QUAMED
Quality Medicines for All

Good Manufacturing Practices; Model Quality Assurance System for Procurement Agencies; Prequalification

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4th July 2016

Norms and standards

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1. Weight and length are measured against “standards” (kilo and meter) → quality of medicines is measured against “norms and standards”.
2. Some international references:
   - International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (***ICH***)
   - Pharmaceutical Inspection Cooperation Scheme (***PIC/S***)
   - World Health Organization (***WHO***)
   - International Pharmacopoeia (http://apps.who.int/phint/en/p/about/)
   - European Directorate Quality Medicines (***EDQM***) (Eur. Pharmacopoeia)
   - European Medicine Agency ***(EMA***)

Our references

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- WHO Technical Report Series. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Technical Report Series 996, 50th Report, 2016, and further updates.
  http://www.who.int/medicines/publications/pharmprep/trs_996/en/
- WHO, UNICEF, UNDP, World Bank. Model Quality Assurance System for Procurement Agencies. In: Annex III of the WHO technical report series 98648th report, 2014.
  http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/ISBN9789241209861-TRS986.pdf?ua=1
- PREQUALIFICATION PROGRAMME. A United Nations Programme managed by WHO. http://apps.who.int/prequal/

Quality assurance (QA)

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The concept of QA

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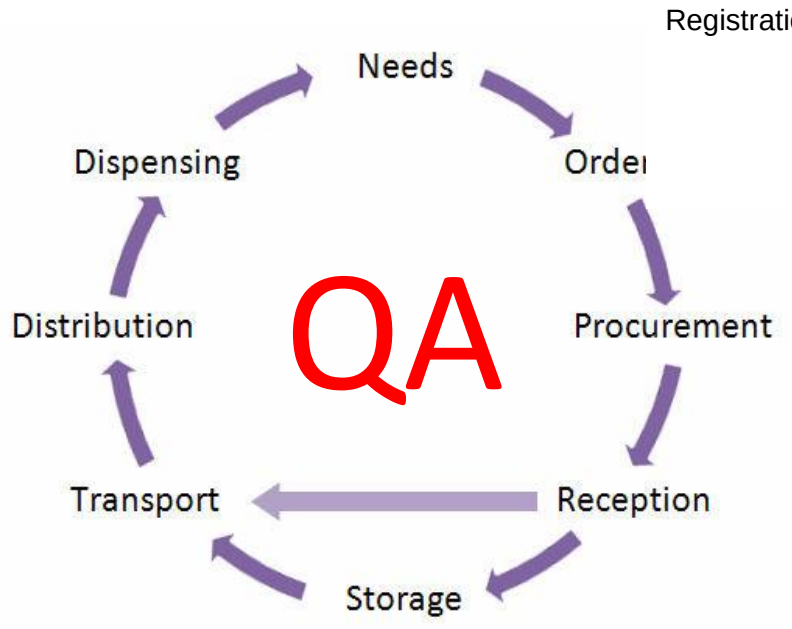
QA is a RISK MANAGEMENT system.
In the pharmaceutical sector, it is essential for protecting individual and community health



All arrangements/activities to assure that medicines are safe, effective, of assured quality for their intended use. Focus on:

- Manufacturing site
- Product
- Good distribution practices

QA vs QC

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"Quality assurance"

VS

"Quality control"

Assessment of the manufacturing site

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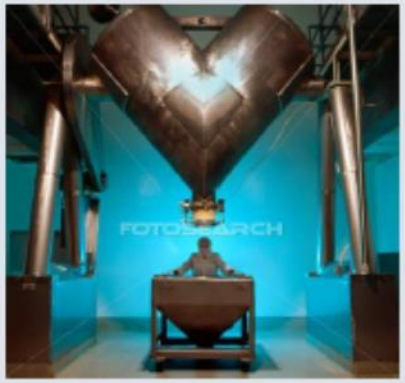

Assessment of the manufacturing site (1)

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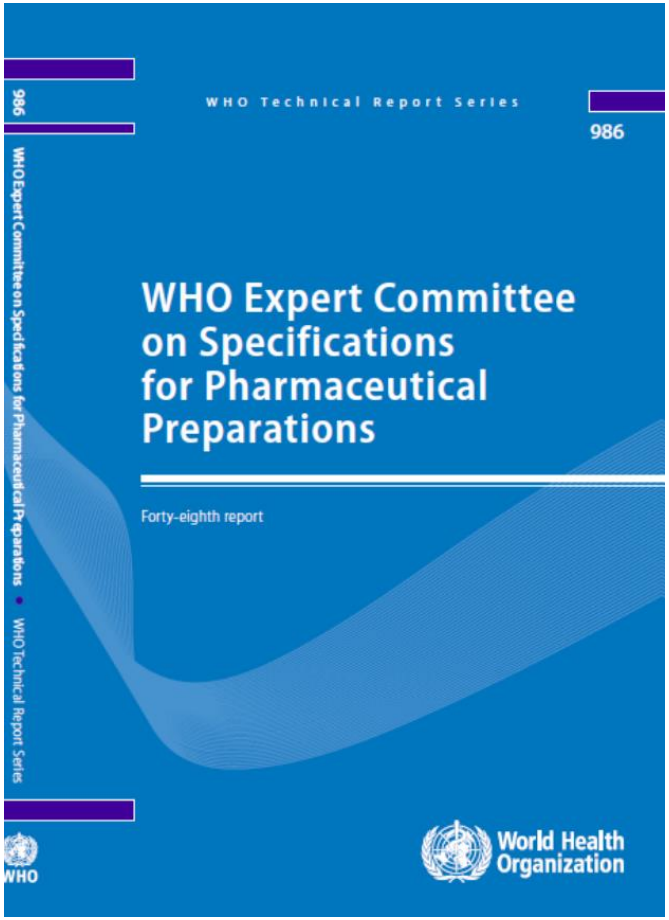
- Good Manufacturing Practices (***GMP***)
  - General principles
  - Principles for APIs, excipients, FPPs
  - Principles for specific products (e.g. sterile, biologicals, radio-pharmacy, hormones…)
- Good Manufacturing Practices (***GMP***)
  - manufactures
  - auditors/inspectors
  - homogenous (intra-batch) quality
  - reproducible (inter-batch) quality



Assessment of the manufacturing site (2)

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- 1. Quality system: risk management & product quality review
- 2. Good manufacturing practices for pharmaceutical products
- 3. Sanitation and hygiene
- 4. Qualification and validation
- 5. Complaints
- 6. Product recalls
- 7. Contract production, analysis and other activities
- 8. Self-inspection, quality audits and suppliers' audits and approval
- 9. Personnel
- 10. Training
- 11. Personal hygiene

Assessment of the manufacturing site (3)

