facilitate harmonization and regulatory convergence; build regulatory capacity of national and regional regulatory authorities and transfer PQ activities to individuals and regional NRA networks from pilots to step-by-step hand-over process in the future.

PQ saves lives. It is not a replacement for NRAs but a mechanism to promote access to quality medicines and provide capacity building.

## **2.10 Discussion**

*Moderators: Dr Farhan Bashir Hassan, Ministry of Health Somalia and Dr Marthe Everard, WHO Regional Office for the Eastern Mediterranean*

It was remarked that the presentation of the WHO headquarters plan 2014 provides a good opportunity for NRAs from the Region to prepare themselves early to benefit from the available WHO headquarters support.

There was a discussion on the available WHO NRA assessment tool and how to do a proper assessment. WHO indicated that countries can apply for assessment for specific NRA functions (e.g. market authorization) and that non-functioning parts will not be assessed. The NRA tool will help countries understand what their weaknesses are.

There was some discussion on regulating traditional medicine products and practice. It was explained that the regulation of products and practice are different, however they can come together in one NRA or be handled separately according to each country's situation. Although traditional medicine is in a different WHO headquarters department, it is within the same cluster and close collaboration between the programmes exists.

Countries sought clarification about how to receive WHO technical support. It was explained that countries need to have a structured IDP with target dates for milestones and activities for addressing all identified challenges. WHO will then focus technical assistance on addressing priority areas. For example, if a specific country focuses on one NRA function, such as market authorization, then WHO can provide the technical assistance by conducting the assessment only for the function in that specific country.

Discussions related to the AMA highlighted that since there are seven countries under Regional Office for the Eastern Mediterranean that are part of the African continent, there is a need to identify a mechanism for linking and working together with AMA; e.g. to establish a joint technical working group and conduct regular joint meetings.

Many clarifications were presented regarding the prequalification procedure, the type of facilities and products that can be prequalified and what procedures and processes are followed. Elaboration was made on prequalification of QCLs in the Region: only one private QCL in Pakistan is prequalified from this Region while another nine QCLs submitted their expressions of interest to become prequalified. WHO has provided technical assistance to some of these QCLs in Egypt, Sudan, Syrian Arab Republic, Tunisia and Yemen.

Participants asked if there was anything that AMA could learn from the EMA experience. It was explained that one of the biggest challenges for AMA is the lack of a continental legal framework. There will be more challenges, but there is a will to create this overall umbrella entity and it is expected that the AMA will learn from other agencies, including EMA. The AMA will provide contributions over and above those provided by NRAs and other regional systems that are being created – collaboration, coordination, and registration of new priority products.

### **3. VACCINES AND MEDICAL DEVICES**

#### **3.1 Regional initiatives to establish network for vaccine regulation**

*Dr Houda Langar, WHO Regional Office for the Eastern Mediterranean*

All 22 countries of the Region have a regulatory system for medicines, however only seven have an operational vaccine regulatory system. Based on requests from Member States, the Regional Office for the Eastern Mediterranean is establishing a regional vaccine network with different technical working groups based on the needs and requests of countries to support registration and control of vaccines. This regional network will focus on three areas: sharing information, regulatory expertise and capacity building in collaboration with

international regulatory bodies; developing and harmonizing vaccine regulatory guidance; and establishing recognized mechanisms for the vaccine regulatory process.

The main objectives of the Eastern Mediterranean vaccine network include identifying the needs and developing regional guidance for strengthening vaccine regulation; facilitating the exchange of experience such as joint product reviews, inspections, lot control and release; building capacity by convening workshops and other activities; and supporting the regional pooled procurement system.

Once the concept, structure and terms of reference of the regional network have been endorsed by the Regional Office, WHO will provide support through annual regional meetings on vaccine regulation including registration, control and lot release; regional workshops for implementation of WHO guidelines and recommendations; provide specialized training courses; regional meetings to strengthen vaccine pharmacovigilance within the existing system; technical assistance for strengthening regulation, production, technology transfer in the area of vaccines and other biologicals.

More information may be obtained by contacting [emrgovrp@who.int](mailto:emrgovrp@who.int).

### **3.2 Medical devices regulation and its linkage to health technology regulation and health technology assessment**

*Dr Adham Ismail, WHO Regional Office for the Eastern Mediterranean*

Medical devices are any instrument, apparatus, appliance, material or other article, including software intended to be used for human beings in diagnosis, prevention, monitoring, treatment or alleviation of disease, compensation for an injury or handicap, or control of conception. A medical device does not achieve its principal intended action by pharmacological, immunological or metabolic means, but could be aided by such means.

There are about 1.5 million medical devices consisting of more than 1000 product groups covering 50 clinical specializations. The devices market was over US\$ 300 billion in 2008. It is difficult to regulate due to the short product cycles (5–20 years) and large variety of mechanisms of action and disciplines involved that allow for failures due to myriad of faults (mechanical, etc.). Medical devices are more multidisciplinary and complex than medicines; therefore a different approach is required for their regulation.

Populations need devices that are safe, effective, affordable, available, appropriate, accessible and of high quality. Poor manufacturing management can produce inconsistency in quality of products. This has led to the development of good GMP for medicines, biological products and medical devices. There are many standardization systems around the world, however the most commonly used are ISO or GMP. Since absolute safety cannot be guaranteed, ideal conditions for Medical Device safety are the shared responsibility of all stakeholders and safety and risk-based classification. Risk-based classification sorts medical devices from low risk (tongue depressors) to high risk (implants). Therefore, regulatory requirements should increase from low to high risk.

The regional regulatory situation of medical devices is difficult to assess given the current gaps in knowledge and scarcity of data. Nevertheless, several reports indicate a number of problems related to the use of low quality and unsafe medical products, re-use of single use medical devices, SSFFC, etc. This is all happening at a time when the regional market for medical devices is growing. Without proper regulation, through integration of medical devices regulation as an integral part of NRAs, it will be difficult for health care providers to maintain minimum quality of service and ensure safety of patients and care providers.

The scope of a medical device regulatory framework includes product development, production, distribution, and use. Two main challenges for regulators: global harmonization of device regulation and coherence of regulations of devices with pharmaceuticals and other adjacent product categories. The Global Harmonization Task Force aims to address these challenges by taking steps towards harmonizing ISO and GMP.

WHO has developed the Health Technology Assessment (HTA) approach, which is a multidisciplinary activity that examines the effect of technologies on: available resources, cost and cost-effectiveness, technical aspects (ex. safety and efficacy), and other aspects such as legal and ethical issues. The goal of the HTA is to provide evidence-based information to decision-makers to help reduce the risks for the decision-maker and help ensure value for money when registering and procuring health technologies. It assesses the efficacy, effectiveness, appropriateness and implementation. The HTA is usually practiced by a unit that is part of a public health system.

The HTA is one of the three domains related to regulation: health product regulation (safety, performance, efficacy), health technology assessment (clinical effectiveness, appropriateness, ethics, social issues), and health technology management (selection, procurement, training, use). While the role of health technology regulation is to prevent harm, HTA aims to maximize clinical and cost-effectiveness. The less resources that are available, the more important it is to make rational decisions on investments made in health technologies, prioritize needs based on evidence and estimate costs versus effectiveness ratios of new and emerging technologies. The three main hurdles to implementing HTA are political buy-in, financial implications and lack of trained professionals to carry the function.

Lavis et al. (2008)<sup>3</sup> identified seven elements to be followed by developing countries in order to ensure advancement of HTA programmes within their existing national health systems, they include:

1. Collaborate with other organizations;
2. Establish strong links with policymakers and involve stakeholders;
3. Be independent and manage conflicts of interest;
4. Build capacity among staff in the organization;

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<sup>3</sup> Lavis J, Oxman A, Moynihan R, Paulsen E. Evidence-informed health policy 1- Synthesis of findings from a multi-method study of organizations that support the use of research evidence. *Implementation Science*. 2008;3(53):1–7.

5. Use good methods and be transparent in work;
6. Start small, have a clear audience and scope, and address important questions; and
7. Be attentive to implementation considerations, even if implementation is not a remit.

One of the recent Eastern Mediterranean Regional Committee resolutions requested WHO to support Member States in building capacity to perform HTA for all health products.

### **3.3 Panel discussion**

*Moderators: Dr Abdul Hafiz Quraishi, NRA Afghanistan and Dr Marthe Everard, WHO Regional Office for the Eastern Mediterranean*

The discussion following these sessions pointed to the need to prioritize and clarify the scope of all of the different “networkings” NRAs are being informed about. It was outlined that the regional vaccine network will respond to needs of NRAs in relation to vaccines. Further, networks provide platforms for exchange of expertise and knowledge. The advantage of networks is that strengthening regulation in one medical product area cross-fertilizes capacity and functioning in other product areas. During the discussion it was clarified that there should be one vigilance system for all medical products – pharmaceuticals and vaccines.

It was commented that there is a need to be consistent in what is considered a medical “device” and what is a “product” in some cases. Price changes depending on how items are classified. There should be no difference between regulation of medicines and that of medical devices, both being based on application of well-defined set of functions and standards.

The importance of spreading the message about the need for HTA was stressed by participants. It was reiterated that the three major hurdles of good HTA are political buy-in; financial implications and lack of trained professionals to carry out HTA. A comment was made highlighting the importance and need for involving stakeholders in the process of health technology regulation with emphasis on the risk of corruption in the process. The example was given of brand loyalty by physicians that can cost the patient or the state more money than needed. In response, it was outlined that the three main steps adopted by WHO to address this issue are: promotion of HTA to Member States and policy makers; provision of WHO technical support in building capacity of those countries interested in establishing HTA units; and efforts made by Regional Office for the Eastern Mediterranean in establishing a regional HTA network

## **4. COUNTERFEIT MEDICAL PRODUCTS**

### **4.1 Global system for monitoring and reporting on substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products**

*Dr Clive Ondari, WHO headquarters*

The manufacture, distribution and sale of counterfeit and substandard medical products is of growing international concern; threatening the health of citizens in every country and region; undermining public confidence in the health care system, in health professionals and in medicines; increasing the risk of treatment failures and the development of drug resistance; creating an unfavourable business environment for pharmaceutical manufacturers and

distributors, and wasting precious resources. Substandard and falsified medical products comprise products that may be substandard due to manufacturing errors, however increasingly they are often quality compromised with the deliberate intent for financial gains and misleading the public.

In response to WHA resolution 65.19, WHO developed the Member State Mechanism to address SSFFC medical products. An eight-point work plan, approved in May 2014, directs WHO activities in this area. One of the activities identified for WHO action is collaboration with Member States on surveillance and monitoring of SSFFC medical products. In 2010, WHO initiated a project to setup a Global Surveillance and Monitoring System based on a global reporting system that gathers data on substandard and falsified medicines through an electronic Rapid Alert Form (RAF). Following a series of regional training workshops over 57 WHO Member States now have the capacity to report on suspected incidents of substandard and falsified medical products through a systematic and structured system, allowing WHO to conduct subsequent thorough analysis.

Incidents of SSFFC medical products have been identified and reported worldwide and across a range of products. To date, WHO has received over 300 reports of SSFFC medical products from all regions of the world. Some of these incidents have resulted in hospitalizations and fatalities – in one tragic case alone SSFFC medical products caused more than 200 deaths. The WHO Rapid Alert Form (currently available in Arabic, French and English) is provided to trained focal points in NRAs and requests the minimum set of information necessary in order to conduct an initial risk assessment. The completed RAF is submitted by email to [rapidalert@who.int](mailto:rapidalert@who.int) where it is automatically translated and downloaded into a database.

There are both operational and strategic benefits when participating in the global surveillance and monitoring system and identifying and reporting suspected cases of SSFFC medical products helps protect public health at country, regional and global levels. Although this is only one of the activities of the work plan of the Member State Mechanism, it highlights the importance of the involvement of all countries from the Eastern Mediterranean Region.

#### **4.2 Pakistan experience on reporting SSFFC medicines**

*Dr Syed Khalid Bukhari, WHO Pakistan*

In 2011, patients appeared in hospitals across Lahore with symptoms similar to Dengue Fever resulting in nearly 200 deaths and about 1000 cases of adverse reactions. It was found that all patients were cardiac patients who had received a contaminated cardiac medicine distributed by one hospital. Contamination was found only in one batch of Isotab 20 mg manufactured by a local pharmaceutical company. Quality tests did not show any contamination in other batches of Isotab 20 mg. The incident was managed through close consultation and coordination by the Government of Pakistan and WHO headquarters, Regional Office for the Eastern Mediterranean and country office. WHO headquarters was contacted immediately when the scope of the situation was noticed. WHO headquarters

coordinated laboratory testing and communicated the identification of a contaminant to the WHO country office immediately. A WHO mission went to Pakistan at the government's request. This incident provided the opportunity for Pakistan to learn from this tragedy and implement measures to minimize the risk of repetition of a tragedy of this kind. It was decided by the government that an independent NRA should be established in accordance with WHO and ICH guidelines; including a national Pharmacovigilance Centre; establishment of clinical pharmacy, drug and therapeutic committees in hospitals and the Lahore High Court Defective Drugs Inquiry Tribunal.

The Tribunal, which received technical support from WHO at the request of Pakistan, found capacity deficiencies in drug quality testing in terms of both equipment and technical expertise. Laboratory staff do not attain any specialized training nationally or internationally on quality testing, and equipment was old. The investigating agencies are carrying out technical investigations without technical experts who do not have technical expertise.

The two key lessons learnt of this event were the grave consequences of failing regulatory systems and the benefits of a timely collaborative response following the incident. The early involvement of WHO in assisting in identifying the source of the problem and in developing a mechanism to ward off future occurrences. Medicine safety requires all parts of the regulatory system to be functioning and to be working together. Quality control alone is not sufficient. The presence of other regulatory components, such as quality assurance, GMP inspection or pharmacovigilance, is needed to help prevent and identify SSFFC cases sooner.

#### **4.3 Panel discussion**

*Moderators: Dr Qais Jaafar Talib, NRA Iraq and Dr Marthe Everard, WHO Regional Office for the Eastern Mediterranean*

There was little discussion following these two presentations. Among the few questions asked was when the Essential Medicines logo stopped being in use. WHO clarified that the logo dates back 20 to 30 years standing for the Action Programme on Essential Drugs and its use by manufacturers and wholesalers in providing essential medicines to parts of Africa. In the case of the SSFFC medical product label shown in the presentation, it was one of the clues used to discover that the product claimed to have been produced by a manufacturer that is no longer in business.

## **5. RECENT DEVELOPMENTS IN REGULATORY AFFAIRS**

### **5.1 Development of a framework for medical devices**

*Dr Alan Kent, WHO Temporary Adviser*

Regulating medical devices and those who manufacture, supply or use them, is important to protect public health. The key challenges of regulating medical devices are the wide range of devices used and the hazards associated with each device differ. Established NRAs have adopted controls where regulatory requirements increase with the hazard presented by a particular device. There is an advantage in establishing controls based on

internationally harmonized practice. The Global Harmonization Taskforce (GHTF) was established in 1992 to develop a regulatory model for medical devices for use by manufacturers and NRAs. The resulting regulatory model is based on the legislation of the five GHTF founding members Australia, Canada, European Union, Japan and the United States of America and not those of less developed countries.

