Medicines Regulation, Regulatory Harmonization, Global Initiatives

Tonya Villafana, PhD, MPH

Senior Health Specialist, World Bank

September, 13, 2012

Presentation Outline

- The importance of regulation
- Attributes of effective regulatory systems
- The case for medicines regulation
- Core elements of a medicines regulatory system
- Enforcement of drug regulation and access to medicines
  - Drug and Vaccine Regulation and WHO Prequalification
- Medicines Harmonization initiatives
  - Benefits to stakeholders
  - Examples of initiatives

The Importance of Regulation

- Indispensable for proper functioning of economies and societies
- Underpin markets, protect the rights and safety of citizens and ensure delivery of public goods and services
- Regulatory policy ensures regulations support economic growth and development, social welfare, environmental sustainability, and rule of law
- Differences in services regulation across countries constitute trade restrictions, standards convergence or international standards can lead to increased services trade

Source: OECD 2011, Regulatory Policy and Governance: Supporting Economic Growth and Serving the Public Interest, OECD Publishing

Attributes of Effective Regulatory Systems

Attribute	*Meaning*
Responsive	Respond rapidly to a crisis Promptly modify policies
Outcome Oriented	Focus on product safety outcomes
Predictable	Clear framework guaranteeing that decisions are neither arbitrary nor capricious
Proportional (Risk-based)	Allocates control based on threat to public health Products with similar risks regulated similarly
Independent	Independent of the political process

Source: Adapted from Riviere et Al. Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad, Institute of Medicine

The Case for Medicines Regulation

- Strengthening governance, regulations and accountability in the pharmaceutical sector is an important component of health systems strengthening
- Can improve patient access to safe, effective, and good quality essential medicines
- Can increase pharmaceutical sector trade at a regional level and contribute to economic development

Core Elements of a Medicines Regulatory System

- Medicines registration
- Clear requirements for licensure
- Provision of unbiased information
- Market entry notification
- Safety and effectiveness surveillance
- Quality control testing
- Inspection of manufacturers for compliance with good manufacturing practices
- Inspection of distributors
- Evaluation of performance through authorized clinical trials

Source: Adapted from Riviere et Al. Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad, Institute of Medicine

Links between Enforcement of Drug Regulation and Access to Medicines

Area of Regulatory Weakness	*Potential systemic effect*
Circulation of low-quality drugs and inconsistent enforcement of manufacturing standards	Lack of confidence in drug quality and preference for more expensive branded or imported drugs
Weak licensing process for businesses and products	Fewer products on the market, potential procurement delays in the launch of new drugs
Inadequate reporting of adverse events and inadequate recall mechanism	Reliance on adverse event data from developed countries, with potentially disastrous health impacts
Sale of prescription drugs over the counter	Risk of irrational use of a drug or use in cases where the drug is contraindicated, with negative impacts on individual's health; drug resistance
Inadequate information provided with drugs	Risk of irrational use of a drug or use in cases where the drug is contraindicated, with negative impacts on individual's health; drug resistance
Unethical marketing practices	Overuse and inappropriate use of certain drugs and skewed advice to committees that develop drug lists for institutions or health insurance
Lack of oversight for clinical trials	Reduction of in-country clinical trials by drug companies and trial data that is unacceptable to regulatory authorities; harm to patients

Source: Seiter 2010, *A Practical Approach to Pharmaceutical Policy, World Bank*

WHO Prequalification and Drug and Vaccine Regulation (1)

- Established in 2001 to ensure that medicine supplied by UN Agencies were safe and efficacious
- Important regulatory oversight for countries lacking capacity
- Five steps:
  1. WHO/UN agency invites drug/vaccine company to submit product for prequalification
  2. Manufacturer submits dossier on product safety/efficacy
  3. Team of experts reviews dossier
  4. Inspectors verify factory, laboratories, and research in dossier meet international best practices
  5. If the manufacturer passes all inspections, WHO grants prequalification

WHO Prequalification and Drug and Vaccine Regulation (2)

- >240 medicines, vaccines, contraceptives have been evaluated through the program
- WHO programs to strengthen oversight of national regulatory authorities gives priority to emerging manufacturing nations that supply vaccines to many other countries
- WHO Prequalification of Manufacturers in China
  - March 2011 WHO recognized China's regulatory system for complying with vaccine production standards
  - Team of international experts assessed China's regulatory system against WHO indicators
  - Opportunity created for China to apply for WHO prequalification and to supply vaccine to UN agencies in next few years

BMJ: China is nearly ready to produce vaccines for the developing world

The Chinese drug industry is on the verge of getting the green light to manufacture the Japanese encephalitis vaccine for the developing world, an event that will signal the emergence of a major new player in global vaccines.