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- 12. Premises
- *ancillary areas , storage, weighing, production, QC*
- 13. Equipment
- 14. Materials
- *starting/packaging materials, intermediate/bulk/finished products, rejected, recovered, reprocessed and reworked materials, recalled products, returned goods, reagents and culture media, reference standards, waste materials*
- 15. Documentation
- 16. Good practices in production
- *cross-contamination, bacterial contamination; processing, packaging operations*
- 17. Good practices in quality control
- *starting materials, intermediate, bulk and finished products; test requirements; batch record review; stability studies; references*

Assessment of the manufacturing site (4)

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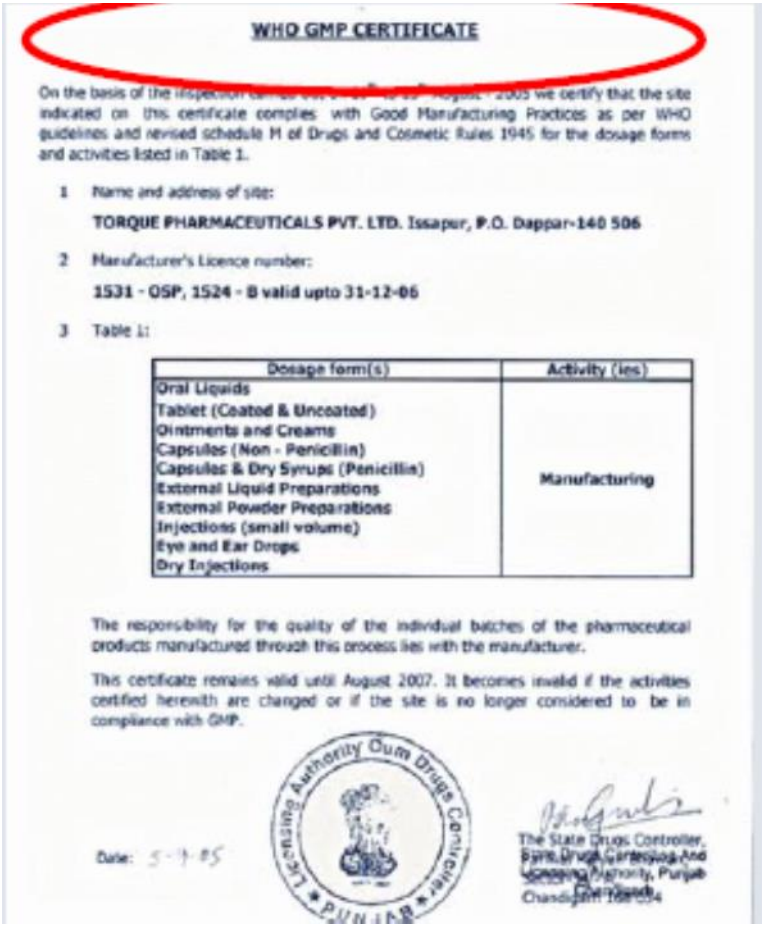
- GMP certificate = proof of compliance with GMP
- Issued by a national regulatory authority (NRA)
- *Not all national standards are equally stringent*
- WHO proposes a format for GMP certificate, but *does not issue GMP certificates!*



WHO GMP CERTIFICATE

On the basis of the inspection [illegible] we certify that the site indicated on this certificate complies with Good Manufacturing Practices as per WHO guidelines and revised schedule M of Drugs and Cosmetic Rules 1945 for the dosage forms and activities listed in Table 1.

1 Name and address of site:

TORQUE PHARMACEUTICALS PVT. LTD. Issapur, P.O. Dappar-140 506

2 Manufacturer's Licence number:

1531 - OSP, 1524 - B valid upto 31-12-06

3 Table 1:

Dosage form(s)	Activity (ies)
Oral Liquids Tablet (Coated & Uncoated) Ointments and Creams Capsules (Non - Penicillin) Capsules & Dry Syrups (Penicillin) External Liquid Preparations External Powder Preparations Injections (small volume) Eye and Ear Drops Dry Injections	Manufacturing

The responsibility for the quality of the individual batches of the pharmaceutical products manufactured through this process lies with the manufacturer.

This certificate remains valid until August 2007. It becomes invalid if the activities certified herewith are changed or if the site is no longer considered to be in compliance with GMP.

Licensing Authority Qum Drugs Controller PUNJAB

Date: 5-7-05

The State Drugs Controller, [illegible] Authority, Punjab

Assessment of the product dossier

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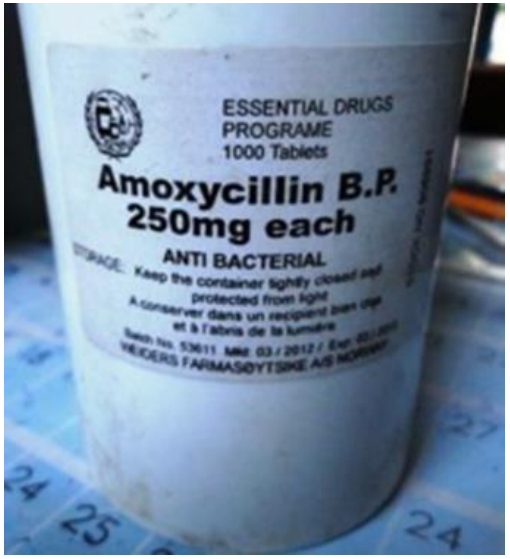

Assessment of the product dossier (1)

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- ***GMP-compliance***
  - Proof of the *general capacity* to appropriately produce medicines
  - Not product-specific
- ***GMP-inspections***
  - Focus on products/dosage form/production lines
  - *A manufacturer can be able to produce a quality-assured tablet of paracetamol, and unable to produce a quality-assured IV fluid*

Assessment of the product dossier (2)

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- Active Pharmaceutical Ingredient(s) (API)
- Finished Product (FPP)
- Stability
- Safety and efficacy /bioequivalence
- Packaging
- Labeling, leaflet

Assessment of the product dossier (3)

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- **APIs** are a critical element of quality, and of *price* of FPP
  - Complex, multiple-step production processes
  - Pharmacopoeial specifications
  - Concentration, purity and stability
  - Authorized *and* GMP-compliant manufacturing site
- **APIs'** quality is assured by the FPP's manufacturer:
  - Audit of manufacturer, QC, monitoring
  - Technical file submitted to NRA (manufacturing process and specifications)

Assessment of the product dossier (4)

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Marketing authorization, granted by NRA

- A medicine can be:
  - Registered AND marketed in the country of origin
  - Registered, NOT marketed in the country of origin
  - Manufactured for EXPORT ONLY

Assessment of the product dossier (5)

