Updated WHO guidelines - implications for manufacturers and procurers

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Technologies Standards and Norms

www.who.int
International norms and standards benefits

For manufacturers: one global approach for dossier submissions and inspections

For procurers: receiving standardized information and enabling data sharing

For NRAs: data sharing, reliance, convergence and collaboration

For patients: enabling access to medicines

For all: Saving time and money
Access and availability to medicines
WHO Global Norms and Standards – Expert Committees

- Established by World Health Assembly or Executive Board to develop international norms and standards
- Official Advisory Body to Director-General of WHO
- Governed through rules and procedures
- Participation in Expert Committee (EC) meetings:
  - Members ("Experts") selected from WHO Expert Advisory Panels
  - Technical advisers
  - Observers:
    - international organizations,
    - NGOs,
    - professional associations…
Outcome of the WHO Expert Committee

• **Report of the WHO Expert Committee:**
  
  • Summarizes discussion
  
  • Provides recommendations to WHO + Member States
  
  • Includes newly adopted guidelines + GXPs
  
  • Is presented to WHO Governing Bodies for final comments, endorsement and implementation by Member States

constitutes **WHO technical guidance**
WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)

Covers today WHO’s guidance for medicines quality assurance:

- Development
- Production
- Quality Control
- Quality related regulatory guidelines
- Inspection
- Distribution and supply

lifecycle of medicines

from development to delivery to the patient
ECSPP - WHO guidance texts and guidelines – medicines quality assurance

Total general QA – (without Ph.Int.):
Approx. **100** CURRENT official WHO guidance texts and guidelines for medicines quality assurance and related regulatory standards

- 11 (5 updates, 6 new published in 2018)
- 9 (5 updates, 4 new published in 2019)
- 13 (6 updates, 7 new published in 2020)

Website:
http://www.who.int/medicines/areas/quality_safety/quality_assurance/en
How are new monographs, norms, good practices and guidelines developed?

- Developed in response to recommendations + requests by WHO Governing bodies, ICDRA, ECSPP, other WHO Programmes or in response to major public health needs, following strict rules and procedures

- Widely circulated for public consultation, drafts and final texts available on the web site: http://www.who.int/medicines/areas/quality_safety/quality_assurance

Your input is wanted!!

- Reviewed by expert groups and discussed in annual Expert Committee meetings

  if consensus, adopted by the ECSPP

  recommended by Director General to Member States
Where can you find “Current projects”?  

WHO Governing bodies ...
53rd WHO Expert Committee on Specifications for Pharmaceutical Preparations TRS 1019 – presented May 2019
53rd ECSPP meeting – new guidelines → implications

- Procedure for development of the WHO medicines quality assurance guidelines
  → Transparency regarding WHO guidelines development

- Guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems – illustrative part
  → Examples and explanations for enforceable GMP text for inspections

- Revised guidance on good manufacturing practices for validation, including the
  • general main text, analytical procedure validation, validation of computerized systems and qualification
  → Enforceable standardized GMP texts for inspections
In the area of interchangeability of multisource medicines:

- Set of priorities agreed for development of a proposal to waive in vivo bioequivalence requirements for medicines included in WHO Model Lists of Essential Medicines

- Outcome of a pilot study was confirmed

- Protocol to conduct equilibrium solubility experiments for the purpose of biopharmaceutics classification system-based classification of active pharmaceutical ingredients for biowaiver was adopted

  → Standardization of procedures when determining APIs qualifying for “biowaiver”

  → Provision of advice how to reduce number of clinical studies for bioequivalence/interchangeability of generic medicines
Such BCS-based classification of APIs promotes access to essential medicines on multiple levels

<table>
<thead>
<tr>
<th>Regulators</th>
<th>Ethics</th>
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<tbody>
<tr>
<td>▪ Optimize regulatory procedures</td>
<td>▪ Reduce human exposure in clinical trials</td>
</tr>
<tr>
<td>▪ Decrease the regulatory burden, diff. regul. capacity</td>
<td>▪ Lower burden for Ethic Committees</td>
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<tr>
<td>▪ Optimize the use of HR, focus on higher-risk products</td>
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<tr>
<th>Patients</th>
<th>Payers</th>
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<tbody>
<tr>
<td>▪ Quicker access to multisource products</td>
<td>▪ Impact on final cost of multisource products (?)</td>
</tr>
<tr>
<td>▪ Potential impact on final costs</td>
<td>▪ Optimization of financial resources</td>
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<tr>
<th>Manufacturers</th>
<th>Procurement (UN/Gov./NGOs)</th>
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<tbody>
<tr>
<td>▪ Reduce time to develop multisource products</td>
<td>▪ Facilitate international procurement</td>
</tr>
<tr>
<td>▪ Reduce costs to develop multisource products</td>
<td>▪ Increase the use of harmonized regulatory tools</td>
</tr>
<tr>
<td>▪ Support post approval changes</td>
<td>▪ Replace the WHO list published in 2006</td>
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53rd ECSPP meeting – new guidelines