Seth Berkley, chief executive of the Global Alliance for Vaccines and Immunisation (GAVI), said that by the beginning of next year Chinese drug firms will be ready for World Health Organization representatives to carry out pre-qualification inspections of production of the vaccine. Once those inspections are carried out, United Nations agencies and other non-governmental organisations will be able to purchase the vaccine for countries that do not have their own regulatory systems.

Berkley was speaking to the BMJ after returning from China, where he met the Chinese health minister and drug companies to discuss collaboration on vaccine production. The Chinese health minister told GAVI that he was confident that China would soon be able to meet large scale demand for a range of vaccines, such as pneumococcal vaccine and human papillomavirus vaccine to protect against cervical cancer. Berkley said that he believed that the manufacturers of Japanese encephalitis vaccine will pass inspections. "It's a new game. There may be some glitches, but from a [Chinese] government perspective they would be very concerned if the first pre-qualification application went up in smoke," he said.

China has been using the vaccine for the domestic market for many years and has exported it to countries in Asia, including India. However, this will be the first time that Chinese manufacturers will have had a vaccine given the green light by WHO, thus enabling use of the vaccine in developing countries. Berkley hopes that the emergence of China as a supplier of vaccine to developing countries will strengthen the vaccine market by reducing the cost of vaccines, ensuring a greater range of suppliers, and widening choice.

He said that competition was healthy in the vaccine market. "With the pneumococcal vaccine, initially we had a seven strain vaccine, but we thought key strains were being missed. Another manufacturer came out with a 10 strain [vaccine], another came out with a 13 strain, and there's a 15 strain vaccine being worked on. That's a result of competition," he said.

China's regulatory body, the State Food and Drug Administration, said that China has 36 vaccine manufacturers, producing 49 different vaccines for 27 diseases, with annual capacity of nearly a billion doses. In March 2011 WHO certified the regulatory body as meeting international standards, an important prerequisite for the pre-qualification of Chinese vaccines. At the time of the announcement WHO said that the ability of UN agencies and other non-governmental organisations to source vaccines from Chinese manufacturers was "expected to have a significant, beneficial impact on global supply of vaccines of assured quality." WHO predicted that it would take between one and two years for the first vaccines to get to the pre-qualification stage.

Chinese firms are currently working on a hepatitis C vaccine, an example of a "vaccine that the world needs," said Berkley.

Berkley acknowledged that there had been problems with safety in Chinese manufacturing in the past, such as the infant formula scandal in 2008.1

"China understands that these have been a real problem for its image. There's an attempt to do things better and better. In the past things were done with much less rigour, but China's changing," he said.