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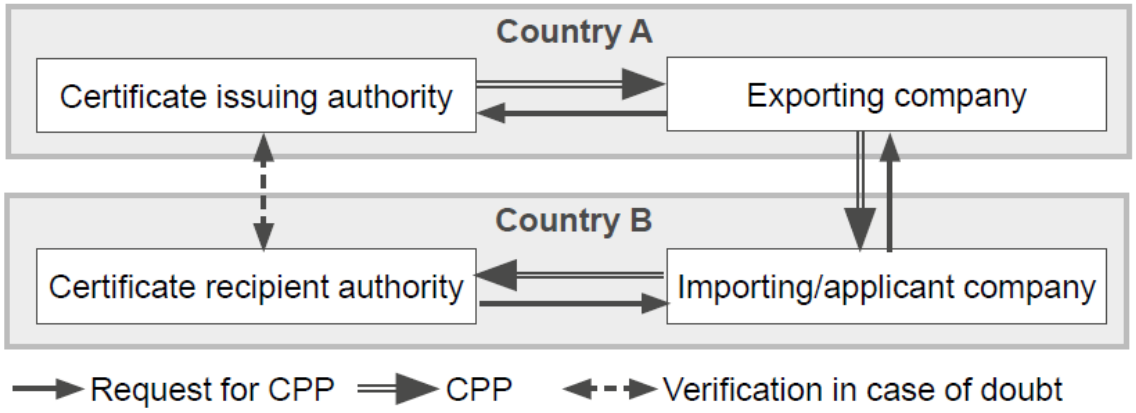
WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

- To facilitate international trade in pharmaceutical products
- A non-mandatory, *administrative* instrument issued by a NRA to the NRA in the recipient country, to certify the GMP-certificate and the marketing status of a FPP/API *in the issuing country*



http://www.who.int/entity/medicines/areas/quality_safety/regulation_legislation/certification/contacts/en/index.html
http://www.who.int/entity/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index.html

WHO Certification Scheme: Q&A WHO Drug Information Vol. 30, No. 3, 2016

Assessment of the product dossier (6)

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Specifications and CoA

- Pharmacopoeial monographs (US, British, International, nationals)
- Key-information on efficacy (API concentration, dissolution rate…) and safety (sterility, absence of toxic degradation products….)
- Technical basis for quality control (QC), to be performed against the specifications stated by the manufacturer
- In absence of pharmacopoeia : *in-house* specifications + methods of analysis + validation + justification of limits
- Certificate of analysis (CoA): a proof of the quality control of *each released batch*

Assessment of the product dossier (7)

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Stability

- It depends on the nature of API, formulation, climatic conditions (temperature, humidity, light)
- Poor stability: loss of activity, degradation products, contamination

- *Shelf life*: time interval during which a medicine is expected to preserve its properties *within the specified limits*
- Instructions such as «store in a cool dry place» are not acceptable

Assessment of the product dossier (8)

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- Shelf-life and storage conditions are established for each product, based on accelerated and real time studies
- WHO: 5 climatic zones, with parameters for stability studies

Climatic zone	Definition	Criteria Mean annual temperature measured in the open air/ mean annual partial water vapour pressure	Long-term testing conditions
I	Temperate climate	≤ 15 °C / ≤ 11 hPa	21 °C / 45% RH
II	Subtropical and Mediterranean climate	> 15 to 22 °C / > 11 to 18 hPa	25 °C / 60% RH
III	Hot and dry climate	> 22 °C / ≤ 15 hPa	30 °C / 35% RH
IVA	Hot and humid climate	> 22 °C / > 15 to 27 hPa	30 °C / 65% RH
IVB	Hot and very humid climate	> 22 °C / > 27 hPa	30 °C / 75% RH

Table 2
Stability conditions for WHO Member States by Region

Member State	Stability conditions Confirmed long-term testing condition
Regional Office for Africa (AFRO)	
Algeria	[25 °C/60% RH][a]
Angola	[30 °C/65% RH][a]
Benin	[30 °C/65% RH][a]
Botswana	[25 °C/60% RH][a]
Burkina Faso	30 °C/60% RH[a]
Burundi	[30 °C/65% RH][a]
Cameroon	30 °C/75% RH[a]
Cape Verde	[30 °C/65% RH][a]
Central African Republic	30 °C/75% RH[a]
Chad	[30 °C/65% RH][a]
Comoros	[30 °C/65% RH][a]
Congo	[30 °C/65% RH][a]
Côte d'Ivoire	[30 °C/65% RH][a]
Democratic Republic of the Congo	[30 °C/65% RH][a]
Equatorial Guinea	[30 °C/65% RH][a]
Eritrea	[30 °C/65% RH][a]
Ethiopia	[30 °C/65% RH][a]
Gabon	[30 °C/65% RH][a]
Gambia	30 °C/65% RH[a]
Ghana	30 °C/75% RH[a]
Guinea	[30 °C/65% RH][a]
Guinea-Bissau	[30 °C/65% RH][a]
Kenya	[30 °C/65% RH][a]
Lesotho	30 °C/75% RH[a]
Liberia	[30 °C/65% RH][a]
Madagascar	30 °C/65% RH[a]
Malawi	25 °C/60% RH[a]
Mali	[30 °C/65% RH][a]

If the study demonstrates the stability at	The label must indicate
25°C & 60% Relative Humidity	Store below 25°C
30°C & 65% Relative Humidity	Store below 30°C

Assessment of the product dossier (9)

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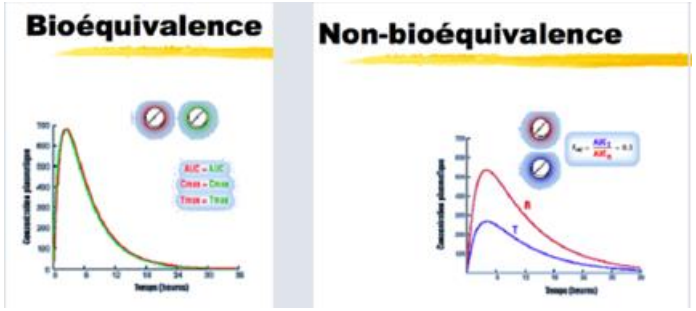
Bioequivalence

- Safety and efficacy of API are established for the *innovator* product
- *Generics* are approved based on proof of interchangeability or therapeutic equivalence (bioequivalence studies)
- Bioequivalence: absence of a significant difference in the rate and extent to which the API becomes available at the site of drug action when administered at the same dose.



