Regulation, Norms and Standards for medical products

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Public health and medicines

- Availability and access to **good quality, safe and effective medicines** is a key contributor to achieving Public health objectives, Sustainable Development Goals and Universal Health Coverage.

- To achieve Global public health objectives **functional and effective health systems** are a must.

- Ensuring quality, safety and efficacy of medicines is done by **national and regional regulatory systems** which are an integral part of health systems.

- To be effective regulatory systems need tools – **science based quality standards and regulatory guidelines**. These are needed for each single product, and more in general, also for manufacture and distribution.
Streamlining regulatory work in WHO HQ

Director General (M. Chan)

HIS Cluster (M.P. Kieny)

EMP Department (Kees De Joncheere)

RHT (L. Rägo)

PAU (G. Forte)

PHI (Z. Mirza)

SAV (C. Ondari)

RSS (M. Ward)

TSN (D. Wood)

PQT (M. Macdonald)
Activities involve medicines, vaccines and other biological products, medical devices incl. in vitro diagnostics with 4 work streams/teams

- Technologies, Standards and Norms (TSN)
- Safety and Vigilance (SAV)
- Regulatory Systems Strengthening (RSS)
- Prequalification of medicines, vaccines and IVDs (PQT)
Usual perceptions may not help in making judgements about medicines …
Why medicines are special category of products?

- Consumers, patients and (even) health care workers have limited capacity to judge there

- **QUALITY**
- **SAFETY**
- **EFFICACY**

In public perception "quality" may involve all three
Are all medicines safe, effective and meet quality criteria?

- No, they are not
- Some are safe, but not effective or necessarily meet the quality criteria
- Some may be effective, meet quality criteria but are not safe
- Some meet quality criteria but are not necessarily safe or have any efficacy
Are quality medicines always safe?

- Yes and No

- Some safety parameters are determined by quality – these can be controlled by quality assurance

- Some safety parameters are determined by the intrinsic properties of active pharmaceutical ingredient(s) – these cannot be controlled completely by any means, including risk management plans and other measures

- For the last reason – all medicines that are effective may have adverse reactions (virtually no 100% safe medicine does exit)
What type of medicines we have? (1)

- Single source originator products – new medicines usually subject to IP and other exclusivity rights

- Multisource (generic) products – usually after exclusivity rights expire, or other mechanisms are used to overcome these
  - KEY – INTERCHANGEABILITY, more important THERAPEUTIC INTERCHANGEABILITY
  - ALL LITERATURE IS BASED ON ORGINATORS
  - No interchangeability – NEED FOR NEW SAFETY and EFFICACY DATA, NEW BOOKS HAVE TO BE WRITTEN
Other type of products
- Biological products including vaccines and blood products, including "biosimilars"
- Advanced therapies - derived from gene therapy, cell therapy or tissue engineering.
- Radiopharmaceuticals
- …
- Traditional (herbal) medicines
- Homeopathic medicines etc.
What type of regulations exist and how they differ?

- For innovator products proof of QUALITY, SAFETY (pre-clinical and clinical) and EFFICACY (clinical) is needed.

- For multisource (generic) products focus is on QUALITY, safety and efficacy data is referred to the originator product providing only evidence about therapeutic interchangeability (usually bioequivalence data \textit{in vivo}, also certain cases \textit{in vitro} comparative dissolution data).

- For traditional (herbal) medicines – focus on quality and safety as efficacy may not be possible to prove.
Regulatory requirements for multisource (generic) medicines

In short a generic medicine must:

(1) contain the same active ingredients as the innovator drug
(2) be identical in strength, dosage form, and route of administration
(3) have the same use indications
(4) be bioequivalent (as a marker for therapeutic interchangeability)
(5) meet the same batch requirements for identity, strength, purity and quality
(6) be manufactured under the same standards of Good Manufacturing Practice (GMP) as required for innovator products
Regulations: Global, Regional vs National

- National regulations still differ a lot
  - Especially for multisource/generic medicines

- What is International Conference on Harmonization (ICH) and what it is not?
  - Originally designed for harmonizing regulatory requirements for NEW, innovative medicines between EU, US and Japan
  - Recent news – ICH is reorganized, more regulators governed, less industry dominant and more open to other regulators