The WHO Regional Office for the Eastern Mediterranean is in the process of developing a framework for regulation of medical devices. Countries cannot progress from an unregulated “open market” to a comprehensive medical devices regulated environment, instead they should follow a “step-by-step” approach with progress linked to increasing size, experience and expertise of the NRA, available financial resources and political support over the long-term. It is anticipated that the framework will be published in the course of 2014.

The objective of the framework is to clarify the purpose of regulating medical devices, the legal framework needed for exercising controls, and the terms of reference of the government department responsible for its implementation and ongoing management. First, steps include the use of the GHTF definitions of medical devices and manufacturer and agreement and acknowledgement publicly that the primary purpose of regulating medical devices, and the organizations that manufacture, supply or use them, is protecting the health of the public. Second, simple controls must be introduced and applied to all medical devices. Third, the staff responsible for medical devices must have a status equal to those responsible for other medical products.

The framework will provide a model for a step-wise approach to set strategic goals and policy commitments; consumer protection, including a procedure to record and report adverse events; market authorization; procurement and funding. Countries in the Region have agreed that this is an area that they need to improve.

## **5.2 Development of global regulatory curriculum framework**

*Dr Samvel Azatyan, WHO headquarters*

The overall objective of NRAs for medical products is to ensure that all medical products (medicines, vaccines, blood products and other biologicals, traditional medicines and medical devices) that are used in a country are of assured quality, safety and efficacy and are accompanied by appropriate information to promote their rational use. To fulfil this task NRAs need to be competent, capable, independent, with strong political backing and to have a clear authority to enforce established regulations.

In reality, between 30% and 90% of NRAs globally have limited capacity to perform all core regulatory functions to guarantee quality, safety, and efficacy. Sponsors (e.g. Global Fund and GAVI) and manufacturers face a landscape of disparate regulations, frequent delays and limited transparency. Human resources are one of the most important challenges for NRAs in performing core regulatory functions. For resource-constrained settings with very limited staff NRAs need generalists rather than specialists to perform basic regulatory functions. Training activities are often ad-hoc and face time constraints.

The Global Regulatory Competency and Curricula project is an initiative that has developed from a 2012 United States Institute of Medicine of National Academies report entitled “Ensuring safe foods and medical products through stronger regulatory systems abroad”. The project will define the competencies needed by NRAs in all settings and will build a modular curriculum to educate, train and continually advance the skills of regulatory professionals as health professionals to develop the required core competencies.

The project engages a number of international partners including: Asia Pacific Economic Cooperation (APEC), International Food Protection Training Institute, International Organization for Standardization (ISO), Pan American Health Organization, Regulatory Affairs Professional Society and WHO.

One of the key concepts underlying the initiative is the recognition of the regulatory profession. Regulatory workforce must be seen as professionals whose work is based on a body of knowledge drawn from areas of science, clinical fields, law, policy, statistics, communication and management. Like other health professions, the regulatory profession should encompass a code of ethics and professional conduct and define professional competencies. Minimal competencies should reflect the minimal core elements of a food and medical product regulatory system. Regulatory curricula should be designed to develop the required regulatory competencies and based on these competencies.

The approach throughout the entire initiative is based on active involvement of multiple stakeholders and content experts, serving on the project advisory committee and expert panels engaged in defining regulatory competencies and curriculum development.

A discussion paper entitled “Developing a Global Curriculum for Regulators” was posted on 11 June 2013 on the IOM website: <http://www.iom.edu/global/perspectives/2013/globalcurriculum.aspx>

### **5.3 Cooperation between medicines quality control laboratories for better access to quality-assured essential medicines**

*Mr Hariram Ramanathan, US Pharmacopoeia*

United States Pharmacopeia (USP) is a not-for-profit private independent self-funded global health organization with facilities in many countries. Its mission is to promote health through public standard setting and related programmes that help Governments to ensure the quality, safety, and benefit of medicines and foodstuff. USP’s standards are used worldwide.

Guided by its mission, USP develops and implements global initiatives that help ministries of health, regulators, and manufacturers use USP standards. The USP Network of Official Medicines Control Laboratories (OMCL) includes networks in Central and South America, Africa, Middle East and North Africa and Asia. The OMCL works with member laboratories to strengthen capabilities, share information between network members and learn through collaboration and sharing of technical expertise. In some cases member labs have achieved ISO accreditation and WHO prequalification. The role of USP in administering

these networks is to provide guidance for compliance to monograph specifications, strengthen Quality Management Systems, coordinate and provide financial assistance for the network activities. The benefits obtained by network members include learning from others facing common challenges, strengthening national labs to ensure local medicine quality, optimize testing capacity and reporting through collaboration, and identify areas that need technical cooperation such as pharmacopoeial use.

The Technical Assistance Programme offered by USP helps to bridge the gap in availability of quality standards for medicines for all diseases. The USP Center for Pharmaceutical Advancement and Training in Ghana provides training to quality control laboratories, manufacturers, and regulators from all OMCL countries.

Collaboration with other like-minded partners helps maximize use of resources and promotes a robust approach towards ensuring the quality of essential medicines. The USP welcomes opportunities to collaborate with other countries, regions and partners.

#### **5.4 Panel discussion**

*Moderators: Dr Rezeq Musa Orthman, NRA Palestine and Dr Adham Ismail, WHO Regional Office for the Eastern Mediterranean*

A number of NRAs expressed the need for urgent action to regulate medical devices to protect the public. During the discussion participants noted that they are told there are big differences between regulating medicines and medical devices and asked what the benefits in highlighting the differences are. Clarification was sought as to whether regulatory structures should be by function rather than product to maximize available resources. In response it was suggested that the organizational structures used respond to the risk level of the products being regulated and that regulating devices the same way as medicines would be very expensive.

Participants asked for the eligibility criteria for receiving support from USP. To access support from USP countries must submit a request.

#### **5.5 The European regulatory systems and approaches to capacity building and training**

*Dr Emer Cooke and Dr Marie-Helene Pinheiro, EMA (by Skype)*

The European Union (EU) regulatory system is an advanced example of regional convergence. The current regulatory systems have been established through a series of incremental steps and reviews since 1952. The EMA is the European Medicines Regulatory Network that comprises of over 40 competent medicines regulatory authorities from 28 member countries and has a pool of 4500 regulatory experts. The EMA does not regulate medical devices.

The pharmaceutical legislation tools used by EMA include regulation, which is binding to all Member States and no national changes or adaptations are allowed (e.g. paediatric medicine regulation). There are directives which result in binding principles but that may be interpreted by Member States (e.g. clinical trials). Finally, there are guidelines which are

interpretations of requirements, that are recommended but not seen as binding such as regulatory guidelines, scientific guidelines and good manufacturing, clinical, distribution guidelines (e.g. readability of labelling and package leaflet). The regulatory systems comprise both centralized and decentralized procedures for products to achieve marketing authorization, including opportunities for mutual recognition procedures by Member States who have received applications for registration of the same products.

The European Medicines Regulatory Network has a joint training strategy that builds on EU experience in addressing training needs of EU accession countries to assist with their integration into the EU system. Training activities include ‘twinning’, participation in inspections, training sessions, and the translation of guidance documents into practice. Other training and capacity building opportunities that have been effective include case studies and active examples, mentoring and inviting local non-EU regulators to participate in (observed) GMP inspections. Many of the training sessions are open to the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (jointly referred to as PIC/S) members, observers, industry and partners. Up to 40 non-EU countries have participated in training opportunities. This approach provides both basic and focused training and offers an opportunity for participants to build networks.

The EMA has a number of tools available, which can facilitate access to medicines in countries outside of the EU, such as the Article 58 procedure (for supporting regulators outside the EU) for certificates issued by EMA. One of the aspects of Article 58 as a capacity building tool is the “hands on” involvement of non-EU regulators as experts or observers in the assessment process. The ability to process Article 58 is limited to submissions by pharmaceutical manufacturers.

In conclusion, the EMA mentioned that the EU regulatory system is an advanced example of regional convergence based on mutual cooperation and efficiencies and that it has evolved (and will continue to evolve) over time. The principles of cooperation used by EMA can be used by other regions.

Among the considerations presented was the importance of being aware of different activities to avoid duplication and facilitate cooperation. In situations where there are limited resources it is important to adopt a coordinated and cost-efficient approach. There is a potential to build on and adapt existing/new emerging initiatives. While the EMA and EU regulatory network are involved in large numbers of training and capacity building activities both within and outside EU and have experience in developing training approaches/training materials, it may need to develop better tools to communicate/share the significant scientific experience existing within the network. A better understanding of non-EU regulators assessed needs to deliver better targeted training rather than providing ad-hoc training opportunities.

## **5.6 Local pharmaceutical manufacturing: Opportunities and challenges in the Eastern Mediterranean Region**

*Dr Hakima Hoseh, Arab Union of the Manufacturers of Pharmaceutical and Medical Appliances (AUPAM)*

The Arab Union of the Manufacturers of Pharmaceuticals and Medical Appliances was initiated in 1986 by a recommendation of the Council of the Arab Ministers of Health. Its membership comprises pharmaceutical manufacturers from Morocco, Algeria, Tunisia, Libya, Egypt, Sudan, Yemen, Saudi Arabia, Oman, Emirates, Iraq, Syrian Arab Republic, Lebanon, occupied Palestinian territory and Jordan.

The Middle East and Northern Africa (MENA) pharmaceutical industry constitutes just 2% of global sales; however its products cover most therapeutic classes and essential medicines. The percentage of locally produced medicines versus imported products is decreasing. If the region has stronger regulatory authorities and better quality products, locally produced medicines would gain a higher market share.

An annual regulatory meeting with health authorities is organized by AUPAM to keep industry updated and discuss obstacles. Manufacturers are assisted by AUPAM to develop and manufacture medicines at the highest quality and benefit from AUPAM's annual training plan for hot topics and new requirements. The steering committees of AUPAM work towards greater harmonization of guidelines across Arab health authorities and increasing network opportunities for its industry members.

Recent developments in regulatory affairs in the MENA region include a new common technical document (CTD) file format and moving towards eCTD, new pricing policies, Arab guidelines of pharmacovigilance, which will be implemented in 2015, release of harmonized bioequivalence guidelines and new packaging requirements.

Challenges for the Region include lack of harmonized guidelines, different processes of dossier submissions and assessments, market entry barriers to protect local industry, price controls, parallel imports, fluctuations in economic conditions, contract manufacturing and licensing out which is not accepted in some countries. There is no uniformity in product patent laws, and there are discrepancies in how intellectual property rights are implemented. These issues impact the sector in a number of ways, such as unpredictable changes made in regulations and difficulties in understanding regulatory requirements.

Opportunities for the sector include a growing population with improving standards of living; government pricing policies leading to more stable prices; increasing local market share by investing in changing product varieties; and lower manufacturing costs. Trends of harmonization of regulatory requirements are seen, which will lead to mutual recognition of market authorization of products; patent expiration will allow for production of more generic medicines, investing in the production of medical devices and adopting of guidelines for biosimilar products.

These opportunities could be attained and challenges overcome through increased inter-sectoral cooperation across the Region between governments, industry and international partners, and strengthened regulatory capacity. Establishing industry centres of excellence may help overcome the challenges of limited resources and experience.

More information can be obtained by contacting [info@aupam.org](mailto:info@aupam.org).

### **5.7 WHO prequalification of medicines: Eastern Mediterranean Region perspective on capacity-building efforts**

*Mr Mohamed Farag, WHO Regional Office for the Eastern Mediterranean*

The PQ programme was a response to the need for better access to antiretroviral (ARV) treatments in low- and middle-income countries. For example, in 2001, first line ARVs cost over US\$ 10 000 per year. They now cost around US\$ 120 per year.

Prequalification activities in the Eastern Mediterranean Region started in 2007, and became more systematic in 2010. Across the Region there was limited awareness and interest among NRAs with their focus being on access and supply issues rather than on quality-related issues, coupled with a low interest expressed by manufacturers who were more concerned about their unclear returns of their own investments than in possibilities of accessing International donor funds) and exporting to “well-regulated” or “matured” markets.

Prequalification activities in the Region are focused on three areas: advocacy and outreach; technical assistance for individual manufacturers tailored to their identified needs; and capacity building of manufacturers, NRAs and QCLs. All of these activities help prepare manufacturers to meet the essential steps of the PQ programme. To date, more than 300 regulators from 15 countries have been trained on international standards in dossier assessment, GMP inspection compliance and bioequivalence studies.

The CTD dossier assessment is one of the priority areas that the Regional Office has identified for capacity-building. Regional training sessions were offered for manufacturers and NRAs targeting key aspects of quality assessment. Another area is GMP inspection and compliance. The Regional Office has also offered training on GMP inspections through national training workshops and mock audits undertaken with potential manufacturers. There is a mock audit planned in second half of 2014. The interactive training workshops result in increased willingness of manufacturers to share relevant information and to receive feedback from inspectors. In addition, manufacturers receive free-of-charge expert advice on improving the identified areas of weakness in medicine production processes and management, and can benefit from increased networking within the sector.

Other possibilities for capacity building include placement of national assessors from the Region on WHO's Prequalification of Medicines Programme (PQP) rotational fellowships after successful completion of assessor courses in Copenhagen. Inspectors from the Region can be placed on the PQ expert roster starting as observer inspectors.

Manufacturers in the Region face a number of production challenges, such as API sourcing and data analysis, repeating bioequivalence studies for GCP/GLP compliance and meeting GMP compliance.

Support from WHO PQ is essential in providing training for NRAs on international standards in quality, safety and efficacy of medicines in the Region. In parallel, the PQ programme is working with both regulators and manufacturers to implement international standards in medicines regulation and manufacturing.

For more information about the WHO Prequalification programme please visit: [www.who.int/prequal](http://www.who.int/prequal).

## **5.8 Panel discussion**

*Moderators: Dr Qais Jaafar Talib, NRA Iraq and Dr Clive Ondari, WHO headquarters*

There was lively discussion following this session starting with questions related to the EMA presentation. Clarification was sought as to whether traditional medicines existed in the EU and how they are regulated. The EMA confirmed that they still exist and are included in their regulatory measures.

The EMA was asked how non-EU NRAs can participate in EMA training or be observers. The EMA inspectors invite local NRAs to observe inspections. It is important that the EMA has the correct contact points so that this is possible. The opportunity is dependent on the potential of local manufacturers in exporting products to the EU. Training opportunities are also open to industry.

The issue of managing intellectual property rights in relation to generic medicines was raised. The EMA does not have responsibility for managing intellectual property. This is done through verification and checking with the Member States as to whether or not they can accept a generic product that has previously been patented. Manufacturers are expected to ensure that patent aspects have expired.