Introduced in US (1984), now a widely accepted regulatory standard

WHO Drug Information Vol. 30, No. 3, 2016

Assessment of the product dossier (10)

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- BE is not always needed:
  - Exceptions: IV, IM, SC solutions, gas, ophthalmic solutions, inhalers, etc.
  - For some products, it can be evaluated *in vitro* (comparative dissolution profile)
- *In vivo* studies require specific skills and competence and are expensive. Frauds have been frequently reported

Inspection program (retrospective) on the bioequivalence studies by the French Regulatory Agency (1995 – 2007)

Evaluations performed	97 dossiers
Inspections	67 sites (CRO, manufacturers)
Geographic location	20 countries / 4 continents
Critical mistakes	53 dossiers (54.64%)
Frauds	27 dossiers (27.84%)

Source : Dr Olivier Leblaye : Agence Française du Médicament) - 2007

Assessment of the product dossier (11)

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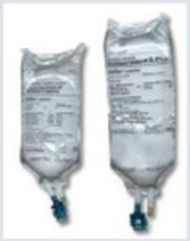
Primary packaging

- Direct contact with FPP (physical and/or chemical interaction!)
- It must preserve the integrity of the medicine during shelf-life
  - Stability studies are «packaging specific»
  - Fragile API require robust primary packaging, e.g. artemisinin derivatives are stable in 100% aluminum blisters (ALU/ALU)

PVC/ALU blisters for tablets

HDPE bulk pacaging for tablets

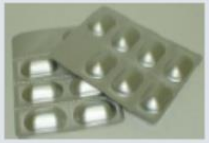
Glass ampoules



Plastic bags for infusions

Aluminium tubes for creams and ointments

Blister ALU/ALU



Blister PVC/ALU

Assessment of the product dossier (12)

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Secondary packaging

- It contains critical information!

Tertiary packaging

- It requires adequate specifications, especially for long-distance shipment.
- Poor-quality cartons affect quality (crashing, humidity)

Assessment of the product dossier (13)

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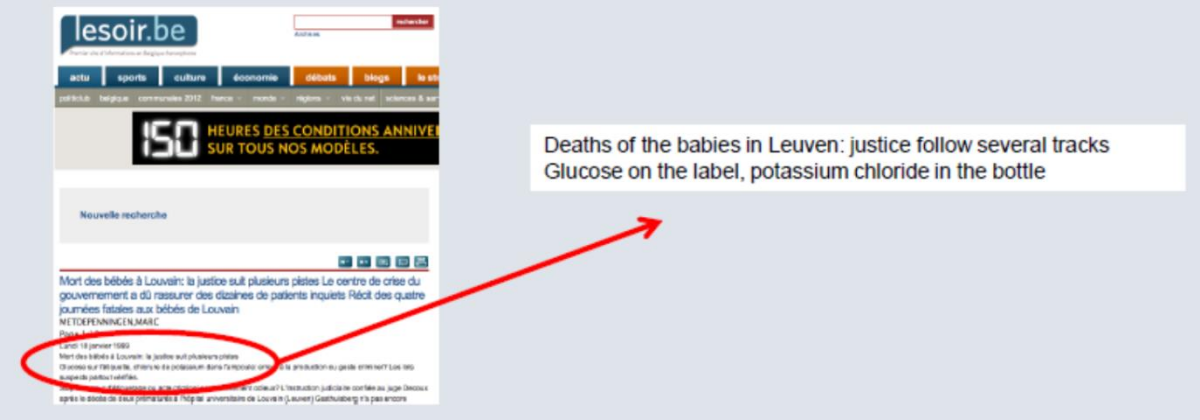
Labeling and leaflets

- Criticalities/risks (e.g., wrong or incomplete information, translation mistakes) are under-estimated, so labels and leaflet are rarely checked by buyers



Assessment of the product dossier (14)

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- Frequent *labeling* deviations:
  - Poor-quality glue : loss of label (e.g. tropical contexts)
  - Poor-quality ink: printings can disappear over the time
  - The text is not validated by the producer, nor by NRA
  - Storage instructions not explicit or not accurate
  - Odd expiry dates

Good Distribution Practices and MQAS

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World Health Organization

Annex 5

WHO good distribution practices for pharmaceutical products

1. Introduction
2. Scope of the document
3. Glossary
4. General principles
5. Regulation of the distribution of pharmaceutical products
6. Organization and management
7. Personnel
8. Quality system
9. Premises, warehousing and storage
10. Vehicles and equipment
11. Shipment containers and container labelling
12. Dispatch and receipt
13. Transportation and products in transit
14. Documentation
15. Repackaging and relabelling
16. Complaints
17. Recalls
18. Returned products
19. Counterfeit pharmaceutical products
20. Importation
21. Contract activities
22. Self-inspection

References

Good Distribution Practices

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- Good Distribution Practices (GDP): often, a weak link in the supply chain:
  - Storage and transport conditions (T, humidity)
  - Cold chain management
  - Storage in ports and transit zones

Microbial contamination of phenobarbital tablets

Overheated chloramphenicol vials (Darfur)

Friability of pyridoxine tablets

Probable impurities due to degradation of unstable acetylsalicylic acid (Togo-2013)

Exposure of glucose 50% at inappropriate temperatures (South Soudan-2010)

WHO MQAS (1)

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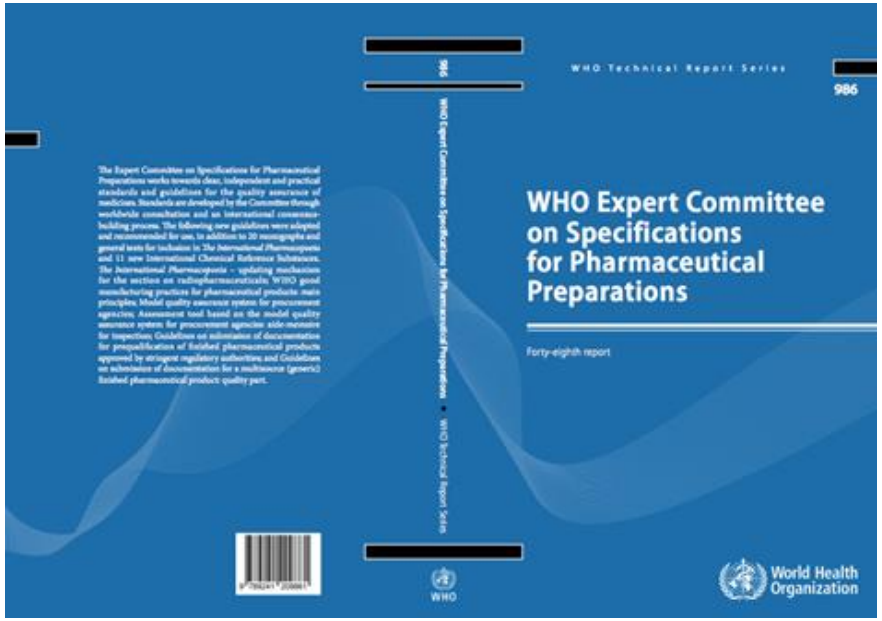
- In absence of strong regulation in LMICs, international distributors or national procurement centers/medical stores play a key role in quality enforcement!
- The WHO issued a Model Quality Assurance System for Procurement Organizations (MQAS, 2007, 2014).



