WHO Activities on Regulation of Medicines and other Health Technologies

WHO Technical Briefing Seminar, EMP
12 October 2017, Geneva
Emer Cooke, Head, Regulation of Medicines and other Health Technologies
Director General’s 5 priorities

1. Health for all
2. Health emergencies
3. Women, children and adolescents
4. The health impacts of climate and environmental change
5. A transformed WHO
Programme of Essential Medicines and Health Products

VISION: A world where every child, man and woman has access to the quality essential medicines, vaccines and other health products they need to lead a healthy and productive life.

MISSION: To support the WHO Member States to improve and sustain access to quality medicines and health products to achieve Access 2030 goals and universal health coverage (UHC):
WHO Cluster of HEALTH SYSTEMS AND INNOVATION (HIS)

Department of Essential Medicines and Health Products (EMP)

Innovation, Access and Use (IAU)

- Innovation/research & Development
- Intellectual property,
- Evidence-based selection of Model List of Essential Medicines
- Pricing, Health technology assessment (HTA)
- Procurement and supply chain management
- Improved use of medicines and health products

Regulation of Medicines and other Health Technologies (RHT)

Head: Emer Cooke

- Technologies Standards and Norms (TSN)
- Regulatory Systems Strengthening (RSS)
- Prequalification Programme (PQT)
- Safety and Vigilance (SAV)
Regulation of Medicines and other Health Technologies (RHT)

Head: Emer Cooke

Technologies Standards and Norms (TSN)
Coordinator: François-Xavier Lery*

Establish/maintain international standards
Promote unified standards, as well as a global nomenclature

*from 2nd November 2017

Regulatory Systems Strengthening (RSS)
Coordinator: Mike Ward

Strengthen NRAs for capacity building and promote harmonization, reliance, best practices & integrate framework for new products

Prequalification Team (PQT)
Coordinator: Deus Mubangizi

Assure quality, safety & efficacy/performance of health products
(vaccines, diagnostics, medicines, medical devices, vector control products)

Safety and Vigilance (SAV)
Coordinator: Clive Ondari

Respond to and minimize health risks from medical products through proactive, end-to-end, actionable, smart safety surveillance

Cross Cutting Activities

• Antimicrobial resistance
• Benchmarking tools
• Data integrity
• Emergency preparedness
• Environmental issues
• Local production
• Non-communicable diseases
• Paediatric medicines
• Shortages
• Substandard & falsified

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To Increase Access to Essential, High-Quality, Safe, Effective and Affordable Medical Products

Two strategic roles of EMP

**Facilitator**
Supporting needs-based innovation and reinforcing health product selection, use, procurement and supply systems to increase access

**Guardian**
Strengthening regulatory capacity and practices to ensure the quality, safety and efficacy of products and improve the efficiency of regulatory system to secure health gains
Access to quality medicines and other health technologies requires an integrated approach across all RHT activities.
Strengthening regulatory capacity to ensure quality, safety and efficacy of medicines and health technologies – focusing on Outcomes

**TSN**
- Global norms and standards
- Common understanding on regulatory requirements by authority and manufacturer
- Standardized approach used by quality control laboratories
- Decreased work for authorities and manufacturers

**RSS**
- Collaborative & harmonized regulatory approaches in LMICs
- Faster/smooth registration
- Increased confidence in product quality, safety and efficacy
- Decreased cost & time of regulatory activities
- Local Production

**PQT**
- Qualify assured medicines, vaccines, medical devices, cold chain equipment, vector control products and more accurate diagnostics for use in LMICs
- Increased competition to shape the market
- Patients to access quality medical products

**SAV**
- Increased knowledge of real life adverse events
- Coordinated actions taken against adverse events
- Protection against substandard / falsified products
- Containing antimicrobial resistance

Decreased regulatory burden
Reduced time for regulation
Increased regulatory capacity in LMIC
Decreased cost of regulation
Reduced mortality and morbidity

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Technologies Standards and Norms (TSN):

Setting international norms and standards
All current WHO medicines quality assurance guidelines are grouped in development, production, distribution, inspection, quality control and other regulatory guidelines

- [https://extranet.who.int/prequal/content/who-technical-report-series](https://extranet.who.int/prequal/content/who-technical-report-series)

For vaccines, biotherapeutics and blood products
- [http://www.who.int/biologicals/vaccines/en/](http://www.who.int/biologicals/vaccines/en/)
- [http://www.who.int/bloodproducts/en/](http://www.who.int/bloodproducts/en/)
Technologies Standards and Norms (TSN): How are the outputs achieved?