A question was raised about mutual recognition of products registered at the country level and through the centralized procedure. An NRA will perform an assessment and issue a national market authorization for that Member State. Once the reference Member State has provided authorization other Member States who have received an application for the same product have 90 days to recognize the registration by the reference Member State.

Participants were interested in learning more about the funding and activities of AUPAM. The funding for AUPAM comes from membership fees from member companies and from participation fees for conferences. The AUPAM has its headquarters in Jordan and they communicate with committee members through email. The organization assists in coordinating regulations by providing recommendations to ministry of health that can be followed up for action. An example is the AUPAM's recommendation for codes for biopharmaceutical products and pharmacovigilance. The information used by AUPAM in its

presentation is collected from the member industry associations in each country in 2012. It was noted that not all MENA manufacturers are members of AUPAM.

The role of AUPAM in guidelines development was questioned. Credit was given to AUPAM by WHO for taking the initiative, however it was pointed out that this work needs to be undertaken in such a way that workspace of regulators and manufacturers are protected respectively.

Discussion was held on the Global Regulatory Competency and Curricula project for regulatory authorities and how existing training offered by different organizations could be considered for inclusion. Alignment of existing training programmes with the new curriculum should be possible but will require the alignment of the objectives as well. One consideration is that WHO does not charge fees for training. WHO links up with industry associations for training logistics and arrangements, but fees are not charged for training participation.

## **6. TOWARDS REGULATORY COOPERATION: SUCCESSFUL EXPERIENCES**

### **6.1 Regulatory cooperation in the Gulf Cooperation Council**

*Dr Mohamed Al Rubaie, Ministry of Health Oman on behalf of Dr Mohamed Al Haidari, GCC*

The Gulf Cooperation Council (GCC) states are similar in language, geography, values, traditions, economic resources, and social and cultural factors. The membership of the Gulf Cooperation Committee for Drug Regulation (GCC-DR) comprises Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen and serves a total population of over 62 million. The pharmaceutical market in these countries reached US\$ 6 billion in 2012 and is expected to reach US\$ 10.8 billion by 2020.

The Executive Board of the Health Ministers' Council for the Cooperation Council States was established in 1976 to coordinate activities and communications between the Ministers of Health of member countries. Its main functions are group purchasing of medicines and medical supplies, central medicines registration, health policies and strategies development, and medical research.

The GCC-DR was established in 1999, with a mission to provide GCC states with safe and effective medications at a reasonable price. Its main role is to register pharmaceutical companies and their products through the joint coordination of assessing scientific safety, efficacy and quality of medicinal products. The responsibilities of GCC-DR include: a centralized procedure for registration of pharmaceuticals; the registration of pharmaceutical companies; inspection of pharmaceutical companies on GMP compliance; post-marketing surveillance and issuance of technical guidelines.

In an effort to promote regional harmonization, the GCC-DR develops regional guidelines based on ICH, WHO, EMA and US Federal Drug Administration (FDA) guidelines. Draft guidelines are circulated to all GCC members and posted online for consultation with

stakeholders. The guidelines are finalized and recommended by a working group to the GCC-DR for adoption. Once adopted by the GCC-DR, the General Director of the Executive Office will submit the guideline to the Council of Health Ministers for final approval.

The main advantages of a central registration system are the effective centralized process, transparency of procedures, divided workload drawing on the strengths of GCC member countries, regulatory harmonization and improved capacity building. Once a medicine is centrally registered it may be automatically registered in all GCC countries where there is an agent representing the pharmaceutical company.

The GCC is working to find solutions for the existing challenges of inadequate trained staff, existence of different regulatory systems with different processes for registration and capacity of NRAs, long registration timelines and slow guidelines implementation.

## **6.2 Regulatory cooperation in the East African Community**

*Dr Samvel Azatyan, WHO headquarters on behalf of Dr Hiiti Silo, United Republic of Tanzania FDA*

Today there are five partner states in the East African Community (EAC). Burundi, Kenya, Rwanda, Uganda and the United Republic of Tanzania, and six NRAs, including the Zanzibar Food and Drug Administration. The total population served is 135.4 million (2012). Chapter 21 (Article 118) of the EAC Treaty provides for harmonization of medicines regulation.

The purpose of the regulatory cooperation project being implemented since 2012 is to harmonize medicines registration in the EAC partner states in order to increase the rapid availability of essential medicines and enable free movement of medicines within the sub-regional EAC. The goal is to have a harmonized and functioning medicines registration system within the EAC in accordance with national and internationally recognized policies and standards. Harmonized technical guidelines and requirements have been developed and endorsed by EAC health ministers in 2014. Approval by the Council of Ministers is anticipated by the end of 2014. The project is the result of an invitation by a consortium comprising WHO, the United Kingdom's Department for International Development (DFID), NEPAD Agency, Bill and Melinda Gates Foundation and the World Bank that encouraged submission of proposals for regional harmonization supported by a multi-donor trust fund.

Harmonization of medicines registration and regulation is now becoming a worldwide agenda. As a result a positive impact will be made on access, availability and affordability of medicines. The EAC NRAs participate in international medicines regulatory forums sharing expertise and best practices from WHO PQP review sessions, and from WHO/EAC joint reviews and inspections.

Activities lead by WHO include the promotion of harmonization through capacity building, regional training on CTD and GMP inspections, and involvement of EAC NRAs in PQP activities. An example of WHO/EAC collaboration is the Joint WHO/EAC assessment

sessions that have engaged all of the EAC NRAs and that resulted in a significantly shorter timeline from dossier submission to registration of the selected medicines. Future activities include a twinning programme of NRAs within the region and targeted training for inspectors, assessors and trainers.

The positive impacts of the project are improved access, communities get quicker, greater access to priority essential medicines; improved availability, through simplified, harmonized, efficient and transparent regulatory approval processes; increased affordability with more generics on the market and the WHO collaborative procedure for fast-track registration of prequalified medicines

The EAC have encountered challenges along the way such as, differences of regulatory development and capacity, sustainability of joint activities after the project ends, fear of loss of income from fees for registration and GMP inspection and of national sovereignty. There is an emerging need to expand capacity building beyond medicines registration by including other regulatory functions such as, pharmacovigilance.

The experience in EAC has found that harmonization and joint activities reduce workload and improve overall regulatory performance. Success requires commitment of partner state NRAs to release experts who can participate in activities. Regional cooperation and collaboration is the way forward for future medicines regulation.

### **6.3 WHO collaborative procedure for fast-track registration of prequalified medicines**

*Dr Lembit Rägo, WHO headquarters*

Two mechanisms to speed up national approval of prequalified products have been launched as outlined in the WHO Drug Information Vol. 27, No. 4, 2013. The joint assessment of selected products with interested regulators allows for prequalification and NRA assessment to be completed together. The collaborative registration procedure enables the exchange of confidential regulatory information about prequalified products to speed up national registration processes.

It was outlined that the collaborative registration procedure is to reduce duplicative efforts and facilitates the national registration of prequalified medicines. This process has been approved by the WHO Expert Committee in 2012 and is currently being piloted in 14 NRAs from 13 countries across Africa, Europe and Asia.

The collaborative registration procedure is based on five principles: 1) At the request of the manufacturer of a prequalified product, the PQP shares the full PQ assessment and inspection outcomes with NRAs participating in the scheme and provides advice to facilitate national regulatory decisions (registrations, variations, withdrawals). This is only for medicines assessed by the PQP and only those for which the manufacturer has given consent. 2) Participating NRAs benefit from the shared information at their discretion, however, they must commit to making a registration decision within 90 days from receiving the PQ assessment and inspection outcomes. The NRAs have the right to decline the collaborative registration

procedure for individual medicines and can decide differently from PQP. Any deviations should be shared with the PQP and reasons provided. 3) The procedure is voluntary for manufacturers and NRAs and does not interfere with the national decision making process and regulatory fees. 4) The product and registration dossier in countries are ‘the same’ as approved by the PQP. Cooperation among the PQ holder (manufacturer), NRA in interested country and PQP is necessary to overcome confidentiality issues, assure information flow and product identity. 5) The “harmonized product status” is monitored and maintained.

The results of the pilot phase have been favourable. NRA are able to build capacity, save their resources and prioritize their focus. Manufacturers experience a faster timeline. Procurers have faster access to a wider range of priority medicines. Patients have faster access to prequalified medicines. The process provides a model for inter-regulatory information exchange to those NRAs and manufacturers, who want to cooperate. The NRA from other Regions are welcome to join the pilot process.

#### **6.4 Implementation of medicines legislation across borders: African Medicines Regulatory Harmonization Programme**

*Dr Samvel Azatyan, WHO headquarters on behalf of Dr Paul Tanui, African Union-NEPAD*

The Second African Medicines Regulations Conference in 2009, made a recommendation to establish a project to explore harmonization. Currently, there are 54 NRAs across Africa, with variations in capacity, different registration requirements, minimal transparency and no clear timelines.

The African Medicines Registration Harmonization (AMRH) Initiative’s overall objective is to achieve a harmonized medicines registration process in countries belonging to the Regional Economic Communities (RECs), based on common documents, processes and shared information systems at the level of RECs. The initiative has the following consortium members: African Development Bank (ADB), African Union Commission (AUC) Bill and Melinda Gates Foundation, Clinton Foundation, Pan-African Parliament (PAP), The World Bank, DFID, UNAIDS, and WHO. AMRH is consistent with the Pharmaceutical Manufacturing Plan for Africa (PMPA). The role of WHO in this initiative is providing technical assistance in developing and implementing harmonized approaches and in supporting capacity building, training and joint inspection activities.

Interventions focus in four areas that will enable accountability and the effective coordination of partners: policy and regulatory reforms, regulatory capacity development, knowledge management and governance. The objective of policy and regulatory reforms is to increase use of harmonized policies, legal frameworks and guidelines by RECs and respective member states. The goal is for a model law for harmonization to be adopted and implemented across the five EAC member countries. The objective for regulatory capacity development is increased human and institutional capacity for regulation through centres of excellence, a database of experts and postgraduate level courses in regulatory science. The commitment to knowledge generation and leveraging aims to increase knowledge assets on

medicines regulation at country, regional and continental levels. The governance objective is to create an enabling environment for the AMRH by establishing the necessary structures at the continental, regional and national levels.

The presentation briefly reviewed the governance structure of the AMRH and progress that is being made in projects submitted by the five EACs, the draft model law and the regional centres for excellence.

## **6.5 Panel discussion**

*Moderators: Mr Faqeer Muhammad Shaikh, NRA Pakistan and Dr Marthe Everard, WHO Regional Office for the Eastern Mediterranean*

During the discussion appreciation was expressed to WHO for the various tools that have been made available for use by NRAs and encouragement given to other Member States to use the tools in order to use resources more effectively. There is no need to start from zero. There are guidelines by NRAs based on science that Member States can use by reference – saving resources or compensating for a lack of resources. It was pointed out that if a country owns the guideline, it must update it at regular intervals but if another country uses guidelines by reference (electronically available) it does not need to update them, as they will be updated “automatically”.

It was suggested that efforts should be made to have a PIC/S member from the Region, as the whole Region would benefit. One way of building capacity in this area is to keep an eye on what is going on internationally and to take advantage of any opportunities to do a fellowship with an international regulator in another part of the world and to make the most of the resources within the Region (Saudi Arabia and the other GCC countries).

To help build capacity of countries of the Region, the GCC suggested that it could post upcoming inspections on their website and that interested NRAs could send an inspector as an observer. While it is good to publish the inspection on the website, WHO suggested that this will need a small group with inspection background to set a road map, and determine how to nominate focal points, and provide joint training. It was also remarked that there is no qualified inspectorate in Eastern Mediterranean Region to meet the requirements.

Part of the discussion was on how EAC recruit and retain regulators. It was reiterated that the challenge of human resources is the same in EAC as it is in other parts of the world and that it is important for NRAs to motivate their qualified regulators so that they will stay as substantial efforts have been made in building their capacity.

Participants asked how they can receive technical assistance from WHO and how to promote the importance of regulatory system strengthening with their ministry of health. For WHO to support any Member State or any region two things are needed. First, a request for technical support, demonstrating the Member State’s willingness to receive assistance is necessary. Second, PQP requires financial resources from the WHO Secretariat or donors to offer technical assistance. It was pointed out that it is important for Member States to voice

their desire for support for regulatory strengthening at the WHA. Also, the discussion of the draft WHA resolution on strengthening regulatory systems will be an opportunity for Ministers to hear of its importance. It would be advantageous for the Region to speak with one voice at the upcoming WHA on regulatory systems strengthening.

The main conclusion of the open session part of EMDRAC was that there is a wealth of experience in the Region that should be leveraged to strengthen regulatory systems across the Region. Member States should be encouraged to engage in more collaboration among themselves. It was proposed that an initiative for SSFFC medical products may be a good starting point to build collaboration. Collaboration could be built by a step-by-step approach beginning with information sharing and joint GMP inspections. Another opportunity may be an initiative to work together on joint clinical trials, joint training and joint GMP inspections. This will not overlap or duplicate with the work of the GCC but rather complement it.

The closed sessions of EMDRAC commenced with an introduction of the agenda, including the country presentations and the expected group work.

## **6.6 Universal health coverage and the role of health system regulation**

*Dr Sameen Siddiqi, WHO Regional Office for the Eastern Mediterranean*

Universal health coverage refers to providing all people with access to needed health services that are of sufficient quality to be effective, while ensuring that the use of these services does not cause financial hardship. Progress towards achieving universal health coverage is measured in three dimensions: coverage of population, services provided and proportion of the costs covered. Medicines, vaccines, biologicals, devices and supplies are an essential part of providing health services.

In 2011, the Eastern Mediterranean Region spent US\$ 125 billion on health, which reflects less than 2% of total world health expenditure for about 8.7% of the world population. Within the Region there are disparities in the average amount spent per capita on health care. Each year, up to 16.5 million people face financial catastrophe and up to 7.5 million become poor due to out-of-pocket payment for health costs. Across the Region pre-payment for health care ranges from 25% in low-income countries to 100% coverage of the population in high-income countries.

Available options for health system performance include financing through prepayment arrangements; provision of quality health care interventions; monitoring; partnering and collaborative or contractual arrangements; and regulation of services and products. The regulatory process considers what to regulate (entry, products) and who to regulate (individuals, organizations, markets), and how to regulate (legislation, code of conduct, control-based regulation and incentive-based regulation).

Regulation is a means to better performance and better outcomes. Control-based regulation uses legislation for licensing and registration, which is used in most countries in the Region however enforcement is weak due to limited capacity and resources. If incentive-

based control is used it often focuses on providers (pharmacists, physicians), but could be used for distributors and manufacturers as well, in the form of tax breaks for manufacturers of priority medicines.

Many of the pharmacies, primary care facilities, hospital beds, laboratories and diagnostic facilities are private. The challenges of having such a high proportion of private service providers in the Region include: huge investments in high-tech imaging technology sometimes motivated by medical tourism; irrational use of biomedical devices and technologies, leading to associated medical errors and high out of pocket payments; weak medicine regulatory systems and poor enforcement; limited control on medicine promotion/advertisement, insufficient patient education; non-prescription sale of antibiotics in private pharmacies, which is a contributing factor for antimicrobial resistance and the availability of core medicines is lower in public compared to private facilities (2006 study in nine Eastern Mediterranean Region countries).