- Regional harmonization initiatives
  - EU fully harmonized, several other regions working on it

- Do global norms exist for generics?
  - WHO has comprehensive set of norms and standards for regulating generic medicines
Main medicines regulatory functions: all supported by different activities of WHO

- Licensing of the manufacture, import, export, distribution, promotion and advertising of medicines
- Assessing the safety, efficacy and quality of medicines, and issuing marketing authorization for individual products – focus on generics and vaccines, assessing clinical trials
- Inspecting and surveillance of manufacturers, importers, wholesalers and dispensers of medicines
- Controlling and monitoring the quality of medicines on the market
- Controlling promotion and advertising of medicines
- Monitoring safety of marketed medicines including collecting and analysing adverse reaction reports
- Providing independent information on medicines to professionals and the public

Quality assurance of medicines – not easy to understand, nor to "fly safe"
Challenges of quality assurance – increasing complexity of manufacture and supply chain

**Past**

- APIs
- Excipients
- Pharmacies
- Hospitals
- Packaging
- FPP

**Current**

- APIs
- Excipients
- M: Manufacturers/Suppliers
- M1
- M2
- M1a
- M2a
- Mx
- Mxa
- M1b
- FPP

**Pharmacies**

**Hospitals**

**Wholesalers**

**Distributors**

**Patients**
Why does quality matter?
Example of contaminated active ingredient
(see more at: http://www.who.int/medicines/publications/drugalerts/en/)

Information Exchange System

Alert No. 126

Contaminated Dextromethorphan Active Pharmaceutical Ingredient.

Increased vigilance is requested for batches of Dextromethorphan Active Pharmaceutical Ingredient produced by Konduskar Laboratories Private Limited, Kolhapur, Maharashtra India

On the 23rd November 2012, a serious incident occurred in Lahore, Pakistan which resulted in the death of approximately 20 persons and a number of other serious adverse reactions. All of those affected had consumed a cough syrup with the brand name Tyno, 120ml, locally produced by Reko Pharmaceutical with Dextromethorphan as the principal active pharmaceutical ingredient.
New WHO quality test specifications to address the problem

Dextromethorphan hydrobromide

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.605/Rev.1, August 2015).

The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidht@who.int.

[Note from the Secretariat. It is proposed the revise the monograph on Dextromethorphan hydrobromide.

In investigations leading to the proposed test for related substances it was found that impurity F may co-elute with impurity D. Manufacturers are invited to submit a reference substance of impurity D and to propose a chromatographic methods that is capable to separate also the two mentioned impurities.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

Molecular formula. C_{19}H_{25}NO.HBr.H_{2}O

Relative molecular mass. 370.3
Common misconceptions

- Quality – excessive reliance on certain isolated elements of regulatory systems e.g. **quality control testing**, without proper use of other regulatory tools and instruments as an integrated regulatory approach

- **Quality can not be tested into the product, BUT**

- **It has to be built into it !**
Convergence and harmonization of regulatory requirements

• Objective of drug regulation: TO IMPROVE AND PROMOTE PUBLIC HEALTH

• Convergence and harmonization should aim to diminish duplicative efforts, creates "common language", facilitate cooperation and access to medicines

• In case of convergence and harmonization of regulations the main objective should be:
  – MEASURABLE PUBLIC HEALTH GAINS

• There may be other gains, but these should be in the centre
Regulatory Convergence and harmonization initiatives

- Inter-regional, regional and sub-regional – ICH/IPRF, ICMRA, PIC/S, IGDRP, APEC, Pan American Network for Drug Regulatory Harmonization (PANDRH), ASEAN, AMRHI with EAC marching, SADC, ZaZiBoNa, Gulf Cooperation Council etc….