→ implications

- Guidelines on import procedures for pharmaceutical products
  - Standardization of import procedures
  - Promotion of efficiency and easing checking and handing of medical products for import and collaboration of interested parties

- Good practice guidance document on implementing the collaborative procedures
  - Transparency and Standardization on “How to proceed”
  - Provision of models and examples of review, checklists, model approach and model letters
54th ECSPP meeting
WHO Governing Bodies

... report of 54th WHO Expert Committee on Specifications for Pharmaceutical Preparations – to be presented in May 2020
What is the outcome of 54th ECSPP meeting?

- 13 new and revised general medicines quality assurance and regulatory guidance texts
- 13 new and revised specifications for active substances and specific dosage forms
- 2 new and revised general chapters for inclusion in *The International Pharmacopoeia*
- 6 new International Chemical Reference Substances
Procedure for the development of monographs and other texts for inclusion in The International Pharmacopoeia
→ Transparency regarding WHO specifications’ development

IAEA/WHO guidelines on GMP for radiopharmaceuticals
→ Enforceable standardized GMP text for inspections

Production of water for injection (WFI) by means other than distillation
→ Harmonization and standardized approach globally allowing new methods
Developed upon request by inspectors to respond to compliance issues in the laboratories and with new computerized procedures:

- **Good chromatography practices - **NEW global GXP

  → Enforceable standardized GMP text
Quality management system requirements for national inspectorates
→ Transparency and opportunity for standardization

Points to consider for manufacturers and inspectors:
Environmental aspects of manufacturing practices for the prevention of antimicrobial resistance
→ Opportunity for “green” manufacturing practices
→ Preparation for possible future environmental inspections
Combining two existing GXPs into one, *Good Storage Practices* and *Good Distribution Practices* for medical products, enlarging the scope

- **Good storage and distribution practices**
  - Enforceable standardized GMP text for inspections
Points to consider on remaining shelf life of medical products upon delivery

Provision of guidance and approach with aim to:
- facilitate national authorization for importation
- prevent wastage and delays
- ensure sufficient stock is available with remaining shelf-life
- prevent stock-out situations
- standardize the requirements for remaining shelf-life upon delivery (examples)
UNFPA-WHO Prequalification programme guidance for contraceptive devices: Male latex condoms, female condoms and intra-uterine devices
→ Harmonization and standardized approach for prequalification processes

UNFPA-WHO Technical specification for male latex condoms
→ Harmonization and standardized approach globally

UNFPA-WHO Specifications for plain lubricants
→ Harmonization and standardized approach globally
WHO “Biowaiver List” - Proposal to waive in vivo bioequivalence requirements for WHO model list of essential medicines immediate-release, solid oral dosage forms
   → Standardization of procedures when determining APIs qualifying for “biowaiver”
   → Provision of advice how to reduce number of clinical studies for bioequivalence/interchangeability of generic medicines

Guideline on the implementation of quality management systems for national regulatory authorities
   → Transparency and opportunity for standardization
The International Pharmacopoeia

• Is based on decision by World Health Assembly

• Contains analytical methods and specifications for
  ✓ active pharmaceutical ingredients (API)
  ✓ finished pharmaceutical products
  ✓ Excipients
  ✓ radiopharmaceuticals

• Focuses on medicines
  ✓ Model List of Essential Medicines
  ✓ Invitations to submit EOI for product evaluation to Prequalification, WHO/UN specific disease programmes

→ Break-out session on Wednesday 4 December 2020 12:45 -14:15:
  The benefits of The International Pharmacopoeia for manufacturers
The International Pharmacopoeia

Outcome of 54th ECSPP meeting

• Workplan 2019–2020

• Polymorphism (new)

• Capillary electrophoresis (revision)

• Water for injections (revision)

• **Omissions**: - Undue toxicity (including the whole of Chapter 3.7 and all reference to undue toxicity test in monographs on kanamycin acid sulfate and kanamycin monosulfate); - Chlorpheniramine hydrogen maleate (monograph); and Chlorpheniramine hydrogen maleate tablets (monograph)
The International Pharmacopoeia

Specifications

For antimalarial medicines

- doxycycline hyclate (revision), doxycycline capsules (revision), doxycycline tablets (revision)
- pyrimethamine (revision), pyrimethamine tablets (new)

For antibacterials, including antituberculosis medicines

- ciprofloxacin hydrochloride (revision), ciprofloxacin tablets (new)
- levofloxacin (revision), levofloxacin tablets (revision)

For antiviral medicines, including antiretrovirals

- atazanavir sulfate (revision)
- sofosbuvir (new), sofosbuvir tablets (new)
Advantages of WHO's international norms and standards