WHO MQAS (2)

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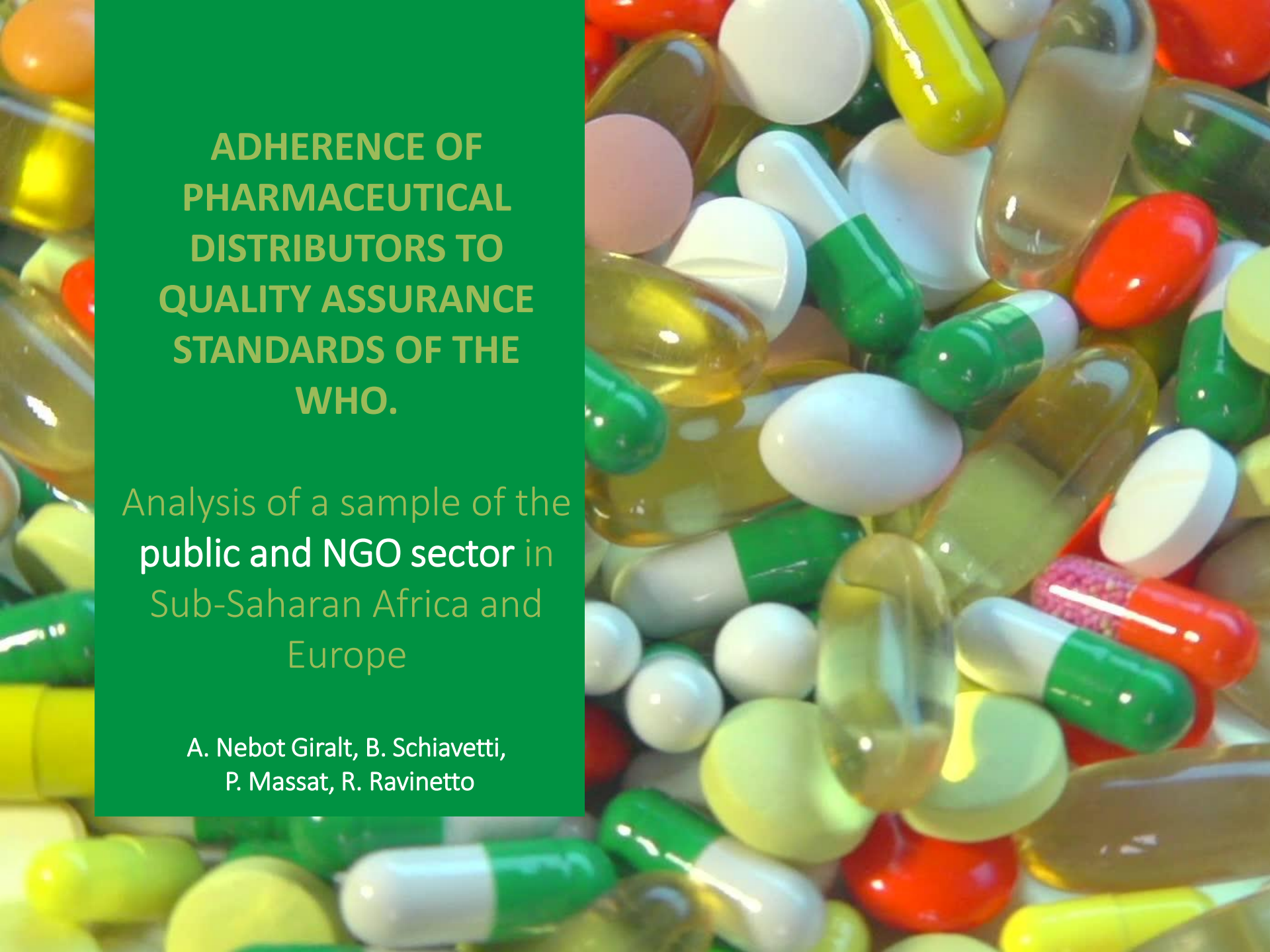
- General requirements
- Prequalification
- Purchasing
- Receipt and storage
- Distribution
- Reassessment

Procurement agencies involved in any key activities of procurement should develop and implement their own internal quality assurance systems based on the Model …

This document provides guidelines for UN procurement agencies

But it may be used by other procurement agencies to establish quality assurance systems for their own activities.



ADHERENCE OF PHARMACEUTICAL DISTRIBUTORS TO QUALITY ASSURANCE STANDARDS OF THE WHO.

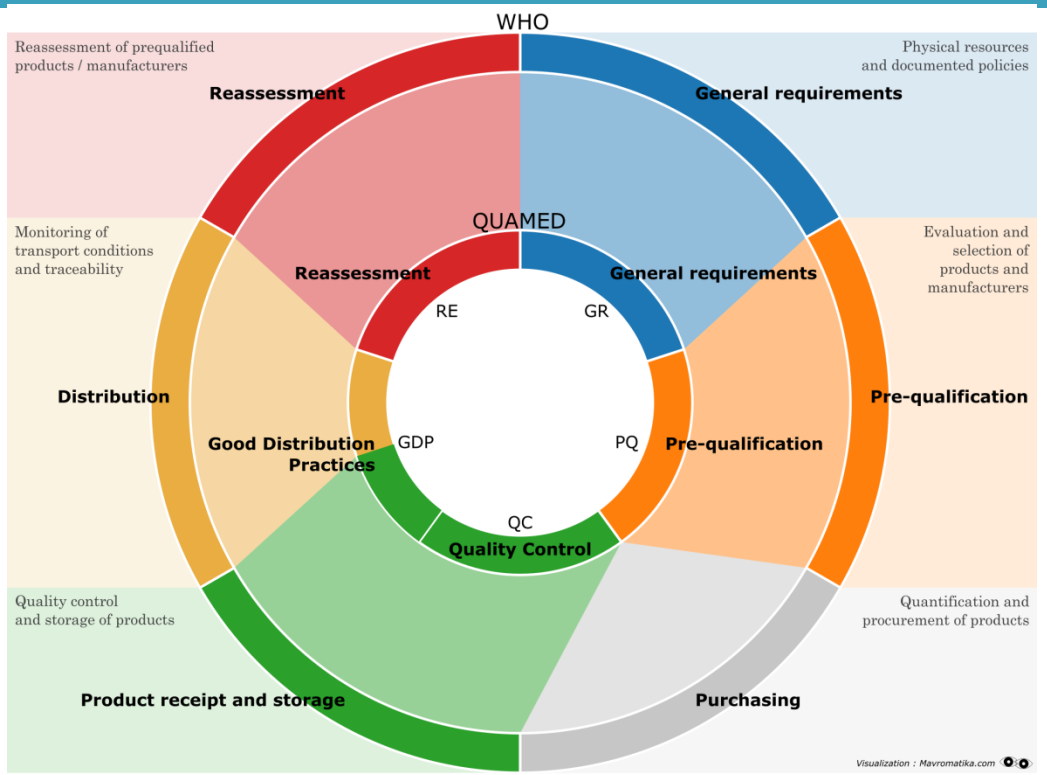
Analysis of a sample of the **public and NGO sector** in Sub-Saharan Africa and Europe