- All not harmonized …– Good Harmonization and Convergence Practice (GHP) needed?
  - Different organization – with or without strong secretariat
  - Different involvement of industries and other parties
  - Different in terms of implementation – some focused on implementation, others rather focused on convergence of regulatory thinking
  - Different focus technical areas/products
  - …
Timely access to (hopefully) better medicines ladder

Good Decision Making Practices

Good Review Practices based on CTD, alignment and effective cooperation and worksharing

Harmonization and convergence of technical requirements in conjunction with harmonized training principles and model core curricula for regulators

Applicable modern laws and enabling legal system

General Good Governance in Public Sector, including transparency and accountability
Regulatory system strengthening for medical products

WHA67.20 – first time system approach only in 2014!
WHA67.20 Urges Member States, among others:

(1) to strengthen national regulatory systems, including – as appropriate and voluntarily – by:

(a) undergoing self-evaluations, including with WHO support, to identify the strengths and opportunities for improvement in regulatory system functions, as a first step towards formulating plans for regulatory system strengthening, including through WHO-coordinated institutional development plans; …

(e) developing needed competencies as an integral part of, although not limited to, the health workforce, and encouraging the development of the regulatory field as a profession;

(f) facilitating the use of relevant guidance and science-based outputs of WHO expert committees and good regulatory practices at the national, regional and international levels; …

(2) to engage in global, regional and subregional networks of national regulatory authorities, as appropriate, recognizing the importance of collaboration to pool regulatory capacities to promote greater access to quality, safe, efficacious and affordable medical products;

(3) to promote international cooperation, as appropriate, for collaboration and information sharing, including through electronic platforms; …

(10) to identify the need to strengthen regulatory system capacity, collaboration and cooperation in the technically complex areas where substantial gaps may still exist, such as the regulation of biotherapeutic products, blood products, and in vitro diagnostics;
WHA67.20 requests the Director-General of WHO, among others:

(1) to continue to support Member States upon their request in the area of regulatory system strengthening, including, as appropriate, by continuing to:

(a) evaluate national regulatory systems; …

(e) provide technical support to national regulatory authorities and governments;

(2) to continue to develop appropriate norms, standards and guidelines, including taking into account national, regional and international needs and initiatives, in accordance with WHO principles; …

(5) to promote the greater participation of Member States in existing international and regional initiatives for collaboration and cooperation in accordance with WHO principles and guidelines; …

(10) to increase support and guidance for strengthening the capacity to regulate increasingly complex biological products with the focus on biotherapeutic products, blood products and associated in vitro diagnostics, and, where appropriate, on new medicines for human use based on gene therapy, somatic-cell therapy and tissue engineering;
Medicines quality assurance

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. With regard to pharmaceuticals, quality assurance can be divided into major areas: development, quality control, production, distribution, and inspections.

The Medicines Quality Assurance Programme, which is part of Quality and Safety: Medicines of the Essential Medicines and Pharmaceutical Policies Department, contributes to public health by enabling quality medicines to reach patients through:

- developing norms, standards and guidelines for quality assurance
- developing The International Pharmacopoeia
- establishing International Chemical Reference Substances (ICRS)
- collaborating with numerous stakeholders
- providing country support

About quality assurance
WHO quality assurance activities;
Advantage of WHO standards;
Partners

Expert Committee on Specifications for Pharmaceutical Preparations (ECSSP)

The International Pharmacopoeia
Free online access; current work plan; current projects

ICRS
International Chemical Reference Substances (ICRS)

About us
Expert committee
International pharmacopoeia
International Chemical Reference Substances (ICRS)
Current projects
Training & Knowledge centre
Publications

Highlights
WHO Expert Committee on Specifications for Pharmaceutical Preparations

TRS 992 - Forty-ninth report
Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

In 1968, during the 16th World Assembly the 16.36 resolution called for “a systematic collection of information on serious adverse drug reactions during the development and particularly after medicines have been made available for public use”. This led to the formation of the WHO Programme for International Drug Monitoring (PIDM).

WHO promotes PV at country level. Initially the WHO PIDM members consisted of 10 countries. As of September 2015, 122 countries have joined the WHO PIDM, and in addition 29 associate members are awaiting full membership. List of WHO programme members
Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) Medical Products

http://www.who.int/medicines/regulation/ssffc/en/

Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) Medical Products

The existence of substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products is an unacceptable risk to public health. They affect every region of the world, and medicines from all major therapeutic categories have been reported, including vaccines and diagnostics. They harm patients and undermine confidence in medical products, healthcare professionals and health systems. WHO is working with stakeholders to minimize the risks from SSFFC medical products by collecting data and transferring knowledge and good practices to countries.