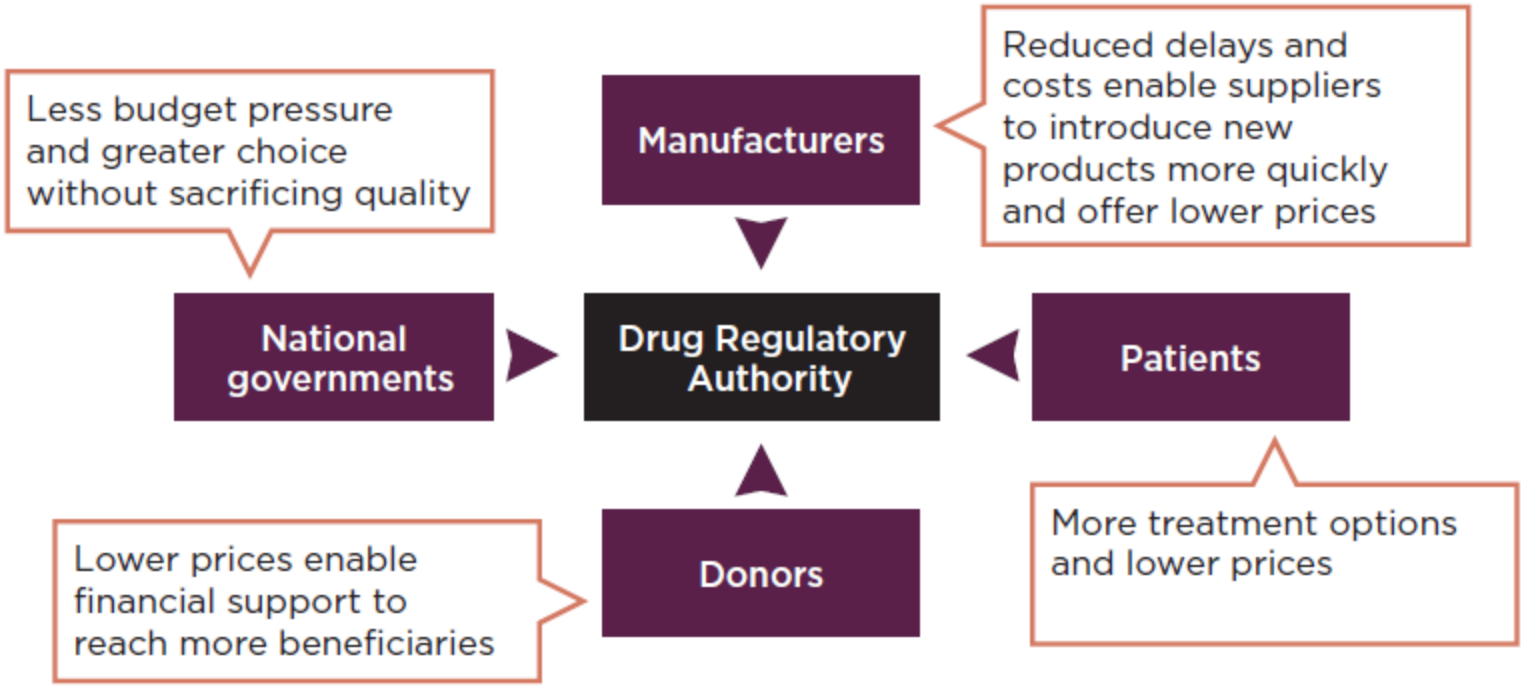
Source: BMJ 2012;345:e6290

Medicines Harmonization Initiatives

- Harmonization of medicines regulations increases product safety and promotes trade by facilitating fair competition
- Ensures internationally recognized standards for quality and safety
- Particularly important in developing countries with weak capacity
- Harmonized and simplified requirements for registration can ensure life-saving medicines are more quickly available in poor countries

Source: Adapted from Riviere et Al. Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad, Institute of Medicine

Benefits of Harmonization by Stakeholders



Source: Ndomondo-Sigonda and Ambali, 2011

Global Medicines Regulatory Harmonization (GMRH)

- World Bank administered multi-donor trust fund initiative established in 2011 with an initial contribution of US$ 12.5 million from the Bill & Melinda Gates Foundation.
- Falls under a larger partnership program in the Bank which focuses on Pharmaceutical Governance and Regulation
- Main objective is to promote the harmonization of medicines regulations as a means to improve access to essential and quality medicines by strengthening governance and regulatory systems of the pharmaceutical sector
- Partners include WHO and New Partnership for African Development
- Initial focus on the Africa region: African Medicines Regulatory Harmonization

Harmonizing registration addresses resource constraints, enabling accelerated product approval and access

How would harmonization impact the registration process?

Today's current environment	A harmonized future environment
~ 50 National Medicines Regulatory Authorities (NMRAs) governing drug registration across Africa	8 regional economic communities (RECs) covering the entire African continent
Paperwork, technical requirements, and other registration steps differ across NMRAs	Common documentation, procedure, and decision-making framework across all RECs
Manufacturers must invest significant time and effort in each registration, so a limited set of countries are targeted	Low cost to register in each additional country, so coverage is more broad and equitable
No clear timelines for a drug to clear registration and be ready for the marketplace	Streamlined process that is faster and easier... starting first with generics
Little transparency before or during the process	Clear understanding of the process by all parties involved

More broadly, regulatory harmonization contributes over time to mar cross-cutting public health and development goals

	Prevention and treatment of infections diseases (overall)	Enhanced access to new health technologies	Broad economic development in the region
Short term	✓ Increased access to generics treating many important diseases		
Intermediate term	✓ Broader, more rapid access to vaccines and other therapies	✓ More efficient launches for vaccines and other PDP products	✓ Foundation for African pharma industry Benefit to other initiatives from REC trust / cooperation
Long term	✓ Drug quality, safety and efficacy with extension to all regulatory functions	✓ Greater impact of new life-saving technologies	✓ Healthier, more productive workforce