A. Nebot Giralt, B. Schiavetti,
P. Massat, R. Ravinetto

Objective

To evaluate the compliance
with the WHO Quality Assurance standards (MQAS),
of a **sample of humanitarian wholesalers in Europe and national procurement centres in sub-Saharan Africa**

- To assess the degree of compliance with 5 quality assurance criteria
- To identify the factors influencing the compliance to quality assurance standards



Methods

Two-phases mixed methods study (QUANT ➔ qual):

Retrospective quantitative analysis of QUAMED data

+

Qualitative data collection; convenience sample

- EU; sub Sharan Africa
- Audit reports 2011-2014
- WHO-MQAS audit-type

18 wholesalers: 10 (ssAfrica) + 8 (Europe)

1. General requirements
2. Selection of products
3. Distribution
4. Quality Control
5. Re-evaluation of suppliers

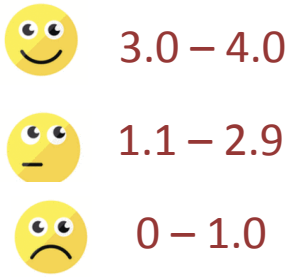
4 in-depth interviews

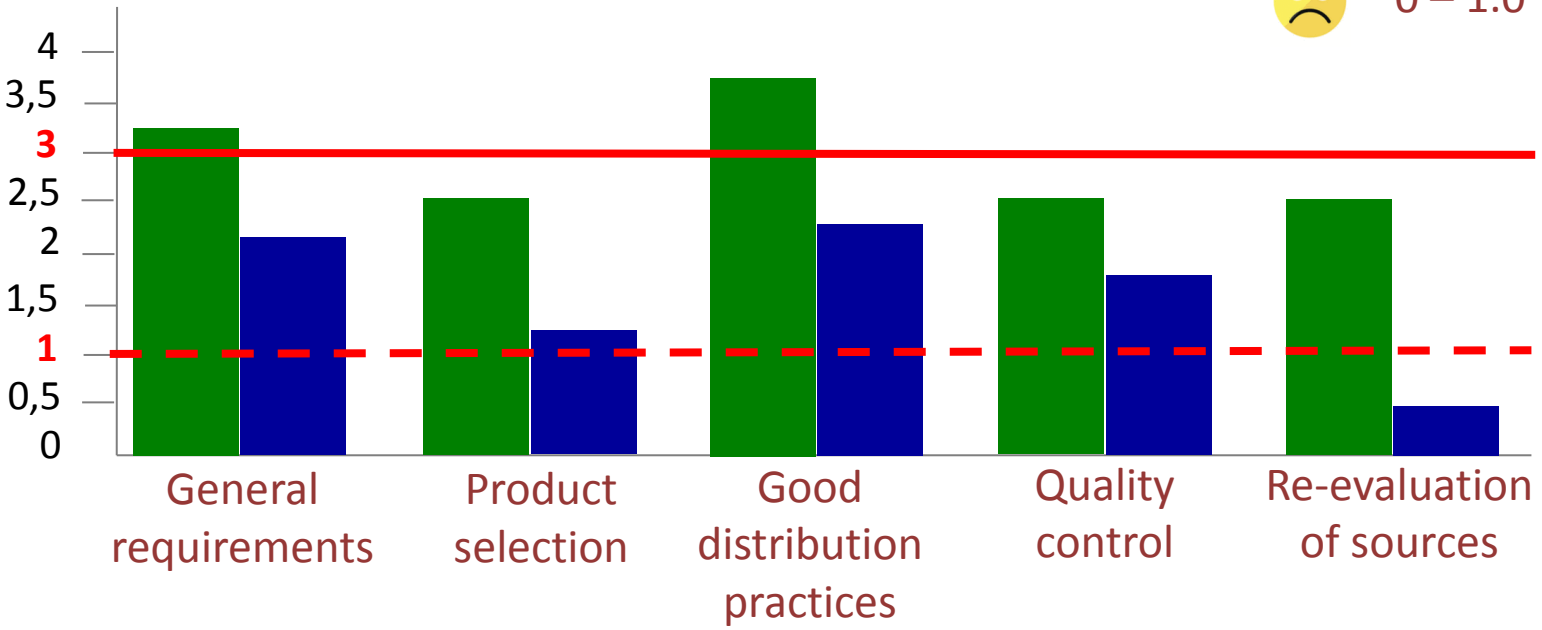
3 informal discussions

- Triangulation
- Helping/hindering factors

Quantitative results

Compliance with the WHO-MQAS



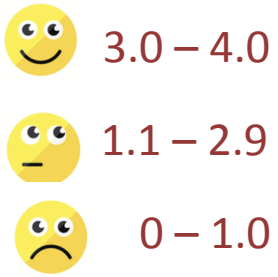


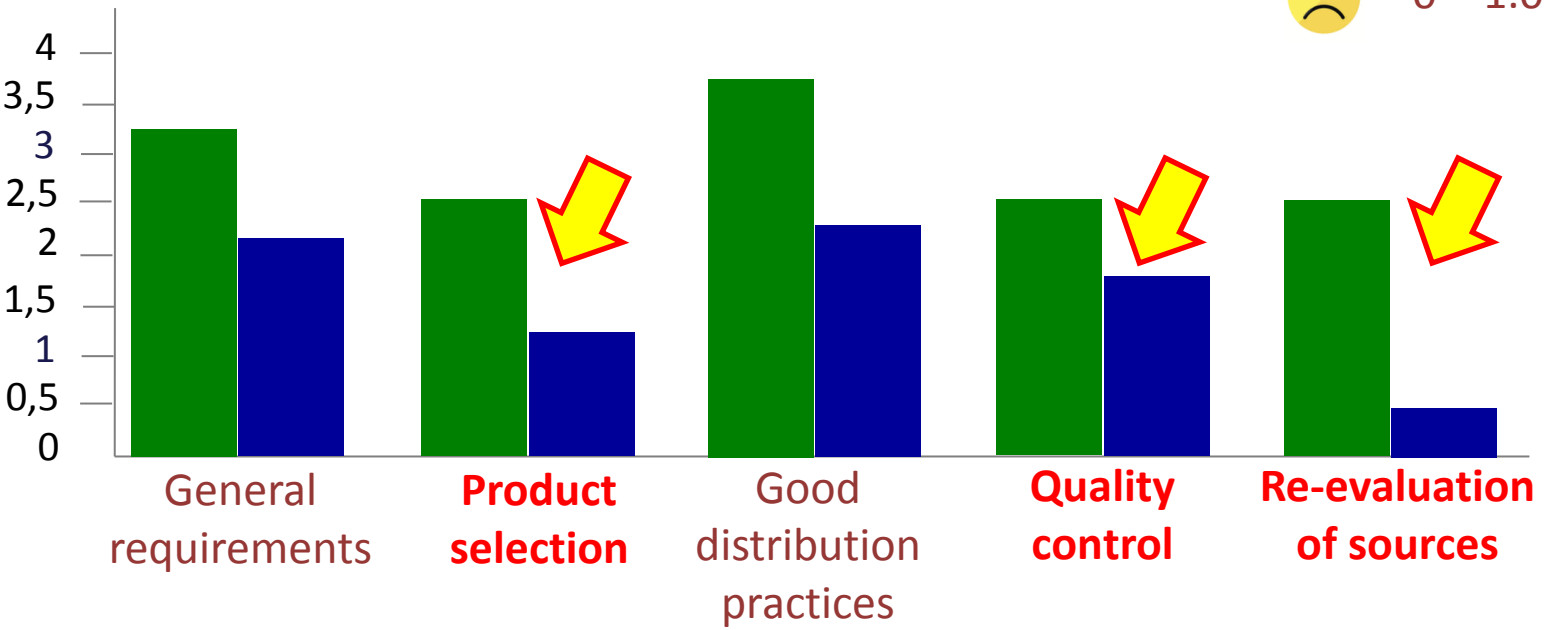
Europe (n = 8)

Sub-Saharan Africa (n = 10)

Quantitative results