- Expert Committees
  - Specification for Pharmaceutical Products
  - Biological Standardization
- International Nonproprietary Names (INN)
- The International Pharmacopoeia
- Blood Regulators Network
Prequalification Team (PQT):

Created in response to procurement agencies and WHO Member States needs to ensure that products supplied through these agencies are consistently safe and effective under conditions of use in resource limited countries.

- **Diagnostics (Dx)**: assessment of in-vitro diagnostics (IVDs) & male circumcision devices (MCDs)
- **Medicines (Rx)**: assessment of finished pharmaceutical products (FPPs) & active pharmaceutical ingredients (APIs)
- **Vaccines (Vx)**: assessment of vaccines & immunization devices (ImDs)
- **Vector Control Products (VCP)**: assessment of finished products (VC-FPs) & active ingredients (AIs)

- **Inspections of manufacturing sites**
- **Laboratory evaluation & testing of Dx, Rx, VCP & Vx**
- **Laboratory prequalification of Rx quality control laboratories (QCLs)**
- **Technical assistance to manufacturers, NRAs and other stakeholders**
- **Facilitation of National regulatory approval for Dx, Rx, VCP & Vx**
Prequalification Updates and challenges

- All product streams involve screening, assessment, inspection, laboratory testing (to a greater or lesser degree)
- Abridged procedures for all product streams
- Current focus on Malaria, TB, HIV, Reproductive Health and Neglected Tropical diseases
- Can model be used for non-communicable disease treatments?
- What would need to change?
- What impact does prequalification have on time to market in countries?
The collaborative registration procedure (CRP): solving the time to registration in countries

**Principles**
- WHO PQ shares the reports that served as the basis for the prequalification decision, so that NRAs do not conduct assessment and inspections
- National registration based on PQT evaluation
- SRA procedure nearing finalisation

**Diagnostics**
- Procedure in development
- Ongoing discussions with NRAs

**Medicines**
- Started in 2012

**As of December 2016:**
- 30 countries participating
- 183 registrations in 20 countries for 73 different products

**Vaccines**
- Procedure published in 2007, harmonized for medicines and vaccines as of 2014

**In 2015:**
- Adopted by expert committee (ECBS)
Median time to registration in Member States via CRP

*Including regulatory time and applicant time

Days

0.0 20.0 40.0 60.0 80.0 100.0

Days*

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As at 12 May 2017
The 5th CRP Annual Meeting
Accra, Ghana, 25 - 26 November 2017
Side meeting on CRP of OCV vaccine with participation of all current involved authorities
Impressive results from CRP already seen

But to build collaborative procedures,

- Requires basic functionality of NRAs
- Investment in regulatory systems strengthening essential
- Increased focus on pharmacovigilance and post-marketing surveillance competences
World Health Assembly Resolution 67.20 requests WHO to support Member States upon their request in the area of regulatory system strengthening, including, as appropriate, by continuing to:

- Evaluate national regulatory systems
- Apply WHO evaluation tools
- Generate and analyze evidence of regulatory system performance
- Facilitate the formulation and implementation of Institutional Development Plans (IDPs)
- Provide technical support to national regulatory authorities and governments
Building regulatory capacity of NRAs

PAHO authorities of reference

Local production

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Building regulatory capacity of NRAs

RHT Vision

- Functional NRAs to take over PQ assessment of generic applications
- Allow PQ to develop capacity in other value-added activities
- Extension to other products on EML
- Progressively cover priority EML or specific products of interest
How can we get help to achieve this goal? Coalition of Interested Partners (CIP)

Build a framework to achieve better coordination, efficiency and outcomes in regulatory strengthening activities in the same target Member States or regions to achieve better public health outcomes.