Potential approach for Africa capitalizes on existing Regional Economic Community (REC) organization and harmonization efforts

COMESA

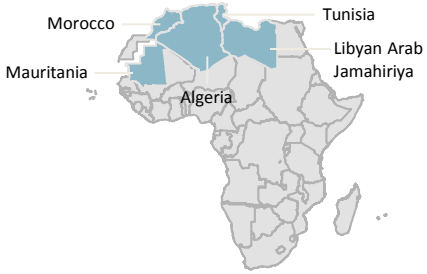
IGAD

UEMOA

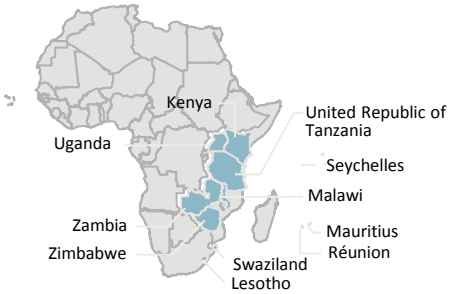
EAC

SADC

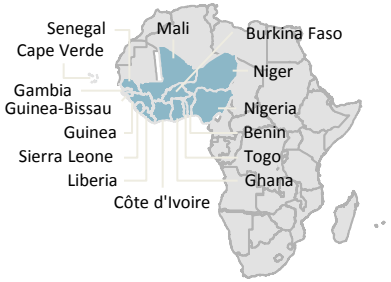
UMA



ECSA



ECOWAS/WAHO



OCEAC

Global Medicines Regulatory Harmonization (GMRH) Project Status

- East African Community Project launched in March 2012
- Includes Burundi, Kenya, Rwanda, Tanzania, Uganda, Zanzibar
- Project steering committee for EAC Project established
- 4 Technical Working Groups:
  - Medicines Evaluation and Registration
  - Good Manufacturing Practices and Inspection
  - Information Management Systems
  - Quality Management Systems
- Planning smaller projects in other regions Latin America, Middle East and North Africa, South Asia, South East Asia

Asian Pacific Economic Community (APEC)

Organization	APEC
Project	APEC Harmonization Center
Objective	Increase regulatory harmonization among member states with the goal of supporting access to best practices, information exchange and clinical trials that meet international standards and improve quality, safety and efficacy of medical products to enhance health outcomes and facilitate international trade.
Activities	Research on harmonization policies and best practices Education and training including fellowship programs Establish strong information exchange networks Maintain online publications Develop and disseminate harmonization models Support international cooperation
Where	Asia Pacific

ASEAN ACCSQ Pharmaceutical Product Working Group

Organization	ASEAN
Project	ACCSQ Pharmaceutical Product Working Group
Objective	The harmonization of pharmaceutical regulations to facilitate the goals of the ASEAN Free Trade Area, particularly eliminating technical barriers to trade, without compromising the quality or safety of medicines.
Activities	GMP Training Implementation of common technical requirements Mutual recognition agreements for GMP Inspections Shared postmarket surveillance information Vaccine regulation capacity building
Where	Southeast Asia

US FDA

Organization	FDA
Project	Office of International Programs, Technical Cooperation and Capacity Building
Objective	Defines regulatory capacity, the ability of national regulatory authorities to perform regularly their core functions to ensure the availability of high-quality and safe food and medical products , as part of the FDA mission to ensure safe products in the United States
Activities	Strengthen information and evidence so the FDA can make informed decisions about how to use its resources Transfer its expertise and identify efforts globally that do not require the use of FDA resources Encourage global information networks to strengthen detection, surveillance, and assessment systems Support surveillance and tracking efforts for global supply chains Support pharmacovigilance capacity
Where	Worldwide

Conclusion

- Medicines regulation and strong regulatory systems are an important part of health systems strengthening and assuring access to safe and efficacious medicines
- Practitioners and researchers are important stakeholders for ensuring a functioning system
- Many efforts are ongoing at a global and regional level to ensure regulatory capacity and collaboration and cooperation among agencies
- China is making strides in this area the SFDA has been recognized by WHO and vaccine manufacturers are close to meeting standards for supplying vaccine to the developing world