Compliance with the WHO-MQAS



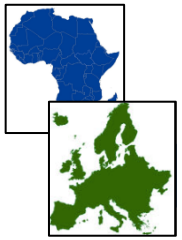


Europe (n = 8)

Sub-Saharan Africa (n = 10)

Qualitative results

Helping factors



- **Harmonisation of the regulation** (international regulation)
- Juridical/financial **autonomy**

- Supporting initiatives (e.g. QUAMED)
- MQAS international audits
- WHO/MQAS role

- **Availability of human/financial resources**
- Healthy competition based on quality specifications

Hindering factors

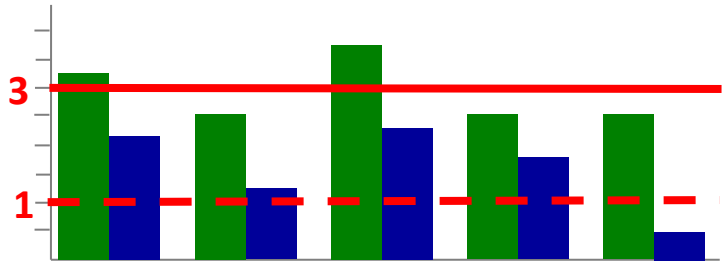
- Lack of knowledge and promotion of MQAS standards

- Historical focus on distribution over product-selection
- **Lack of financial/HR resources**
- Lack of transparency (suppliers)
- **Weak national regulation**

- EU's export legislation
- Lack or limited **commitment** on medicines quality

Conclusions

1



Compliance with WHO-MQAS still too weak

2

Important gap between European & ssAfrica wholesalers

3

- ✓ Commitment
- ✓ Autonomy
- ✓ Regulation
- ✓ Capacity

Helping factors to implement and use MQAS

4

MQAS: a very useful tool for the 'big wholesalers'

WHO Prequalification

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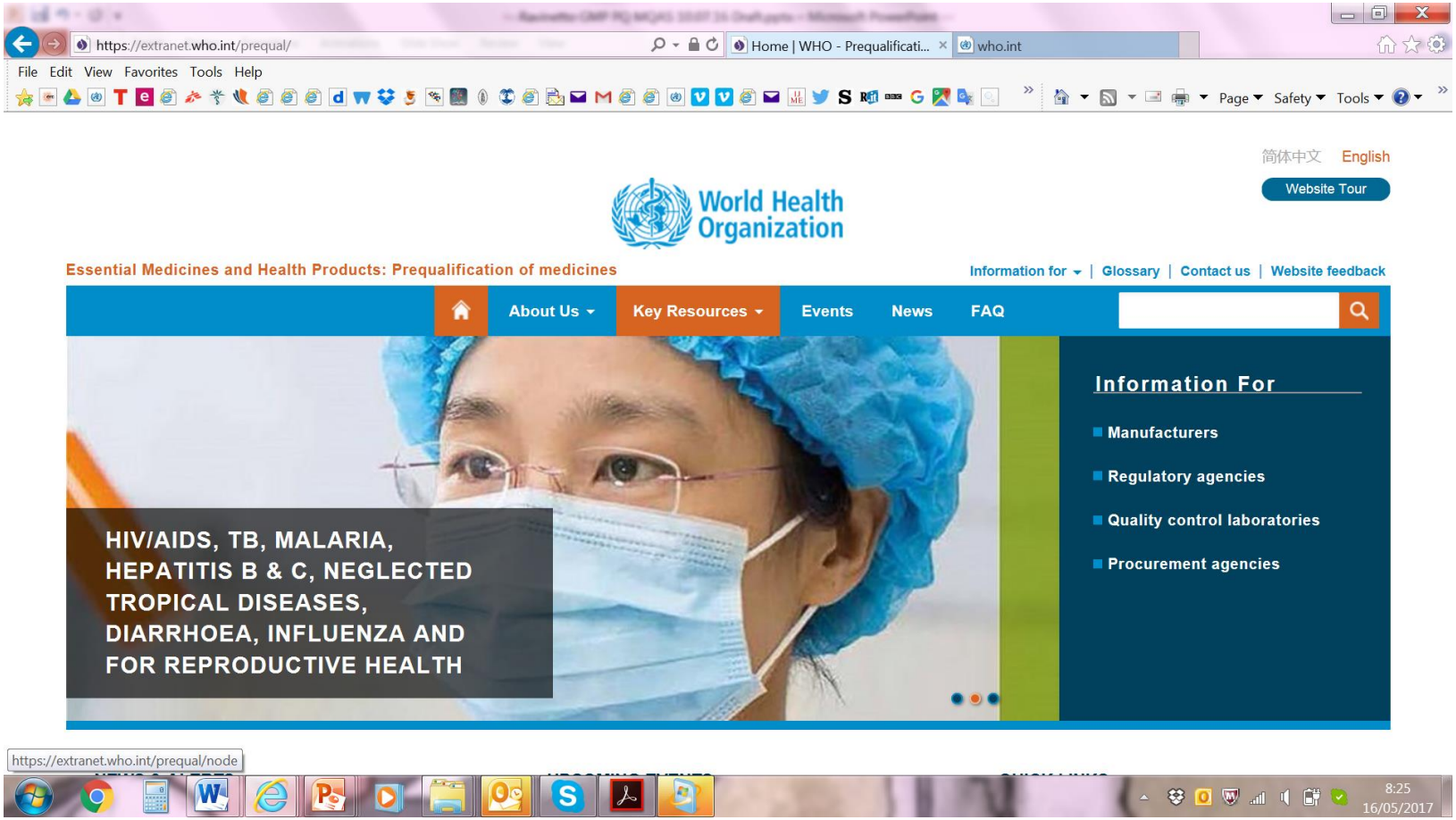