Establishing health sector regulation and universal health coverage would help to address these challenges. Policies for engagement between public and private sectors are evolving in most countries, including private sector regulatory mechanisms. However, policies regulating the private health sector require updating and there is limited ministry of health capacity to fulfil policy and regulatory requirements. Although WHO focus has been on public sector it is starting to explore what can be done to regulate the private health sector. Steps are being taken to address this and guidelines will be developed in the near future.

The rationale for effective legislation and regulation for the pharmaceutical sector is based on a number of factors: pharmaceuticals concern the whole population; many parties are involved (patients, health care providers, manufacturers and sales and distribution persons, governments); serious consequences, including injury and death can result from the lack or misuse of medical products; the consumer has no way to detect product quality and informal controls are not sufficient. NRAs contribute to promoting and protecting public health by ensuring:

- medicines are of the required quality, safety and efficacy
- health professionals and patients have the necessary information to use medicines rationally
- medicines are appropriately manufactured, stored, distributed and dispensed
- illegal manufacturing and trade are detected and sanctioned
- promotion and advertising is fair, balanced, and aimed at rational use
- access to medicines is not hindered by unjustified regulatory work.

## **7. COUNTRY EXPERIENCES: ENSURING QUALITY, SAFETY AND EFFICACY OF MEDICAL PRODUCTS**

### **7.1 The Jordanian system of improving efficiencies and timelines in assessment of medical product dossiers**

*Dr Maha Jaghbeer, FDA Jordan*

The presentation provided an overview of the Jordanian Food and Drug Administration (JFDA) structure and the medical products that are regulated by the drug directorate and medical equipment and supplies directorate. The JFDA was established in April 2003 and has about 530 employees. The regulatory system is supported by legislation and guidelines.

Requirements for registration include manufacturing site accreditation (GMP); CTD files for quality, safety and efficacy; and laboratory testing. There are two systems for GMP, one based on documents only and the other using both documents and inspections. A different review process is used for GMP inspection of ordinary medicines and for biological products including biosimilars. The CTD files for medicines are adapted for different products.

The review process and timelines for registration within JFDA for scientific assessment and bioequivalent evaluation is six months. After site approval, the technical committee assessment and approval procedures, and pricing evaluation may take up to six months. The applicant has 30 days to respond to the recommended price prior to the registration being complete. If the applicant does not agree with the price or if the application is refused then there is an objections review process with related timelines. Post approval changes require different types of process and timelines using commitment evaluation, registration department and ranging up to 60 days. All of the bioequivalent centres in the Eastern Mediterranean Region are in Jordan and are approved by the JFDA. All bioequivalent studies must be reviewed and approved by the JFDA committee. According to the drug law of 2013 there is a committee, composed of JFDA and external experts to study different parts of the products and review any objections from companies. There is no mechanism to submit and study a CTD for herbal products' registration and there is no inspection of the manufacturing sites for herbal products.

The challenges in the assessment process are limited resources; post-marketing surveillance receiving little feedback from health care providers; available international guidelines on biologicals and biosimilars do not specify number of subjects. This is decided on a case-by-case basis.

The JFDA has recently amended manufacturing site criteria, defined stability requirements and drafted biosimilar regulations. The next steps include completing the stability guidelines; defining requirements for annual reporting; revising drug registration and re-registration requirements; adopting biosimilar regulations and implementing the eCTD.

## 7.2 The Saudi system of GMP inspections

*Dr Hajed Hashan, FDA Saudi Arabia*

The Saudi Food and Drug Authority (SFDA) was founded in 2003, by Royal decree and is headed by a CEO who regularly reports to a council of ministers. It covers food, drugs and medical devices and has over 2000 employees.

The presentation provided an overview of the structure and responsibilities of the organization. The focus of the presentation was on the role of the enforcement and inspections section, particularly its responsibility for GMP. The other activities of the section include: inspections of medicine warehouses, scientific offices and blood banks; monitoring of quality and availability of medical products in local markets through post-marketing surveillance; monitoring of pharmaceutical products advertisements; receiving complaints from professional health care providers and public and managing recalls from manufacturers and international authorities; cooperating with the international organizations regarding the quality of marketed products (GCC) and clearance of imported medicines and raw materials.

National inspectors are recruited from industry and are paid a competitive salary including during any training that is required. There are three types of GMP inspection: inspection for newly established manufacturers; regular inspections for local manufacturers and overseas manufacturers; and unannounced inspections, which are used in the case of complaints and recalls received or as part of a regular inspection procedure, if necessary.

The inspection risk assessment programme prioritizes inspections based on an inspection priority calculation:  $P = 2R + T + C$ . Where P is priority, R is risk, T is year of last inspection and C is compliance. This programme provides inspectors with electronic requests for inspections and a calendar of upcoming inspections.

The duration of GMP inspections depends on the purpose of the visit, size of the company and number of inspectors. Each team comprises of a scientific committee member, new staff in training period and a team leader who is responsible for submitting the inspection report within two days noting critical, major and other deficiencies. Teams are selected based on the individual inspector's expertise and the needs of each mission. An inspection typically consists of an opening discussion, site inspection, documentation check, and closing meeting. Overall, 46% of observations focus on quality, such as the absence of written procedures. Six per cent of observations represent critical deficiencies such as issues in manufacturing that could cause significant health hazards.

There is a fee structure for all of the functions the SFDA conducts based on the products being registered, which could make the organization self-funded. As of yet, the annual income does not cover the annual costs, so the SFDA receives still an annual budget from the government. Once it is able to cover its annual costs, the annual budget allocations will stop.

Some achievements of the SFDA include 224 GMP inspection visits, 251 GDP inspection visits for licenses and 1131 periodic visits. The post-market surveillance sampling programme performed periodic sampling of more than 2500 products. The annual pharmaceuticals anti-counterfeit study sampled over 6000 items. There is regular contact with WHO and GCC and a daily recall reporting system is in place. A number of guidelines have been issued and training programmes are offered.

Further information can be obtained from [www.sfda.gov.sa](http://www.sfda.gov.sa) or [hmdhashan@sfda.gov.sa](mailto:hmdhashan@sfda.gov.sa).

### **7.3 The Omani system of quality control of medical products**

*Dr Mohammed Hamdan Al Rubaie, NRA Oman*

The Directorate General of Pharmaceutical Affairs and Drug Control is located within ministry of health and was established in 1977. It is responsible for licensing manufacturers, importers, distributors, wholesale and retail outlets (premises, persons and practices); marketing authorization for drug products; monitoring import/export of medicines; quality control laboratory testing; provision of drug information; GMP inspection of manufacturing premises; and post-marketing surveillance. The pharmaceutical market in Oman has seen a 230% growth in the past ten years and has a value of around US\$ 1 billion, largely due to growing population.

The review process contains five steps from receiving the application, acceptance for review, scientific review, registration committee procedure, through to clarifications and approval or rejection. The overall registration timeline is four months, if there is no objection by the company.

Current challenges facing the NRA are shortage of experienced personnel; lack of independent budget (within the Ministry of Health) and inadequate regulatory guidelines. However, Oman has a good tracking system for every step of the review process; good management plan; and well qualified, trained and experienced reviewers. The NRA is moving toward electronic applications for licensing.

The Central Quality Control Laboratory within the NRA was established in 1984, and is responsible for quality assurance, safety and efficacy of pharmaceutical products available on the market. It has been recognized as a reference laboratory for the Central Drug Regulatory Committee of the GCC for all dosage forms. The laboratory analyses all products and provides training in analytical techniques. There has been a 100% increase in dossiers evaluated between 2009 and 2012.

### **7.4 Panel discussion**

*Moderated by Dr Abdul Hafiz Quraishi, NRA Afghanistan*

The discussion following this session included questions for Saudi Arabia and Jordan on their use of external inspectors as part of their inspection system. It was explained that in Saudi Arabia “external” inspectors are persons from outside SFDA and may be drawn from scientific committees, universities and hospitals. All are required to sign confidentiality

agreements and declare any conflict of interest. The JFDA also uses external inspectors through an agreement with academia in Jordan.

Participants discussed sampling procedures and random sampling. It was discussed that the best approach is random sampling testing on shipments into the country as it is not possible to test every batch/shipment. Testing every batch/shipment would delay getting products to patients and waste human and financial resources. The best use of resources is to analyse when the product is in the market – all three steps such as pre-market, post-market and shipments are verified at the same time. If a product has been registered in the Region, then there is no need to analyse it in the pre-registration process but rather analyse it once it is on the market in the country. It was advised to concentrate on those products that may be affected by the Region's climate and weather for safety in post-market conditions. It was remarked that laboratory testing is not everything. The whole quality control and assurance system must work together. It is one system, and it is a linked system. No one part of the system can work in isolation of the others.

It was remarked that countries without NRA capacity should have the latest GMP inspector reports from local manufacturers. These NRAs can rely on other countries like Canada for these reports. Ask another country for assistance. Even if NRA cannot do a full inspection, NRA should go and see the site to verify that there is an existing manufacturing site – that it is not just a room. It was mentioned that if a company has been inspected by another GCC country, there is a coordination mechanism for sharing inspection data.

The discussion highlighted efforts in the Region to establish one regulatory authority for all GCC countries. It was further suggested that a harmonized regulatory authority for the entire Eastern Mediterranean Region would allow for better use of human and financial resources and enable pooling of regulatory expertise and decision-making.

## **7.5 The Iranian clinical trials system: oversight and assessment**

*Dr Alireza Hosseini, FDO Islamic Republic of Iran*

The presentation outlined the regulatory structure and function of clinical trial system in the Islamic Republic of Iran. The National Clinical Trials Committee (CTC), Iranian Registry of Clinical Trials (IRCT) and National and Regional Ethic Committees all fall under the Ministry of Health and Medical Education. The clinical trials system is based on the WHO Good Clinical Practices as the minimum standard for different functions in conducting clinical trials. The Islamic Republic of Iran has adapted the WHO and ICH Good Clinical Practice (GCP) guidelines in 2003 to create the IR-GCP. These regulations, legislation and seven related guidelines comprise the basis for the system. The number of clinical trials registered in the Iranian registry, IRCT, has grown from 183 to 1695 between 2009 and 2013 respectively.

The CTC ensures compliance to GCP and to national regulations, issues clinical trials authorization, conduct inspections and provides training and workshops on clinical trials and ethics, among other activities. The CTC members must declare their conflict of interest and sign a confidentiality agreement. The committee includes nine members drawn from the CTC

secretariat, professional offices, universities of medical science, and the Food and Drug Organization (FDO) research centre. The CTC network includes over 90 experts from various medical specialties. Ethics Committees have been established at the national and regional levels and there are scientific ethics committees in place at universities and hospitals. The committees are involved in reviewing clinical trial assessment and oversight.

The clinical trials protocols require details of the sponsor, principle investigator, target populations, declarations of conflict of interest, inclusion and exclusion criteria, sample size, randomization, blinding, interventions, primary and secondary outcomes, ethical considerations and data management. Other documentation required includes the patient consent forms approved by the Ethics Committee, insurance of sponsor's liability for subjects participating in the study, case report forms, other forms and questions used for patient recruitment, random sampling, and adverse drug reactions.

Once clinical trials authorization is issued, the clinical trials must report any serious adverse events encountered, and any major and minor changes made to the protocol. Upon completion, they must supply interim and final reports, monitor's report and GCP inspection. If a problem is reported the clinical trial is stopped and capacity building efforts are used to address problems. GCP inspection checklist has been adapted from WHO. It reminds users what to check for – documentation; clinical trials conduct protocols are being followed and that the investigators team has been trained; storage and labelling of medicines; source data and case report forms; and informed consent of patients (this may include interviewing patients) and financial compensation.

Current challenges and areas for improvement include: oversight of clinical trials, design and choice of control products for clinical trials for biosimilars, insurance coverage for subjects in clinical trials, need to increase compliance to national regulations by pharmaceutical companies and research institutions, capacity building of clinical trials reviewer network, develop review practice guidelines and promote professionalism.

The Iranian Registry of Clinical Trials can be accessed at [www.irct.ir](http://www.irct.ir). All trials should be registered on this site before they begin.

## **7.6 The Jordanian system of regulating bioequivalence studies for generic medicines registration**

*Dr Wesal Alhaqaish, FDA Jordan*

The presentation presented the way that the JFDA engages in transparent and open dialogue with all relevant stakeholders in the Region and internationally to exchange information and build capacity. Guidelines and legislation are continuously updated according to scientific and international standards. While the launch of generic products provides patients with access, it is important to ensure that quality, safety and efficacy are not compromised, control measures are followed and bioequivalence is confirmed. The bioequivalence guidelines identify accepted approaches to confirming bioequivalence and provide assistance to industry

on how to comply with regulations. The guidelines have been developed taking into consideration the need for global harmonization while recognizing the unique needs of Jordan.

Bioequivalence is the absence of a significant difference in the rate and extent to which the API or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Bioequivalence is conducted on the highest strength of the product unless there are safety concerns with using this strength or if a different strength would be more sensitive to testing. Studies should be conducted on bio-batches from the same manufacturer, with the same composition of the product intended to be marketed. Testing must be completed for release in both fasting and fed states. It is essential to API source during assessment of bioequivalence studies. Centres conducting bioequivalence studies must be accredited for QCL and GLP. Not all products require bioequivalence studies. For example, biowaivers are acceptable for some class I and class III drug substances. Bioequivalence should then be completed post-approval if there are formulation changes or manufacturing process changes.

Some questions to consider when evaluating bioequivalence studies are: Is the reference product suitable? Was the study design as such that variability due to factors other than the product was reduced such as sample size, sampling protocol? Is the assay validation adequate? Is the pharmacokinetic analysis appropriate? Is the statistical analysis appropriate? Are acceptance criteria met?

All related legislation, regulations, forms, current applications and more are available on the JFDA website: [www.jfda.jo](http://www.jfda.jo)

## **7.7 Pharmacovigilance: establishing a pharmacovigilance centre and programme**

*Professor Rachida Soulaymani, WHO Collaborating Centre (Pharmacovigilance), Morocco, and on behalf of Dr Alex Dodoo, WHO Collaborating Centre (Pharmacovigilance)*

Pharmacovigilance comprises science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem for patient safety and benefit.

An adverse drug reaction or event is any response to a drug that is noxious, unintended and occurs at doses normally used in human for the prophylaxis, diagnosis or therapy of disease. But also any reaction due to: acceptance and tolerance, misuse and therapeutic errors, pharmacodependance, resistance, effect on pregnancy and children, failures or SFFFC medical products.

Pharmacovigilance originally focused on pharmacological and immuno-allergic responses. Now we know that reactions can be caused by quality or distribution and storage;

the patient and drug utilization; and risk evaluation based on registration process and risk management. Active pharmacovigilance requires adequate equipment and human resources.