**Ready for use for adoption** in national legalization, including step-wise or need-based

**Enabling collaboration** with other authorities and agencies

**Enabling work-sharing**, e.g. when used in regional regulatory networks and by procurement agencies

**Enabling reliance** on decisions from other regulatory authorities, laboratories and by procurement agencies

**Facilitating sourcing** of pharmaceutical starting materials and finished pharmaceutical products
WHO priorities

Coherent approach for sets of norms and standards and their implementation

Global applicability – no "double standards"

Filling the gap and addressing need of Member States
WHO Governing Bodies

World Health Assembly (WHA)
- Meets in May (annually)
- All 194 WHO Member States

Executive Board (EB)
- Executive Board meets in January + after WHA in May
- Main functions of EB:
  - Advise WHA
  - Facilitate its work
  - Prepares agenda of the next Assembly
Director-General’s priorities
Draft 30th general programme of work (GPW) 2019–2023

Mission

Promote health – keep the world safe – serve the vulnerable

Strategic Priorities (and goals)

Ensuring healthy lives and promoting well-being for all at all ages by:

Achieving universal health coverage – 1 billion more people benefitting from universal health coverage

Addressing health emergencies – 1 billion more people better protected from health emergencies

Promoting healthier populations – 1 billion more people enjoying better health and well-being

Strategic shifts

Stepping up leadership – diplomacy and advocacy; gender equality, health equity and human rights; multisectoral action; finance

Drive public health impact in every country – differentiated approach based on capacity and vulnerability

Policy dialogue – to develop systems of the future

Strategic support – to build high performing systems

Technical assistance – to build national institutions

Service delivery – to fill critical gaps in emergencies

Focus global public goods on impact – normative guidance and agreements; data, research and innovation

Organizational shifts

- Measure impact to be accountable and manage for results
- Reshape operating model to drive country, regional and global impacts
- Transform partnerships, communications and financing to resource the strategic priorities
- Strengthen critical systems and processes to optimize organizational performance
- Foster culture change to ensure a seamless, high-performing WHO
“**WHO will step up its global leadership:** Major changes in health come from combining normative and technical work with advocating for high-level political support. This will support leadership at every level of the Organization.”

“**WHO will drive impact in every country:** WHO will become more operational by: delivering services in a limited number of fragile States; providing technical assistance in these and additional countries; providing strategic support in many countries; and supporting policy dialogue in all countries.”

“**WHO will strengthen its normative work:** This is a unique feature of WHO and a source of its comparative advantage. WHO will focus its normative work more towards impact and supporting country needs.”

“**WHO will health emergencies, and will also establish “flagships” to address key issues such as climate change in small island States, antimicrobial resistance, noncommunicable focus on the strategic priorities of UHC [Universal Health Coverage] and diseases including mental health, and human capital.”**
Norms and Standards

WHO's mandate is (inter alia) to

“develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products”

(Article 2, WHO Constitution)
When does the ECSPP start development of a guideline/guidance?

Based on recommendations by:

- **World Health Assembly resolutions** (e.g. WHA1.27 - PhInt, WHA 20.34, GMP - Good manufacturing practices)

- **Executive Board resolutions** (e.g. EB37.R9 delegating certain functions of INN Programme to DG based on advice from Experts)

- **International Conference of Drug Regulatory Authorities** (e.g. 10th +11th ICDRA – FDC guidelines + Certification Scheme for pharmaceutical starting materials moving into international commerce)

- **International organizations and UN agencies** (e.g. MQAS)

- **Other WHO programmes** and clusters (e.g. necessity for quality control specifications for specific medicines of major public health interest)

- **Expert Committee** (e.g. revision of general methods included in The International Pharmacopoeia)
Who are the WHO Partners in the Expert Committee on Specifications for Pharmaceutical Preparations?

- National and regional authorities

- International organizations (e.g. IAEA, UNAIDS, UNFPA, UNICEF, WCO, WIPO, World Bank, WTO)

- International professional and other associations, non-State actors (NGOs) (e.g. FIP, IFPMA, IGPA, WSMI)

- Members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations
Who are the WHO Partners in the Expert Committee on Specifications for Pharmaceutical Preparations (2)?

- Specialists from all quality assurance related areas, including regulatory, university, industry
- WHO Collaborating Centres (official nomination process) – usually national quality control labs
- Pharmacopoeia Authorities and Secretariats, national institutions and institutes
- Regional and interregional regulatory groupings (e.g. APEC, ASEAN, GCC, ICH, PANDRH)
Procedures governing the ECSPP

General procedures and processes of Expert Committee guided by rules and procedures set out in:

- WHO’s eManual
- Basic legal texts of WHO


Procedures governing the ECSPP