- More effective use of overall resources
- Better outcomes and impact through coordinated action at regional and/or country level
- Wealth of expertise available across the member organizations
- Greater capacity and sustainability
- Sharing and adoption of best practices
Assessment Tools and other current challenges – some examples

- Pilot Prequalification for similar biotherapeutics
- Snake Antivenoms - Assessment and Listing process introduced
- Dealing with Smallpox vaccine stockpile risk assessment
- Dealing with global shortages - Rabies, Diphtheria anti toxin, other gaps?
- Dealing with emergencies – Emergency use and Assessment Listing
Pilot for prequalification of similar biotherapeutics (SBP)

- 2 mAb biotherapeutics selected from the WHO Essential Medicines List: Trastuzumab and Rituximab
- Two assessment pathways
  - SRA approved and Non-SRA approved
- Original branded Biotherapeutics to be used as Reference

Why this pilot?
- Currently no global mechanism for evaluating SBP
- Significant international experience by “SRAs”
- How to extend this experience to LMICs?
- Importance of appropriate regulatory framework to address potential risks including product quality, product specific issues, pharmacovigilance….
SBP Pilot: Risk-based Assessment Approach

• SRA approved product:
  o independent “verification” focusing on labelling, storage and identicality

• Non-SRA approved products:
  o fuller assessment to be undertaken by WHO

• Possibility to perform independent laboratory testing and inspections

• Consultants with expertise in assessment of SBPs to conduct the WHO pilot assessment
Public Health Burden:

About 5 million snake bites/year, causing up to 2.5 million envenomings and around 100’000 deaths in women, children and farmers in resource-limited countries in Africa, Asia and Latin America

- Snake Antivenoms - Listing is a time-limited special procedure under special public health circumstances
- Current listing focused on Sub-Saharan Africa
- Used for UN procurement decision-making
- Intended to support highly impacted countries in their regulatory decision-making
Snake Antivenoms: Risk-based Assessment Process

• Joint review by group of regulatory, herpetological, medical and scientific experts, including key African regulatory agencies

• Risk-based approach:
  o Reasonable likelihood that the quality, efficacy and safety present an acceptable balance and that usage of a product to treat snakebite envenoming in any of the countries in which that product is marketed has benefits that exceed foreseeable risks
  o Listing to be valid for 24 months with specific restrictions (snake species, geographic coverage, etc), pending reviews and reassessment based on further data becoming available

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Dealing with emergencies: Some of the Gaps in regulatory preparedness

• Lack of coordinated emergency regulatory processes
  o Link regulatory processes with overall national preparedness planning for public health emergencies

• Weakness of drug regulatory systems and lack of capacity
  o Strengthen regulatory collaboration and capacity

• Limited capacity and experience in stakeholder communication
  o Need for guidance in communicating with the media and public

• Poor engagement of product developers with affected regulators

• Weakness in regulation of supply chains
  o Need to minimize entry of substandard and falsified products in supply chains
Assessment pathways for medicines, vaccines & diagnostics:

- Full/Traditional
- Conditional Marketing Approval
- "Animal Rule" Approval
- "Accelerated" approval
- Other SRAs
- Prequalification
- Article 58 Scientific Opinion
- Approval under Exceptional Circumstances
- Emergency Use and Assessment Listing (EUAL)
Pathways in LMICs (likely to be first hit by epidemic)?

Most authorities have “full” or “abbreviated” (based on reliance), but not conditional, emergency, exceptional use, compassionate use options..
EBOLA RESPONSE: Regulatory activities – what we supported

- Support to member states on the review of Clinical trials of Ebola vaccines through AVAREF and collaboration from relevant Regulatory agencies and ethics committees
- Pharmacovigilance preparedness
- Development of WHO guidelines
- Development of EUAL procedures for IVD, pharmaceuticals and vaccines
Technologies Standards and Norms (TSN): Guidelines and standards

WHO Guidelines: Published

- Guidance on Managing Ethical Issues in Infectious Disease Outbreaks
- Good participatory practice guidelines for trials of emerging pathogens
- Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries
WHO International Reference Materials for Ebola Assays

- WHO IRR Anti-EBOV plasma, human (1unit/mL): NIBSC code 15/220
  American Red Cross EBOV convalescent sample