The international pharmacovigilance system involves WHO, four collaborative centres, 144 national centres and an Advisory Committee on safety of medicinal products. Model policies, guidelines, norms and standards are developed by WHO. The WHO Collaborating Centre in Sweden manages the pharmacovigilance database with over nine million entries. The other WHO Collaborating Centres promote pharmacovigilance and patient safety, advocate for national pharmacovigilance centres, provide training, and assist in performing pharmacovigilance assessments. When the pharmacovigilance programme started in 1968 there were 10 national centres. Now, most of the countries in the world implement pharmacovigilance. In the Eastern Mediterranean Region, only 10 countries are official members of the pharmacovigilance network, while four are associate members.<sup>4</sup> Of the nine million inputs in the global system, only 0.4% has been reported by the Eastern Mediterranean Region.

Each country should have a pharmacovigilance system and a pharmacovigilance centre. The system engages partners, patients, industry, health professionals and the pharmacovigilance centre. The national centre receives input from all partners, reports adverse drug reactions (ADRs) and adverse drug events (ADEs) to the global system and takes action within the country if there is a problem. The electronic system used to report ADR is Vigiflow. Reporting should be done on a regular and frequent basis.

A well-functioning pharmacovigilance centre works within the broader pharmacovigilance system and is an essential part of the overall regulatory environment. Establishing a pharmacovigilance centre requires human resources (medical expertise, pharmacy expertise and administrative support), physical resources (computer and database access) and financial resources. The centre collects and validates information, analyses information to generate a signal if there is a risk, assesses the risk and takes necessary steps. Training and technical support is available through the WHO Collaborating Centre in Morocco.

The big challenge ahead for pharmacovigilance globally is integrating all vigilances into one structure for all medical products and all ADRs and ADEs. For the Eastern Mediterranean Region, the key challenges are: integrating the international pharmacovigilance programme; thinking public health and patient safety rather than regulatory and industry processes; be inspired by the international pharmacovigilance programme but avoid their mistakes; harmonize terminology, tools and methods and build local capacity and expertise.

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<sup>4</sup> Official members: Egypt, Iraq, (Islamic Republic of) Iran, Jordan, Morocco, Oman, Saudi Arabia, Sudan, Tunisia, and United Arab Emirates. Associate members: Bahrain, Pakistan, Qatar, and Syrian Arab Republic.

## **7.8 Panel discussion**

*Moderated by Dr Hajed Hashan, FDA Saudi Arabia*

The discussion highlighted the need for further consideration of post-marketing surveillance and pharmacovigilance. It was noted that post-marketing surveillance is about the safety and quality of the drug while PV applies to all elements of what happens to patients once a product enters the market, including efficacy or lack of efficacy. The data in the database is reviewed to identify products that may be causing concerns in regard to the patients. Member States are urged to work with the WHO Collaborating Centre including the issues related to SSFFC medical products.

Each country needs to adapt international models to suit their unique situation and practices must be adapted accordingly. A lesson to be learnt from international pharmacovigilance centres is that they do not collaborate across product types – it is better to have integrated pharmacovigilance systems. The Eastern Mediterranean Region should consider this approach. It is also important to promote domestic reporting by physicians and patients either by phone, email or paper. Less than 10% of ADRs are reported to the system and signals can still be identified.

In relation to the presentations on clinical trials and bioequivalence, it was stressed that it is essential to ensure that patients and citizens are protected in clinical trials. If protection is not ensured through legislation and regulations, clinical trials should not be undertaken.

## **7.9 The Moroccan inspection system of manufacturers**

*Dr Mohamed Wadie Zerhouni, Ministry of Health Morocco*

Inspection is an important part in guaranteeing the quality of medicines. The presentation provided an overview of the structure, regulatory and legislative frameworks, and responsibilities of the Pharmaceutical Inspection Service and noted that an inspection process for medical devices is currently being developed.

Every two years there is a meeting of pharmacy inspectors and plans are made for upcoming inspection missions. Each mission is usually three to five days. There are three steps in the inspection process: preparation (notifying the manufacturer, prepare inspectors), inspection (meeting with site team, review documentation, review the function and training of the team, check the site for cleanliness and maintenance, check the QCL, closing meeting that informs the site team of the inspectors findings), post-inspection (written report is shared with manufacturer, decisions made regarding need for follow up inspections, make decision regarding certificate for GMP, debriefing of inspection team). Random inspections are completed in response to complaints or safety concerns. A total of 25 missions were completed in 2013.

The strengths of the pharmaceutical inspection services include: good regulatory framework and monitoring standards that follow international standards, all procedures and checklists are in place, QCL is recognized as accredited by ISO and being compliant with

WHO guidelines. The challenges, which need to be addressed, are: delayed publication of certain decrees of the Law 17-04; dual function of pharmacists as inspectors; initial and continuous training of inspector-pharmacists; and lack of a streamlined methodology for inspection.

### **7.10 The Lebanese inspecting system of pharmacies and warehouses**

*Dr Naguib Boaraam, Ministry of Public Health Lebanon*

The presentation covered the structure and function of the Pharmacy Department in Ministry of Public Health of Lebanon, which includes the Inspection Department and the Department of drug importation and exportation. The inspections also cover narcotic and psychotropic medicines for importation. The health of citizens is a priority and every box of medicine is related to the health of citizens.

The ministry of health has a database of all importation records for registered medications that are kept on file for seven years. This assists with tracing medications from the warehouse to the pharmacies. Inspection of pharmacies and warehouses help to ensure that the medicines are stored properly. All products are given a batch number. If there are any violations or irregularities in this registration system, there would be legal action taken in coordination with customs or other relevant authorities as per laws number 82 and 84 and the law number 367/94 for regulating and practicing the pharmacy profession in Lebanon.

Counterfeit trafficking can be punished by five years in jail or US\$ 100 000. This penalty has reduced the incidence of counterfeit medicines in Lebanon. The ministry of health has a counterfeit reporting system for citizens to report any of their concerns or doubts about a medicine or its labelling or pricing, so that it can be investigated.

The inspection of pharmacies supports the decisions for recall of medicines based on notices received from WHO, EMA, or others. All notices are published at [www.moph.gl.le](http://www.moph.gl.le).

Medications are sold from warehouses to pharmacies to the public. Warehouses are inspected for counterfeit medicines, storage conditions, etc. Ministry of Health inspections also check for pricing. This has led to a 17% decrease in the prices of medicines.

Guidelines for good manufacturing practices and good inspection practices are followed. Some manufacturers have to review their practices to achieve GMP. The ministry of health is engaged in continuous education offered at the university or by WHO.

Inspectors work in teams and use a checklist/roadmap. Sometimes a Committee chair will go without a team, depending on the situation, or may be supported by staff from customs or police. There is direct communication between inspectors and the Ministry of Public Health. The Ministry of Public Health moves very swiftly. “The way a mother looks after her child, so we should be looking after our country.”

### **7.11 Managing the licensing process of manufacturers in Pakistan**

*Dr A.Q. Javed Iqbal and Dr Faqeer Muhammad, DRAP Pakistan*

The Drug Control Organization in Pakistan was enacted by the Drug Act of 1976. The current Drug Regulatory Authority of Pakistan (DRAP) was enacted in 2012, as an autonomous body that reports to the Ministry of Health Services, Regulation and Coordination and is responsible for medicines and medical devices. Drug regulation functions are the jurisdiction of both the federal and provincial government. The federal government is responsible for manufacturer licensing, import-export, pricing, registration of medicines, GMP compliance, post-marketing surveillance, clinical research and promotion. Provincial governments oversee drug sales, distribution, GMP compliance and post-marketing surveillance.

There are a reported 591 manufacturing sites in Pakistan. Over 56 000 products are registered, with more than 41 000 being made domestically and 7000 imported, in addition to veterinary medicines.

Licensing of drug manufacturing facilities involves receiving applications, site inspection, approval of site and application for approval of products. When manufacturers are approved, licenses are granted for five years and are then eligible for renewal pending a successful inspection. There are five types of licenses for manufacturing facilities: basic manufacture, semi-basic, formulation, repackaging and for experimental purposes.

The DRAP is committed to becoming a stringent regulatory authority by following best practice and bilateral cooperation at regional and international levels; capacity building to meet international standards; ensuring GMP; achieving WHO PQ of public drug testing laboratories; implementing quality management system with support from WHO and international health partners.

### **7.12 Panel discussion**

*Moderated by Dr Farhan Bashir Hassan, Ministry of Health Somalia*

During the discussion clarification was sought from Morocco as to how they distribute their inspectors to cover all of the pharmacies. Morocco has one pharmacy for every 3000 citizens. Morocco has 170 inspectors spread out across the Kingdom. The Ministry of Health used to coordinate all inspections, however as of 2009, inspections were decentralized to the regional level.

In relation to the presentation made by Pakistan participants indicated that many of their medicines are imported from Pakistan. Discussion touched on the types of licenses issued in Pakistan and whether a manufacturer can make multiples of any one generic medicine. It was confirmed that contract manufacturing is allowed for manufacturers whose facilities have been licensed to produce that product. It was also confirmed that no licenses for experimental purposes have been issued to date and that this type of study is not yet covered in Pakistan's regulations. All research initiatives must be reviewed by the Ethical Committee. Experimental licenses are for product development only.

## **8. COUNTRY EXPERIENCES: REGULATION OF SPECIFIC MEDICAL PRODUCTS**

### **8.1 The Egyptian system of market surveillance**

*Dr Osama Badary, NODCAR Egypt*

The mandate of National Organization for Drug Control and Research (NODCAR), the national quality control laboratory in Egypt, is to check the quality of newly registered, locally manufactured and imported pharmaceutical products by performing physical, chemical, biological and other pharmaceutical evaluations. It is also responsible for informing the government of test results so that action can be taken if products are not compliant for safety and effectiveness and contributing to the overall “delivery of quality healthcare services to all Egyptians”.

Pre-marketing and post-marketing reviews are completed for safety, efficacy and quality of medicines. Post-marketing review is also required for post-approval changes, safety/pharmacovigilance, quality surveillance and good manufacturing practices. Samples are sent to NODCAR for registration through the registration unit or quality control through the imported drug unit or the inspection and specification unit.

Samples are tested for physical properties, chemical analysis, microbiological tests, and biological tests. The process is applied to biologicals (vaccine, plasma derived products, anti-sera, allergens, and biotechnological products) and conventional pharmaceuticals (finished products, bulk products and raw materials). Marketing authorization is granted after three samples conform from finished products imported from reference and seven samples conform from finished products from non-reference countries. If samples from reference countries do not pass then entry is denied and the process must start again. Following initial market authorization random sampling is performed.

The sampling and permission for distribution of local finished products requires that the first three batches, regardless the dosage form or the product pharmacological category, must be sampled just after marketing authorization. Based on the first three batches, 100% of the manufactured batches of large volume parenterals, antibiotics in the form of vial or ampoule and medicinal products assumed to be supplied for tenders are sampled and analysed by NODCAR; 30% of the antibiotics are sampled and permission for distribution granted after conformity reporting by NODCAR. For other locally-manufactured finished products, “random” sampling is applied. Recall is initiated in the case of non-conformity reporting by NODCAR.

Different sampling procedures apply to bulk products supplied in one of the two accepted forms. Bulk products that are supplied in its primary packaging such as blistered tablets or capsules and bulk products not supplied in their original packaging. Active and inactive raw materials have each a different sampling procedure.

The Egyptian Pharmacovigilance Centre was established in 2009. It actively reports events to the global system and identifies signals for action. Reports are received by paper

form and telephone. Training of partners (physicians, pharmacists) on how to recognize and report signals is underway.

The largest challenge facing NODCAR is the large number of registered medicines and the high number of dossiers for submission.

## **8.2 Vaccines pharmacovigilance (intussusception) in Sudan**

*Dr Mohamed Elhassan Mohamed Imam, NRA Sudan*

Sudan has 18 states, 174 districts and a population of 34 million people more than 1 million of which are infants. The country has an infant mortality rate of 107. Its immunization programme was established in 1976. The Adverse Events Following Immunization (AEFI) programme surveillance pilot began in 2005, with the programme expanded to all states in 2009. A variety of vaccines are in use with most procured through UNICEF. Plans are underway to introduce vaccines for yellow fever, inactivated polio vaccine (IPV) and meningitis A.

The objectives of the AEFI programme are to detect, correct and prevent immunization errors and identify problems with vaccine lots or brands. The programme also aims to prevent false blame from coincidental events and maintain confidence by properly responding to parent and community concerns while increasing awareness of the public and health professionals about vaccine risks.

Cases are detected and reported by health workers providing immunization services, health workers treating AEFI in clinics, parents and researchers conducting clinical trials. Cases are reported to the AEFI register, to the local authority and upwards. In addition to incident reporting there is regular monthly reporting. Any ADR occurring within four weeks of vaccinations should be reported to the AEFI register.

The AEFI surveillance programme comprises national expanded programme on immunization (EPI) staff and pharmacovigilance, state surveillance officers, locality operation officers, vaccinators, health workers and pharmacists.

The roles and responsibilities of the AEFI system are spread across the community health unit level, the NRA and the State Investigation Committee. For example, the community health unit is responsible for the detection, management and reporting of AEFI; communicating with the parent, community and NRA; and maintaining documentation. The role of the NRA is the registration of vaccines and biologicals, monitoring the AEFI surveillance system and reviewing cases of rare and serious adverse events. Serious cases of AEFI are referred to the State Investigation Committee for review, management, follow-up and reporting. The Committee also assists with AEFI training at the state level. Finally, the National Causality Assessment Committee will review and classify the reported serious cases. Reports are made to national stakeholders and NRA and vaccine suppliers such as WHO and UNICEF.

In 2012, there were 27 cases reported while in 2013, 127 cases were reported as a result of better reporting through the AEFI system. Of the 127 cases, 79% required hospitalization. Planning is underway to expand pharmacovigilance to include other pharmaceuticals.

After the introduction of the rotavirus vaccine (Rotarix), a system for intussusceptions surveillance was established. Between 2011 and 2014 there have been 244 reported cases of intussusceptions resulting in 12 deaths. More than 60% of these are in children less than one year old. With the data gathered through surveillance it has been concluded that there is no relation between rotavirus vaccine and the reported intussusception cases so far.

Vaccine pharmacovigilance surveillance needs collaboration between the immunization programme and the NRA, as both parties are responsible for the safety of vaccines. In Sudan, they have agreed on the following:

- Convening regular meetings between EPI and NRA to review vaccine safety issues;
- Jointly participating in national AEFI committee reviews as members in the causality assessment committee;
- Jointly participating in the Investigation Committee at state level;
- EPI reports submitted regularly to the NRA who should communicate it to relevant bodies and to Uppsala monitoring centre;
- NRA agreed on the existing AEFI surveillance guidelines and both institutions will jointly update it whenever necessary;
- NRA participates as observer in the campaigns to overview safety concerns; and
- Both parties committed to upgrade the capacity of the National and State staff relevant to the safety of vaccines through training or any other applicable method at both national and international levels.