WHO Prequalification (1)

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- Assesses products for HIV, TB, malaria (+ reproductive health, avian flu, NTDs, hepatitis B and C, and cancer biosimilars)
- Publishes the list of approved products (product-manufacturer couple) and the summaries of inspection reports (WHOPIR)

- Pre-qualified medicines: http://apps.who.int/prequal/
- Pre-qualified vaccines: http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/
- Pre-qualified in vitro diagnostics: http://www.who.int/diagnostics_laboratory/evaluations/en/
- Medicines QC laboratories:
- https://extranet.who.int/prequal/content/medicines-quality-control-laboratories-list

WHO Prequalification (2)

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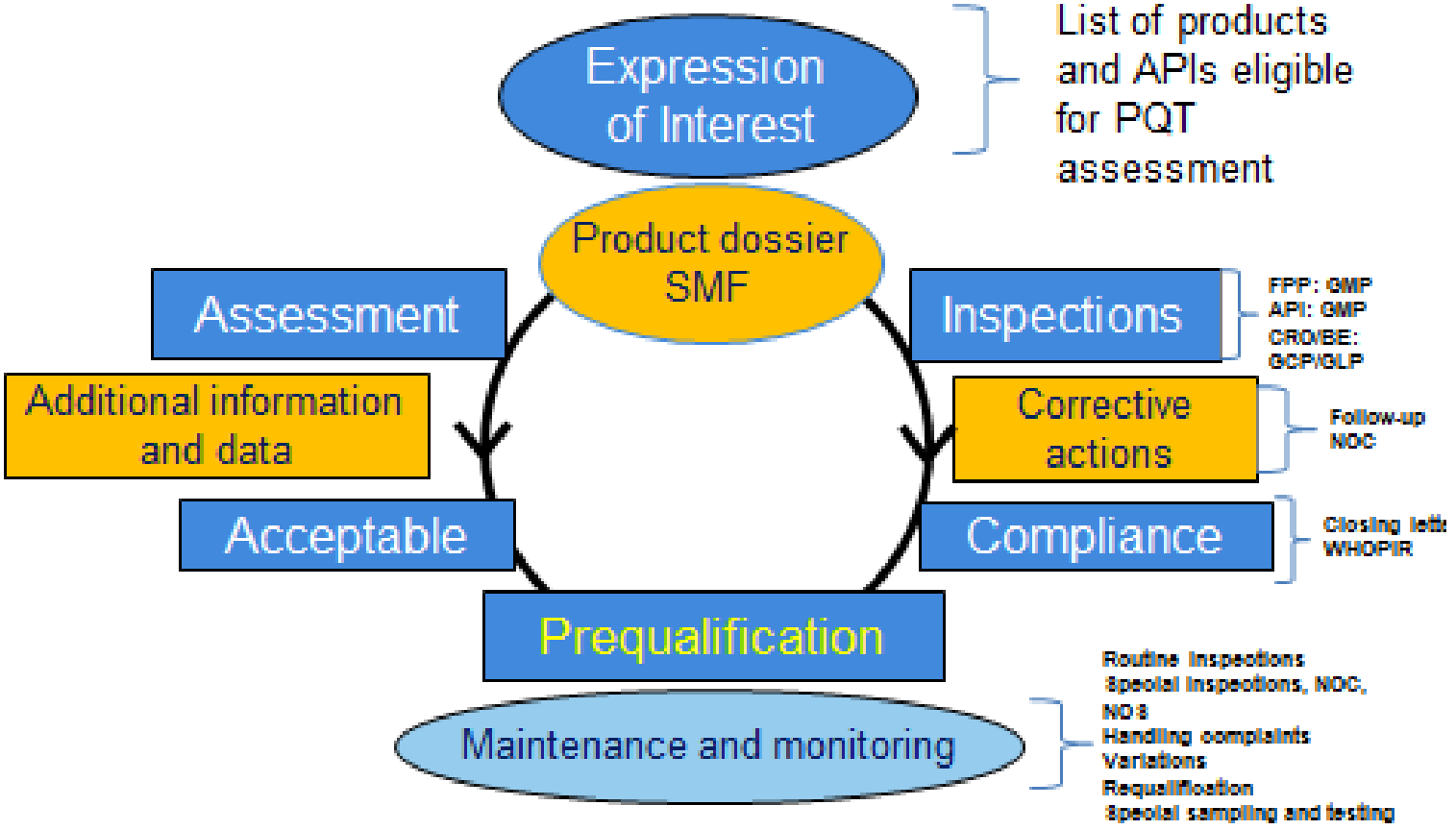
WHO-PQTm process



WHO Prequalification (3)

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Collaborative procedure for assessment and accelerated registration of WHO-prequalified pharmaceutical products and vaccines

- NRAs have access to confidential assessment outcomes, to make their decisions and train national regulatory staff
- Feedback from NRAs allows WHO/PQT to ensure that the outcomes of its assessments are relevant to NRAs
- Patients and vaccinees gain faster access to pre-qualified products
- Of particular relevance in emergency situations
- NRAs can participate in the WHO/PQT assessments and inspections
- Manufacturers of prequalified products get faster approvals

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex08.pdf?ua=1

The Lancet Commission Essential medicines for universal health coverage

Recommendations on assuring quality and safety

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- To promote the harmonisation of QA efforts, through an international standard regulatory dossier that covers format and content
- WHO PQ should have moving focus on new essential medicines
- Payers and procurement agencies must adopt good procurement practices, with effective and transparent QA mechanisms
- Governments must redirect NRAs' activities towards those that add value and reduce duplication of effort, and engage with a system for independent and public assessment of NRAs' performance
- NRAs must encourage the involvement of other stakeholders and general public in promoting quality and safety of essential medicines
- WHO and national governments must establish concrete targets and a public accountability mechanism for the performance of NRAs

QA: a way to prevent!

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