- Candidate WHO IS Anti-EBOV Convalescent Plasma Pool Sierra Leone (unitage tbc): NIBSC code 15/262

- Candidate WHO IRR Anti-EBOV Convalescent Plasma Panel (unitages to be calibrated against the IS): NIBSC code 16/344
  Convalescent samples from 4 repatriated patients and a negative sample

- WHO IRR EBOV RNA NP-VP35-GP standard (7.5 Log10 units/mL): NIBSC code 15/222

- WHO IRR EBOV RNA VP40-L calibrator (7.7 Log10 units/mL): NIBSC code 15/224

- WHO IRR EBOV RNA VP40-L in-run control (calibrated against the IRR: 3.5 Log10 units/mL (95% CL 3.3 – 3.7; n=5)): NIBSC code 15/136

- WHO IRR EBOV RNA VP40-L in-run control (calibrated against the IRR: 3.7 Log10 units/mL (95% CL 3.1 – 4.3; n=3x)): NIBSC code 15/138
Joint ethics committee platform:
- AVAREF platform brings together regulators and national ethics committee representatives from Africa;

Joint review of clinical trial applications:
- Joint reviews through AVAREF successfully used in Ebola crisis;

Other networks and collaborative activities:
- A joint review of clinical trial applications for candidate Zika vaccines?
- Options for coordinated and accelerated country assessment
WHO Emergency Use and Assessment Listing (EUAL) for candidate vaccines – not prequalification

✓ A time-limited special procedure for assessment of candidate products under special public health emergencies
✓ Used for UN procurement decision-making
✓ Intended to support highly impacted countries in their regulatory decision-making

• EUAL for use in the context of a public health emergency for:
  - candidate in vitro diagnostics
  - candidate vaccines
  - candidate medicines

WHO Information Consultation on Options to Improve Regulatory Preparedness to Address Public Health Emergencies

17-19 May 2017, Geneva

• 44 external participants from 22 countries:
  o Belgium, Brazil, Cambodia, Canada, France, Georgia, Germany, Ghana, India, Japan, Nepal, Norway, Rep Congo, Rep Korea, Saudi Arabia, Senegal, Sierra Leone, South Africa, Switzerland, Tanzania, UK and USA
  o Academic, CEPI, Civil society, Foundation, Industry, National Regulatory Authority (NRA), Product Development Partnership, Reference Laboratory, Research institute, Pharmacy board member from Sierra Leone, WHO AFRO

• 20 representatives from NRAs or Reference Laboratories from 13 countries

• Collaborative multi-cluster/department efforts
Preliminary Outcomes of Informal Consultation: May 2017

• Map current emergency provisions in LMICs and address legal or regulatory deficiencies

• Consider a “pre-EUAL” submission process for priority diseases

• Revision of the current EUAL process based on the experience gathered
  o Use experiences from Pandemic Influenza Preparedness and Smallpox as input on vaccine side
  o Clarify what happens next – e.g. by local regulators, by procurers, import issues, liability issues…
Preliminary Outcomes of Informal Consultation: May 2017

• Determine a set of **minimum competencies** that NRAs and ethics committees should have for handling the emergency use of unlicensed medical products during a public health emergency.

• Develop guidance, procedures and pathways, for the use of unlicensed medical products during a public health emergency.

• Explore a “diagnostics preparedness consortium”

• Explore “mock-up” practices for expedited review of assessments or clinical trials in emergency contexts.
Facilitating pharmacovigilance preparedness

Defining monitoring and follow-up mechanisms – does the model need to be adapted for products that go first to LMICs?

Measures to detect and prevent falsified and substandard vaccines, diagnostics and other therapeutics
Key messages

- WHO is committed to contribute to access to safe, effective and quality medical products for every patient

- This can only be achieved with stakeholders and member states

- WHO encourages collaboration at regional and global level between member states for efficient use of resources

- Needs to adapt to a changing world – countries at the centre

- Pre-market safety assessment and post market surveillance are equally important, specifically substandard and falsified product require full attention of every stakeholder and authority
A world where every child, man and woman has access to the quality essential medicines, vaccines and other health products they need to lead a healthy and productive life.

RHT is there to help achieve the WHO Vision!