The conclusion of the Sudan experience is that success in vaccine pharmacovigilance requires collaboration and leveraging of resources by all stakeholders.

### **8.3 Registration of medicines in Tunisia: regulation of immunoserums (anti-venoms) in Tunisia**

*Dr Samiha Toumi and Dr Somaia Milad, Ministry of Health Tunisia*

The presentation provided a brief overview of the structure and scope of the regulatory system in Tunisia. The focus of the presentation was on the regulation process for immunoserums, which is the same as the process used for all other medicines.

Three types of dossiers (files) are submitted for registration:

1. Administrative dossier
2. Chemical and biological dossier
3. Clinical, toxicological and pharmacological dossier.

The chemical and biological file should contain the composition, ingredients, pharmaceutical development process, stages, stability studies, certificate of analysis from API and finished pharmaceutical product (FPP), samples from final products and should be sent to

the QCL for analysis. The clinical file is reviewed by the specialized committee. The technical committee reviews all files before licenses are granted. The committees are comprised of more than 200 multi-disciplinary experts divided into 16 committees that each focus on a product type. The committees each meet twice a year to review products. Committees include representatives from the national lab, pharmacovigilance, physicians, experts from medical disciplines, trade. The decision of the technical committee is submitted to the minister for approval and licenses are then granted. The entire process usually takes a year.

Further information is available at [www.dpm.tn](http://www.dpm.tn).

#### **8.4 Panel discussion**

*Moderated by: Dr Qais Jaafar Talib, Ministry of Health Iraq*

During discussion questions were posed to Egypt about the separate registration processes for medicines and biologicals and whether there are plans to bring the two together. While there are no plans to merge the two processes efforts are being made to improve the process, increase professional capacity, increase the number of experts and the number of labs. Clarification was sought on sampling criteria used for market surveillance. Samples are taken from different regions and different manufacturers sites. WHO expressed appreciation to Egypt for releasing NRA staff to assist with assessments. Most recently NODCAR staff participated in an assessment in China.

Discussion touched on the complaints rate on ADR of vaccines and concern that vaccination centres may be afraid to report ADR. In Sudan, the EPI is engaged in reporting from vaccination campaigns. All vaccines are provided through UNICEF and have been prequalified by WHO, so the incidence of ADR may be lower.

#### **8.5 Regulation of Blood products in Islamic Republic of Iran**

*Dr Alireza Hosseini, FDO Islamic Republic of Iran*

Regulation of plasma-derived products and medicines are managed by the Iran Food and Drug Organization (FDO) while blood products are regulated by the Iranian Blood Transfusion Organization (IBTO). Therefore, blood derivatives such as immunoglobulin, albumins and anticoagulants are regulated by the FDO and supplied by the private sector. Other plasma-derived medicines, red blood cells and platelets are regulated and supplied by IBTO. Both IS FDO and IBTO are within the Ministry of Health and Medical Education.

The FDO manages the regulation and registration of plasma derivatives. Activities by the FDO include: registration of plasma derivatives; GMP audits of plasmapheresis, pooling and plasma-collecting centers; lot releases of products; laboratory tests of samples; post-market surveillance and affordability activities such as pricing and subsidizing.

Essential documents required for registration include the demonstration of compatibility with the Iranian drug list, drug master file, plasma master file, site master file and certificate of pharmaceutical products. For the plasma master file, items such as country

of plasma origin, plasma-collecting centres, donor selection criteria, good donation practices and gastroenteropancreatic of plasma, and history of blood diseases are essential.

Plasmapheresis centres where plasma is collected and frozen must meet a number of requirements among them a license for operation from FDO, rules matched with religious norms of the society, a diagnostic laboratory and a separate technical director, GMP conditions that meet PIC/S and Iranian GMP, meet national guidelines and plasma donation based on humanitarian purposes and no compensation costs. In all cases the final decision is made by the “Legal commission of Article 20” as the highest decision-making body in FDO.

The IBTO is the nationwide centralized blood transfusion service integrated in the national health system. It follows the laws and regulations of ministry of health and criteria set by the FDO. Guidelines and standard operating procedures have been developed on a number of procedures. IBTO is heavily involved in educational programmes on safety, rational use, GMP, production, and blood collection. Countries in the Region have participated in some of these training sessions.

Blood donation has increased in recent years and the blood safety profile has improved. Plasma is sent to Germany for fractionation and the end products are returned to Islamic Republic of Iran. This requires an investment by IBTO. Currently, 20 IBTO centres have GMP certification from Paul Erlich Institute in Germany. Viral testing using EU/FDA licensed test systems are completed in IBTO collection centres. Plasma derived medicines are considered as medicine and require marketing authorization from the NRA. Costs of clotting factors are covered by the Ministry of Health and Medical Education.

For more information [www.ibto.ir](http://www.ibto.ir) and <http://fdo.behdasht.gov.ir>.

## **8.6 Regulation of medical devices in Saudi Arabia**

*Dr Hassaan Alwohaibi, FDA Saudi Arabia*

Medical devices are one of the sectors under the SFDA. Its vision is to be a regionally distinguished regulatory authority for medical devices and related electronic products, working towards safeguarding the public health in Saudi Arabia. The mission is to ensure safety, effectiveness, and quality of medical devices and their performance according to their intended purpose, and to ensure the safety of related electronic products. This sector is responsible for medical devices, in vitro diagnostics, prescription eyeglasses, contact lenses and solution, radiation emitting electronic devices, and cosmetic laser surgery devices and accessories.

The Medical Devices Interim Regulation published in 2009, was developed in cooperation with international experts and after careful consideration of systems used in many other countries. The system was tailored to meet the needs of Saudi Arabia and is consistent with Global Harmonization Task Force (GHTF) guidance. A number of implementing rules for the process have been developed from designation and oversight of assessment bodies to establishment registration and licensing of authorized representatives. Guidance has been developed for pre- to post-market surveillance. The Medical Devices

electronic system is expansive with applications for use by manufacturers, vendors and end-users covering marketing authorization through to post-market surveillance and reporting.

The SFDA participates in two international harmonization initiatives, the GHTF and the Asian Harmonization of Medical Devices, as an active chair, vice-chair and member in a number of technical working groups.

For more information see [www.sfda.gov.sa](http://www.sfda.gov.sa).

## **8.7 Panel discussion**

*Moderated by: Mr Faqeer Muhammad Shaikh, DRAP Pakistan*

The Islamic Republic of Iran's support in helping other NRAs and providing training programmes was acknowledged. It was noted that many countries are not yet considering putting blood products on the same list as medical products. Islamic Republic of Iran has listed over 6000 medicines and medical devices. Although blood products and plasma are regulated by different organizations – both are part of ministry of health. They are separate entities because of the capacity of the IBTO.

During the discussion it was noted that the SFDA has good experience. SFDA has issued over 3000 market authorizations and nearly 2000 manufacturers have been registered. The regulator checks the products, licenses them and approves them for sale in Saudi Arabia. The decision about what devices and how many should be purchased, is up to the ministry of health. It is worth looking at what SFDA has done to see how it can be applied to the unique systems and situations of other Member States in the Region. Other NRAs were encouraged to visit the SFDA website.

## **9. TOWARDS A COMPREHENSIVE NATIONAL REGULATORY AUTHORITY**

### **9.1 WHO policy to strengthen NRAs**

*Dr Lahouari Belgharbi, WHO headquarters*

Support for NRAs is provided by WHO in two ways. First, WHO develops model norms, standards and guidelines for use by Member States. Second, WHO provides guidance, technical assistance and training to enable countries to implement global guidelines. WHO's role is to focus on improved access to health products and health technologies and contribute to the achievement of the WHO's leadership agenda, such as: universal health coverage, acceleration of achievement of Millennium Development Goals (MDGs) expected for the end 2015 and the reduction of deaths from non-communicable diseases.

Effective medicines regulation and good regulatory practices include six principles as follows:

1. Medicines are of the required quality, safety and efficacy;
2. Medicines are appropriately manufactured, stored, distributed and dispensed;
3. Illegal manufacturing and trade are detected and adequately sanctioned;

4. Health professionals and patients have the necessary information to enable them to use medicines rationally;
5. Promotion and advertising is fair, balanced and aimed at rational drug use; and
6. Access to medicines is not hindered by unjustified regulatory work.

To provide sound regulation for citizens, NRAs must take a risk benefit assessment in deciding what products to regulate and how to regulate them. Government responsibilities in regulation of health products and health technologies include: functional national regulatory authorities; NRA accountability to government and the public; monitoring and evaluation of regulatory system and policies.

In the areas of medicines, devices, diagnostics, blood and traditional medicines WHO's work has included: assessment, guidelines and best practices, capacity building through training and learning opportunities, communications tools such as a model website, model system for computer assisted application, certification of pharmaceutical scheme, conferences and consultations of regulators, experts or advisory committees, international cooperation and harmonization.

In relation to vaccines, WHO has provided lessons learnt and a proposed an ideal model system for vaccines regulation. The regulatory process functions for vaccines include: registration, licensing, pharmacovigilance, quality control, regulatory inspections, and oversight of clinical trials. Pre-market phase involves product evaluation – through application and laboratory testing, quality – through regulatory inspections and licensing facilities, safety and efficacy – through clinical trials, before issuing market authorization. Post-market phase provides lot release with laboratory testing, post-marketing AEFI surveillance, quality inspections and monitoring.

WHO's NRA five-step capacity building tool took the ideal and developed a capacity building plan benchmarking: (1) development of NRA assessment tool that is assessed by experts every two or three years; (2) assessment of NRA based on a re-assessment every two to five years and a self-assessment for planning purposes; (3) development of an institutional development plan, with or without a roadmap for the prequalification of products; (4) providing technical support, training, learning, networking through WHO global learning opportunities, technical support and in-country training; and (5) monitoring progress and impact through the WHO electronic platform, NRA information, institutional development plan and training.

The objective of the NRA assessment is to identify gaps in the system, develop a roadmap, and or an institutional development plan to address the gaps and flag items for follow-up. Global learning opportunities on the assessment tool and regulatory functions are available through free active and e-learning courses offered by WHO. Also, capacity building is offered through in-country support, placements and twinning arrangements. The Eastern Mediterranean Region has had over 700 NRA officials trained by WHO since 1996.

The WHO harmonized NRA assessment tool can assess regulatory functions for medicines, vaccines, diagnostics, medical devices. Blood and traditional medicines will be

included in the tool by the end of 2016. Not included are reproductive health products, promotion and advertising, and narcotic substances. The tool is now available on the WHO website for feedback and testing and will go to a WHO working group for review, with an aim to being fully endorsed by WHO by end of 2015.

Between 1996 and 2014 WHO has assessed NRAs in 114 of 194 countries, engaging over 950 regulatory experts and more than 350 assessors worldwide. This is an important step in identifying capacity building needs and informing the development of IDP. Currently, 36 functional NRA regulate more than 90% of the global population.

The NRA progress and vaccine production in China between 2001 and 2014 was highlighted as a success story in the application and use of NRA assessment and capacity building. The first Chinese vaccines were PQ by WHO in 2013, following 10 years of capacity building.

The WHO NRA intelligence and repository system includes information of what WHO has done in the area of regulatory support since 1996 in all Member States. The site is regularly updated. Access to this website is by request.

## **9.2 WHO NRA assessment tool demonstration**

*Dr Alireza Khadem Broojerdi, WHO headquarters*

The presentation provided participants with a demonstration of the WHO NRA assessment tool. Participants were invited to have the software installed on their computers during the meeting.

The tool generates reports of the information input by the NRA including: major findings and identification of gaps, proposed institutional development plan, indicator status and implementation progress, institutions visited and persons met, documents reviewed, functions and indicators. The tool also has the capacity to generate PowerPoint presentations of the findings.

Access to the tool is password protected and should be approved by the head of the NRA. Assessors should be granted access for the purpose of completing the assessment. Beyond the assessment access should be limited to those who will need the information for decision-making. The programme has the capacity to compare information with other NRAs, however an agreement from that regulatory authority's country is required. The use of the information is at the discretion of the Member State.

Completing a comprehensive self-assessment would take between two to three weeks or up to three months. NRA should consult with WHO prior to beginning the assessment to confirm that all information is properly prepared and to receive advice to ensure that use of the tool is well understood and information is correctly entered. The self-assessment should be followed up by an assessment by WHO to validate findings and recommend steps to

address gaps. It was noted that pre- and post-assessment consultations with WHO may be done by Skype or phone and may not necessarily require country visits.

During the discussion immediately following this presentation it was noted that in addition to the manual and a help menu built into the assessment tool, WHO can also offer further training on the system together with NRA that have already used the system. Technical assistance from WHO to conduct the assessment is dependent on country priorities. Countries should submit requests through the relevant regional offices. The cost of completing the assessment is minimal – using WHO assessor and an assessor from another country who has already conducted an assessment. It was suggested that a list be compiled of interested resource people from NRAs in the Region who are willing to travel to other countries to provide this service. Countries may benefit from including areas requiring technical assistance or capacity building in the WHO-ministry of health biennial work plan and approaching the Global Fund, GAVI and UNICEF for funding support.

It was suggested that the name of the tool should be changed given the current use of harmonization in regulatory affairs. Participants were advised that a WHO working group is looking at terminology.

There was a clarification on the scoring and weight of each assessment indicator (i.e. not all indicators have the same weight and so cannot have the same score). It was mentioned that the scoring is used for prequalification purposes. For self-assessment purposes, WHO reviews the entered information and rescores it accordingly.

### **9.3 Developing integrated NRAs for all medical products in the Region**

*Dr Sultan Ghani, WHO Temporary Adviser*

Regulatory science and technology demands more regulation oversight to ensure reasonable protection from potential of harm with medicines. Human tragedies are associated with the safety of medicines and played an important role in sharing and reshaping regulatory systems around the world. Beside the safety, efficacy and quality of medicines, we must also consider the accessibility and affordability at a reasonable cost is important to understand from the perspective of developing countries. The development of globally recognized standards creates challenges, difficulties and barriers to the timely access of medicinal products. In applying these NRA must exercise flexibility in adapting them to be appropriate to their needs.

In considering proposed regulatory models each regulatory authority must consider where they can place themselves in terms of knowledge, national priorities, human and financial resources; using a progressive step-by-step approach in designing and implementing a regulatory programme for Eastern Mediterranean Region. The model provides guidance in the design, planning and implementation of effective and affordable national programme for the regulatory control of medical products of their country. There is no way of ensuring absolute safety, but rather ensuring maximum protection based on science.

The presentation presented a proposed classification of NRAs in the Eastern Mediterranean Region based on the four models. The criteria and recommendations for priority actions for each model are outlined as follows.

Model 1 (limited knowledge, no manufacturing base, procured products, limited financial resources). It is expected that the NRA should perform a comprehensive documentation review, physical quality assurance and ensure that the procured medicine is manufactured in a GMP compliant facility.

Model 2 (limited knowledge, reasonable financial resources, limited manufacturing base, some legislative instruments and guidelines). It is expected that the NRA should enhance their activity towards some basic assessment, GMP compliance, post-marketing analysis as well as periodic testing based on risk. They should consider moving toward model 3 requirements.