- SSFFC Medical Products - Background
- WHO Medical Product Alert

SSFFC Medical Products Activities

| WHO Member state mechanism | Surveillance and monitoring system | Regulatory Strengthening and capacity building |

Frequently asked questions

Scope, Scale and Harm | WHO Activities | Advice to Patients and Consumers

- Q&A’s on scope, scale and harm
Assessing national medicines regulatory systems

Assessing national medicines regulatory systems National Medicines Regulatory Authorities (MRAs) are responsible for the regulation and control of medical products such as medicines, vaccines, blood products and medical devices. They contribute to promoting and protecting public health by ensuring that:

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

Intensification of international commerce and increasing technological complexity of manufacturing and product specifications have created additional challenges for national regulatory authorities and manufacturers, particularly to those of developing countries. This requires that national regulatory capacity is regularly assessed, areas of weakness are identified and appropriate, necessary measures are taken. Assessments are conducted using a standardized WHO Data Collection Tool for the review of Drug regulatory Systems.

Objective of assessments of national regulatory systems
PQ creates a visitor feedback survey to improve its website - click button below to enter survey

Cadila's isoniazid prequalified

Emergency Use Assessment and Listing (EUAL) procedure

Electronically dispatched letters to replace paper-based assessment letters

WHO tackles snake bites to spur production of antivenoms

2015 joint WHO-UNICEF-UNFPA meeting with pharmaceutical and

http://www.who.int/medicines/icdra/en/

The International Conference of Drug Regulatory Authorities (ICDRA) is a strategic opportunity to drug regulatory authorities to become closer, discuss trends and challenges, but also to share solutions found at different parts of the globe. ICDRA provides a forum to determine priorities for action in national, regional and international regulation of medicinal products. The Pre-ICDRA conference offers a unique opportunity for industry to engage in this discussion. At the end of the day, regulatory authorities, WHO and industry, all benefit from the regulatory convergence facilitated by ICDRA.
African Medicines Registration Harmonization Initiative (AMRH)

- African Medicines Registration/Regulatory Harmonization Initiative (AMRHI)
  - Partners: BMGF, DFID, CHAI, NEPAD and WHO; World Bank manages the trust fund to finance the activities
  - First regional economic block to start harmonization – East African Community (EAC)
  - EAC Technical Working Groups: Medicines Evaluation and Registration, Good Manufacturing Practices (GMP), Information management systems (IMS) and Quality Management System (QMS) – WHO provides technical support

- WHO in 2010-11 and 2013-14 has organized two series of joint assessments of priority product dossiers submitted simultaneously to EAC countries and to the WHO Prequalification Programme.
  - As a result of these joint assessments 7 products were successfully prequalified by WHO and subsequently registered in EAC countries within the timelines which were much shorter than usually
  - Joint assessments - efficient way of getting priority products authorized in several countries with shorter timelines (more in WHO Drug Information Vol. 28 No. 1, 2014)
ZaZiBoNa Initiative

- Initiative taken by heads of agencies in Zambia, Zimbabwe, Botswana and Namibia

- Involves cooperation and joint activities in order to minimize duplications, save resources and make registration process more efficient

- Close cooperation with and support from WHO

- Good experience with WHO collaborative procedure – applies for WHO prequalified product in which case national authorities rely on WHO scientific assessment
Ebola response

- Assisted assessments of Ebola vaccine clinical trial applications
- Assessing Ebola diagnostics – WHO PQT has listed 6 diagnostics
- EUAL procedures for Dx, vaccines and Rx
Concluding remarks

- NOT ALL national regulators can themselves do all in a timely manner and decisions have to be made nationally on which areas to focus and build capacity, and in which areas rely on other regulators work.

- Harmonization and convergence alone cannot help, but can form a solid basis for the new regulatory paradigm to evolve in the future -

  Doing locally what nobody is doing/can do for you, (added value), cooperate and rely in a transparent systematic way on other regulatory decisions, and decide in which area you invest to specialize to be a "world class player" contributing to the Regional/Global Regulatory Network.