Model 3 (well-developed countries, have knowledge based resources, good manufacturing base, available legislative instruments, manufactured and imported products, and available financial resources). It is expected the NRA implement the activities outlined above. If financial and scientific resources and political commitment is available they should then consider moving toward the highest international standards.

Model 4 (countries with strict regulatory authorities, ICH standards and guidelines, enhanced tools of assessment, continuous compliance and surveillance, integrated electronic infrastructure, and contemporary science and innovation). Once fully accomplished in all the recommended activities, NRA should then consider following strict regulatory authority systems.

A regulatory pathway for modernization of legislation and regulations based on science was presented. Keep legislation simple and straightforward. It is easier to change regulations than to change legislation. Ensure the assessment and registration of medicinal products through a rigorous, uniform and consistent process using committees only when necessary. Perform compliance and enforcement for domestic manufacturers and products as well as manufacturers of imported products based on calculated risk. It was advised that for assessment and compliance always consider whether a requirement can be achieved using another NRA report. In establishment of licensing, GMP applies to laboratories, manufacturers with the ultimate goal of protecting the population from medicines of questionable quality. Regulatory pathway of national medicinal control laboratory should take into consideration that labs cannot possibly complete all testing required for all medicines. In Canada, regulations placed the onus on importers to test medicines that are imported. Ensure a strong regulatory pathway for post-marketing surveillance. In some countries the manufacturers are required to perform the post-marketing surveillance.

Regional harmonization and cooperation is very important. It is not as common in Eastern Mediterranean Region as it is in other regions. Use each other's resources in a constructive and meaningful way. This reduces the burden of any NRA. Cost recovery and

user fees should only be used to make up the balance of what the government provides through appropriation. Consult with stakeholders to agree on user fees. All countries do not use price controls. Where price controls are in place there must be some justification for the rates.

The four key areas for NRA to focus their energy and resources are assessment and registration of medicinal products; compliance and enforcement; national medicinal control laboratory; and post-marketing surveillance.

Proposed strategic directions for NRAs require a clear mission, vision and value; regulatory scope; strategic objectives; key result areas; strategic priorities; and programme culture and philosophy of integrity. Reinforce the regulatory culture through performance standards. This must be based on a sound scientific foundation as basis for regulatory decisions. Use ICH, as this is the best foundation. A risk management approach is advisable when human and financial resources are limited. Further it was advised to learn from the experience and best practices of other NRAs.

It was concluded that in the Eastern Mediterranean Region, political willingness and commitment are necessary for an independent innovative regulatory body capable of managing risk in order to achieve excellence and efficiency. NRA should use a sound scientific foundation as a basis of regulatory result-oriented decision-making. NRA should be transparent, accountable and responsive with timely communication. Effective regional and global harmonization would benefit the Region.

Discussion immediately following the presentation cautioned against classifying Member States at this time and that criteria that define the different levels of the model need to evolve and have some flexibility. This model is based on qualitative data not quantitative data and case studies from the Eastern Mediterranean Region have been used. For the purposes of this presentation post-market surveillance included pharmacovigilance, SSFFC and quality control.

#### **9.4 Group presentations and discussions**

*Moderated by Dr Sameen Siddiqi, WHO Regional Office for the Eastern Mediterranean  
Group rapporteurs: Abdul Qadir Javed Iqbal, Dr Wesal Haqaish and Dr Mohamed  
Oudie Zerhouni*

Participants were assigned to three working groups. Groups were asked to identify next steps for NRA to strengthen their current regulatory system for medicines and medical devices in each of the following areas: assessment and regulation of medicinal products; compliance and enforcement; national medicinal control laboratory; post-marketing surveillance. Groups were then asked to report on their discussion with two or three recommendations of what should be done across the Region. The results of these discussions are presented below.

*Assessment and registration of medical products*

- Countries should perform a situation analysis of the processes being followed by NRAs and their capabilities using assessment tool.
- Develop a roadmap that aims to harmonize NRA regulations and processes. Establish a step-wise approach on how to move from dossier to CTD format.
- Establish units for medical device regulation.
- Build capacity (good review practice) and facilitate sharing of the experience and best practices between NRAs.
- Assess (self and external) the current situation in each member state using assessment tool (WHO, NRA).
- Harmonize regulations in Member States (bioequivalence, GMP, pharmacovigilance, MD).
- Develop a customized information technology application and update it to ease evaluation process and registration (e.g. Morocco, Djibouti).
- Provide immediate technical support for medical devices regulation.

*Compliance and enforcement*

- Revisit regulatory laws to improve the compliance level and meet international standards.
- Ensure good and solid governance structure and improve personnel competencies.
- Develop checklists at regional level to bring harmony in the compliance with regulations to ensure same level of registration.
- NRA should be independent in authority and decision-making, and ensure transparent and sustainable financial resources (NRA).
- Establish the legal basis to ensure implementation of above point (independence) and to ensure strengthening NRA position in implementation of its regulation (NRA).
- Each Member State should have a strategic plan (WHO).
- Empower professional and protect them against abuse or misuse or turnover.

*National medicines quality control laboratories*

- Complete a situation analysis of the quality control laboratories and their capacities.
- Strengthen regional collaboration and encourage information sharing.
- Establish regional reference laboratories for medical products.
- Improve the system for testing medical devices in the existing quality control laboratories.
- Establish a centralized reference laboratory for the medical devices in the Region, enabling NRA to access expertise not available in their own country.
- Prequalification of pharmaceuticals quality control laboratories in the Region (WHO).
- Facilitate cooperation between national quality control laboratories (WHO).
- Promote access to recognized national quality control laboratory services.
- Support the capacity-building of newly established laboratories.

*Post-marketing surveillance*

- Establish post-marketing surveillance activities in countries where it does not exist, with the technical support of WHO if needed.

- Enhance and harmonize existing pharmacovigilance establishments.
- Share information within the Region.
- Include post-marketing surveillance as part of national regulatory system, and create a database (NRA).
- Encourage WHO to make the Collaborating Centre more active and proactive as focal point in the Region (WHO).
- Assess and develop action plan. Ensure that all Eastern Mediterranean Region countries become members of WHO/Uppsala Monitoring Centre (UMC) pharmacovigilance network and use the Vigiflow system.
- Disseminate existing pharmacovigilance training for Francophone and Arab countries and make use of existing Collaborating Centres when relevant.
- Conduct training on post-market surveillance inspections.
- Ensure that all countries develop and promote best practices on rational use of medicines.

A number of cross-cutting themes and short term recommendations were identified:

- promote and develop institution with autonomy and adequate resources
- share information and exchange of assessment report
- ease immediate access to country WHO guidelines or scientific information (towards harmonization)
- strengthen and speed the delivery of specialized training
- WHO to advocate and promote strong commitment and support from decision makers.

Discussion following the presentations of the group work highlighted the need for more discussion and clarification on the use and scope of the terms of post-marketing surveillance and pharmacovigilance. It was noted that guidance is available for those starting a pharmacovigilance programme, as best as they are able. Efforts should be made for pharmacovigilance programmes to harmonize with existing activities in the Region. A pharmacovigilance focal point in each country could assist with exchanging information between countries. This already exists for traditional medicines. WHO will look at a systematic approach for this issue and how this work can be expanded in a sustainable way.

During the discussion it was suggested that WHO should develop ethics guidelines/code of conduct for each regulatory function that NRA can then enforce; that WHO should identify a centre of excellence for bioequivalence studies within the Region; and that WHO should help develop Member State capacity to evaluate the bioequivalence reports.

It was noted that each country should ensure that there is at least a unit, whatever form it takes, to regulate medical devices to resolve the current disparate situation where some countries are quite strong in this area while other countries have nothing in place. Participants were reminded that there are three legs required for medical devices – regulation (independent body), health technology assessment (within the ministry of health because it gives evidence for decision making), needs assessment and training (ministry of health or at hospital level if necessary).

## 9.5 Review and discussion on recommendations of EMDRAC 2011

*Dr Marthe Everard, WHO Regional Office for the Eastern Mediterranean*

The recommendations from EMDRAC 2011 and their current status are as follows.

### *To WHO*

- Draft concept note on mechanism for collaboration between Eastern Mediterranean Region RAs including proposed mechanism for funding a permanent secretariat.

#### *Status*

- Completed. Draft concept paper on strengthening NRAs for medical products has been presented by Dr Alan Kent and Dr Sultan Ghani and discussed in EMDRAC 2014.
- Assist NRAs in mobilizing political support in countries through communication from WHO to ministers of health, highlighting the importance of establishing independent medicines regulatory authorities.

#### *Status*

- Completed. Draft WHA resolution on strengthening regulatory systems for medical products will be discussed and most probably endorsed in WHA May 2014. This may generate more political support for investing in a national regulatory framework and NRA functions.
- Make available secured web area for regulators to benefit from sharing information and exchanging confidential regulatory documents.

#### *Status*

- Completed. This is made possible through the new WHO comprehensive NRA assessment tool.
- Encourage sharing inspection plans and reports among Eastern Mediterranean Region NRAs using this secure platform.

#### *Status*

- Ongoing. WHO PQ web site provides reports and other relevant information that NRAs can access.
- Encourage assessments for medicines regulatory authorities to identify priority needs using the new WHO comprehensive NRA assessment tool.

#### *Status*

- Ongoing. Pakistan is one of the pilot countries for using the new WHO comprehensive NRA assessment tool.

### *To Member States*

- Identify national financial resources available to NRAs and mapping it to capacity building plans including joint activities where applicable using WHO technical expertise.

*Status*

- 50% of NRAs have financial resources available for capacity building of NRA staff.
- 83% of NRAs have used WHO technical expertise in the area of medical products regulation.
- Investigate the possibility of engaging with WHO in some collaborative mechanisms to fast-track registration of WHO prequalified products.

*Status*

- 42% of NRAs have established a mechanism to fast-track registration of WHO prequalified products.
- SFDA to provide access to secure area for sharing medicines price information between NRAs.

*Status*

- 42% of NRAs are sharing medicines price information with other NRAs but not on a secure platform.

Major achievements in the field of medical products regulation since 2011, identified by Eastern Mediterranean Region NRAs include:

- new NRA structure and decentralized branches
- new legislation, regulations and guidelines for medicines, medical products, including clinical trials, biosimilars, procurement, stability guidance and suppliers.
- implementation of e-services, automated and information systems
- adoption of CTD and e-CTD
- manufacturing sites accreditation criteria
- change of marketing authorization holder
- new requirements for re-registration of pharmaceuticals
- independence of financial resources
- pharmacovigilance launched
- first and second phase of Good Governance for Medicines (GGM) programme launched.

## **9.6 Discussion of recommendations for EMDRAC 2014 and 16th ICDRA 2014**

During this session participants discussed and agreed on a list of 14 recommendations, which are included in section 12 of the report. Additional suggestions for consideration include setting up a matrix to track implementation of recommendations, categorizing the recommendations for short and long term completion for better follow up and ensuring active follow up on the recommendations. It was agreed that Afghanistan will present the EMDRAC 2014 recommendations at the 16th ICDRA 2014 to be held in Rio de Janeiro, Brazil, 26–29 August 2014.

## 10. CLOSING SESSION

*Dr Clive Ondari, WHO headquarters, Dr Sameen Siddiqi, WHO Regional Office for the Eastern Mediterranean*

Dr Siddiqi encouraged participants to provide feedback as to how they will take action on the various recommendations and to demonstrate the commitment of the Member States they represent to these items. He extended thanks to the government of Jordan for hosting the conference. He thanked Member States for their participation, noting that the success of the meeting is due to their involvement and contributions. He noted that NRAs in Eastern Mediterranean Region have progressed since 2011. However, while some have done very well and have gained a lot of experience, others have still a long way to go. He stressed that it is about consolidating the gains that have been made and that the group work identified areas where work needs to be done. He encouraged NRAs to look at how to implement the recommendations and assured them that WHO is there to provide support. He noted that there is some work to be done in reconciling the areas of post-market surveillance and pharmacovigilance. He confirmed that the meeting report will be circulated for comments as it is the official record of the conference. He reiterated that WHO is committed to providing support at the country level and will take this to the regional committee to help raise the profile with Ministers of Health. Further he expressed appreciation to all those who helped to organize the meeting, particularly Dr Marthe Everard and her team in the Regional Office for the Eastern Mediterranean.

Dr Clive Ondari, extended a big thank you to the Government of Jordan and the Jordanian FDA for their excellent efforts in assisting with the meeting. He acknowledged the support and active participation of the NRAs in the Eastern Mediterranean Region. He gave a special thank you to his Regional Office colleagues for their efforts and assistance during the meeting and to colleagues from WHO headquarters for attending and their valuable interventions. He remarked that it had been a productive four days with three remarkable achievements: large and deep information sharing; identified opportunities for collaboration in strengthening regulatory systems; and re-affirmation of willingness to work together. He expressed that WHO looks forward to seeing progress on the recommendations made and is committed to providing continuing support.

Dr Ikhlas Hadidi, from JFDA, thanked WHO for giving Jordan the opportunity to host this important event. She noted that they are always willing to host events about medical product regulation as it is a priority for the country. She emphasised the importance of Jordan being invited to participate in any further action and working groups relating to the follow up of the meeting recommendations.

## 11. CONCLUSIONS

The meeting reviewed progress and challenges identified in regulation of medical products and possible solutions recommended for the Eastern Mediterranean Region; agreed on a plan of action for strengthening regulatory capacity in the Region; and finalized recommendations and selected a Member State to present them during the 16th ICDRA.

During the discussions it was stressed more than once that Member States should collaborate closely together in regulatory activities with the overall aim to facilitate access to new medical products with public health importance. Sharing relevant information and assessment and inspection reports may shorten the registration period. The importance of a well-functioning national regulatory authority for medical products to safeguard their quality, safety, and efficacy, was acknowledged but insufficient political commitment and limited financial and human resources contribute to inefficient regulatory systems. Another pertinent advice that was provided was that any regulatory function can start small and can grow in strength and importance over time. Regulatory convergence is based on streamlined procedures, agreed standards and guidelines and collaborating together.

## **12. RECOMMENDATIONS**

### *Member States*

1. Begin collaboration across the Region with a step-wise approach beginning with joint on-site GMP inspections, sharing relevant information and joint training in a way that complements existing initiatives.
2. Actively participate in the new Member State mechanism on SSFFC medical products and having a functional national monitoring and surveillance system that can report SSFFC medical products to the global WHO monitoring and surveillance system.
3. Take steps towards regulating medical devices and building capacity to apply the health technologies assessment as an evidence-informed decision making tool.
4. Undertake a self-assessment using the WHO comprehensive NRA assessment tool.
5. Build capacity of the NRA through WHO support and bilateral collaboration between Member States in joint training and orientation visits.
6. Continue to build broad-based pharmacovigilance/post marketing surveillance systems for all regulated medical products (medicines, vaccines, biologicals, diagnostics and medical devices).
7. Attend the 16th ICDRA 2014 in Brazil.

### *WHO*

1. Support Member States in strengthening NRA capacity through a step-wise approach to comply with international norms, standards and guidelines by providing guidance, technical assistance, coaching and training.
2. Strengthen regulatory collaboration by mapping the expertise of the NRAs and creating a roster of regulatory experts in various functions.
3. Advocate for Member States support for strengthening and resourcing NRA, including the provision for adequate legislative and regulatory frameworks for medicines, vaccines, biologicals, diagnostics, herbal and traditional medicines, and medical devices.

4. Enable a secure web-based platform for regulators to facilitate harmonization and convergence activities and share information including best practices, GMP inspection reports, HTA reports and other assessment reports.
5. Promote effective networking activities for medicines, vaccines and medical devices in all functions of regulation in the Eastern Mediterranean Region
6. Define terms of reference and identify strengths of national regulatory authorities in specific areas such as assessment and regulation of medicinal products; compliance and enforcement; national medicinal control laboratory; post-marketing surveillance, including pharmacovigilance for all medical products.
7. Support Member States in completing NRA assessments and developing institutional development plans.

**Annex 1****PROGRAMME****Day 1. Monday, 5 May 2014**

08:30–09:00	Registration	
09:00–10:30	<b>Opening Session</b>	
	Welcome	<i>Dr Marthe Everard, EMRO</i> <i>Dr Ahmad Basel Al-Yousfi,</i> <i>a/WR Jordan</i>
	Regional Director's Speech	
	Key note speakers:	
	<ul style="list-style-type: none"> <li>• Organization of Islamic Cooperation</li> <li>• League of Arab States</li> <li>• Jordan FDA</li> </ul>	<i>OIC representative</i> <i>LAS representative</i> <i>Jordan FDA representative</i>
	Remarks by EMP headquarters:	
	EMP headquarters representative	<i>Dr Lembit Rägo, HQ</i>
	Minister of Health's Message	<i>Dr Ikhlas Hadidi, JFDA</i>
	Objectives of EMDRAC 2014	<i>Dr Marthe Everard, EMRO</i>
	Introduction of participants	
	<b>Session 1 – Global and regional overview</b>	
10:30–10:50	WHO reform and how medicines regulation is key to universal health coverage	<i>Dr Clive Ondari, HQ</i>
10:50–11:10	Medicines regulation in Eastern Mediterranean Region: results from the survey	<i>Dr Marthe Everard, EMRO</i>
11:10–11:30	Good Governance for Medicines: transparency and accountability framework	<i>Dr Mohamed Ramzy, EMRO</i>
11:30–11:50	Good Governance for Medicines: a model for evidence-based selection of medical products	<i>Prof Ibrahim Alabbadi,</i> <i>University of Jordan</i>
11:50–12:20	Panel discussion	<i>Moderators: NRA Djibouti</i> <i>Dr Adham Ismail, EMRO</i> <i>Dr Samvel Azatyan, HQ</i>
12:20–13:30	Information on the forthcoming 16th ICDRA	
	<b>Session 2 – Global and regional initiatives</b>	
13:30–13:50	WHO's regulatory support to Member States	<i>Dr Samvel Azatyan, HQ</i>
13:50–14:10	Establishing an African Medicine Agency: challenges and future prospects	<i>Dr Ossy Kasilo, AFRO</i>
14:10–14:30	WHO prequalification team (PQT): Medicines/vaccines/diagnostics	<i>Dr Lembit Rägo, HQ</i>
14:30–15:30	Panel discussion	<i>Moderators: NRA Somalia</i> <i>Dr Marthe Everard, EMRO</i>
	<b>Session 3 – Vaccines and medical devices</b>	
15:30–15:50	Regional initiative to establish network for vaccine regulation	<i>Dr Houda Langar, EMRO</i>
15:50–16:10	Medical devices regulation	<i>Dr Adham Ismail, EMRO</i>
16:10–16:30	Links between medical devices regulation and health technology assessment	<i>Dr Adham Ismail, EMRO</i>

16:30–17:00 Panel discussion  
*Moderators: NRA  
 Afghanistan  
 Dr Lembit Rägo, HQ*

**Session 4 – Counterfeit medical products**

17:00–17:20 Global system for monitoring and reporting on SSFFC medical products and Member State mechanism  
*Dr Clive Ondari, HQ*

17:20–17:40 Pakistan experience on reporting of counterfeit medicines  
*Dr Syed Khalid Bukhari,  
 WHO Pakistan*

17:40–18:00 Panel discussion  
*Moderators: NRA, Iraq  
 Dr Ossy Kasilo, AFRO*

Wrap-up

**Day 2. Tuesday, 6 May 2014**

**Session 5 – Recent developments in regulatory affairs**

09:00–09:30 Development of a framework for medical devices regulation in Eastern Mediterranean Region  
*Dr Alan Kent, Temp Adviser*

09:30–09:50 Development of global regulatory curriculum framework  
*Dr Samvel Azatyan, HQ*

09:50–10:10 Cooperation between medicines quality control laboratories for better access to quality-assured essential medical products  
*Dr Hariram Ramanathan,  
 US Pharmacopoeia*

10:10–11:00 Panel discussion  
*Moderators: NRA Palestine  
 Dr Marthe Everard, EMRO*

11:00–11:40 EU Medicine Agency: regulatory reforms in the EU  
 EU Pharmacopoeia  
*EMA representatives by  
 Skype*

11:40–12:00 Discussion  
*Moderators: Dr Alan Kent,  
 Temp Adviser  
 Dr Lembit Rägo, HQ*

12:00–12:20 Local pharmaceutical manufacturing: opportunities and challenges in the Eastern Mediterranean Region  
*AUPAM representative*

12:20–12:40 WHO prequalification of medicines: Eastern Mediterranean Region perspective on capacity-building efforts  
*Mr Mohamed Farag, EMRO*

12:40–14:00 Panel discussion  
*Moderators: NRA Yemen  
 Dr Clive Ondari, HQ*

**Session 6 – Towards regulatory cooperation: successful experiences**

14:00–15:00 Joint review and joint inspections: experience from the Gulf Cooperation Council  
 Regulatory cooperation in the East African Community  
*Dr Mohamed Al Haidari,  
 GCC-Central Registration  
 Dr Hiiti Sillo, Tanzania FDA*

15:00–15:20 WHO collaborative procedure for fast-track registration of prequalified medicines  
*Dr Lembit Rägo, HQ*

15:20–15:40 Implementation of medicines legislation across borders: African Medicines Regulatory Harmonization Programme  
*Dr Paul Tanui, African  
 Union-NEPAD*

15:40–16:30	Panel discussion	<i>Moderators: NRA Jordan Dr Samvel Azatyan, HQ</i>
16:30–17:00	Pan American Network for Drug Regulatory Harmonization (PANDRA): experience of regional cooperation in NRA assessments	<i>WHO/PAHO representative by Skype</i>
17:00–17:20	Discussion	<i>Moderators: NRA Pakistan Dr Lembit Rägo, HQ</i>
17:20–17:30	Wrap-up	<i>Dr Clive Ondari, HQ Dr Marthe Everard, EMRO</i>
17:30	Closure of EMDRAC 2014 open sessions	

### Day 3. Wednesday, 7 May 2014

08:30–08:50	Importance of regulation in health system development	<i>Dr Sameen Siddiqi, EMRO</i>
08:50–09:00	Introduction of EMDRAC closed sessions	<i>Dr Marthe Everard, EMRO</i>
<b>Session 7 – Country experiences: ensuring quality, safety and efficacy of medical products</b>		
09:00–09:20	The Jordanian system of improving efficiencies and timelines in assessment of medical product dossiers	<i>FDA Jordan</i>
09:20–09:40	The Saudi system of GMP inspections	<i>FDA Saudi Arabia</i>
09:40–10:00	The Omani system of quality control of medical products	<i>Ministry of health, Oman</i>
10:00–11:00	Panel discussion	<i>Moderator: NRA Sudan</i>
11:00–11:20	The Iranian clinical trial system: oversight and assessment	<i>FDO Islamic Republic of Iran</i>
11:20–11:40	The Jordanian system of regulating bioequivalence studies for generic medicines registration	<i>FDA Jordan</i>
11:40–12:10	Pharmacovigilance: establishing a PV centre and PV programme	<i>Prof Rachida Soulaymani, WHOCC-PV Morocco and WHOCC-PV Ghana</i>
12:10–12:40	Panel discussion	<i>Moderator: NRA Saudi Arabia</i>
12:40–14:00	The Moroccan inspection system of manufacturers	<i>Ministry of health, Morocco</i>
14:00 – 14:20	The Lebanese inspection system of pharmacies and warehouses	<i>Ministry of health Lebanon</i>
14:20–14:40	Managing the licensing process of manufacturers in Pakistan	<i>DRA Pakistan</i>
14:40–15:10	Panel discussion	<i>Moderator: NRA Somalia</i>
<b>Session 8 – Country experiences: regulation of specific medical products</b>		
15:10–15:30	The Egyptian system of market surveillance	<i>Ministry of health, Egypt</i>
15:30–15:50	Vaccines pharmacovigilance (intussusception) in Sudan	<i>Ministry of health, Sudan</i>
15:50–16:10	Regulation of immunoserums (anti-venoms) in Tunisia	<i>Ministry of health, Tunisia</i>
16:10–17:00	Panel discussion	<i>Moderator: NRA Iraq</i>
17:00–17:20	Regulation of blood products in Islamic Republic of Iran	<i>FDO Islamic Republic of Iran</i>
17:20–17:40	Regulation of medical devices in Saudi Arabia	<i>FDA Saudi Arabia</i>

17:40–18:00 Panel discussion  
18:00–18:10 Wrap up

*Moderated by: DRA Pakistan*

#### **Day 4. Thursday, 8 May 2014**

##### **Session 9 – Towards a comprehensive NRA for all medical products**

08:30–09:30	WHO policy to strengthen NRAs	<i>Dr Lahouari Belgharbi, HQ</i>
09:30–10:30	WHO NRA assessment and tools - demonstration	<i>Dr Alireza Khadem Broojerdi</i>
10:30–11:00	Developing integrated NRAs for all medical products in Eastern Mediterranean Region	<i>Dr Sultan Ghani, Temp Adviser</i>
	Introduction to group work	<i>Dr Adham Ismail, EMRO</i>
11:00–14:00	Group work	
14:00–15:00	Group presentations and discussion	<i>Group rapporteurs</i> <i>Moderator: Dr Samvel Azatyan, HQ</i>
15:00–15:30	Review of recommendations of EMDRAC 2011 and ICDRA 2012	<i>Dr Marthe Everard, EMRO</i>
	Recommendations for EMDRAC 2014	
	Selection of Member State to present EMDRAC 2014 recommendations in ICDRA 2014	
15:30–16:00	<b>Closing Session</b>	
	Closing remarks	<i>Dr Clive Ondari, HQ</i>
	Closure of EMDRAC 2014 closed sessions	<i>Dr Sameen Siddiq, EMRO</i>

**Annex 2**

**LIST OF PARTICIPANTS**

**AFGHANISTAN**

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**Annex 3****RESULTS OF ONLINE NRA QUESTIONNAIRE (MAY 2014)**

Prior to EMDRAC, a survey was sent to the 17 participating NRAs of countries of the Eastern Mediterranean Region. Responses on the 21 questions were received from 15 NRAs (Afghanistan, Egypt, Islamic Republic of Iran, Iraq, Jordan, Libya, Morocco, Oman, Pakistan, Palestine, Saudi Arabia, Somalia, Sudan, Tunisia, and Yemen) and presented during EMDRAC. One section of the questions included in the survey was on the implementation of the recommendations of the last EMDRAC held in 2011. The survey revealed that:

- The majority (80%) of reporting NRAs in the Region have core regulatory functions in place.<sup>5</sup>
- All NRAs in the Region already cover medical products: medicines, vaccines, biologicals, diagnostics, diagnostic kits, blood products, radiopharmaceuticals, medical consumables, and herbal medicines. Some NRAs cover also veterinary medicines, prostheses, cosmetics and food.
- Of the reporting countries, 60% of NRAs are using a common technical document (CTD) for submissions. Only 20% of NRAs have the CTD available electronically.
- Of the reporting countries, 73% of NRAs are within/under the ministry of health, 27% are either independent or under a different ministry.
- A written code of conduct is in place for 53% of NRA staff.
- A model format for declaration of conflicts of interest is in place for 53% of NRA staff.
- Of the reporting countries, 47% of NRAs have financial resources available for capacity building of their staff.
- Joint activities (training, information sharing, technical expertise, and technical functions) with other NRAs are implemented among 47% of NRAs in the Region.
- WHO technical expertise in the area of vaccines (fast-track vaccine registration, GMP inspection) has been used by 80% of NRAs in the Region.
- Of the reporting countries, 40% of NRAs have established a mechanism for fast-track registration of WHO prequalified products.
- Of the reporting countries, 58% of NRAs have established a secured platform for sharing medicine pricing information.

Functions that are merely undertaken by the Ministry of Health are:

- licensing pharmaceutical wholesalers and retail pharmacies
- licensing pharmacists and pharmacy assistants
- inspecting hospital pharmacies and community pharmacies in the public sector

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<sup>5</sup> National regulators assess product safety, quality and efficacy/performance through scientific assessment of documentary evidence for quality, safety and efficacy; site inspections for GMP, GLP and GCP; control of variations to products and their manufacturing processes; post-approval monitoring of quality and safety.

Major challenges that were encountered by the 15 reporting countries in the regulation of medical products are:

- limited qualified human resources
- limited financial resources
- capacity building opportunities
- legislation and enforcement of regulations
- regulation of clinical trials
- pharmacovigilance/surveillance system
- bioequivalence centers at international standards in the Region
- prequalified laboratories for quality control of medical products
- selection of essential medicines based on evidence
- resistance to independent status of NRA
- appropriate infrastructure
- investment in IT solutions
- collaboration between different government bodies (e.g. customs, police...)

Major challenges that were identified by NRAs in the regulation of medical products within the Region included:

- limited collaboration/coordination between NRAs in the Region
- no efforts in harmonization of regulatory requirements
- limited collaboration between research centres and universities
- complex intellectual property rights issues
- no regulation of medical devices
- independence of regulatory agencies
- lack of database or electronic platform for secured sharing of regulatory information

Major achievements by reporting countries in the regulation of medical products since 2011, included:

- new NRA structure and decentralized branches
- new or revised legislation for medicines, pharmacies, and NRA
- new or draft regulation for biosimilars
- new or modified regulation guideline, over-the-counter (OTC) guidance and list, guidelines for importing medical devices, procurement guidelines, stability guidance and manufacturing sites accreditation criteria
- implementation of e-services; common technical document (CTD) and electronic CTD (e-CTD)
- increased local pharmaceutical production in relation to imported medicines
- pharmacovigilance launched
- first phase of Good Governance for Medicine programme launched



**Figure 1. Functions undertaken by national regulatory authorities in 15 countries of the Region**



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