JOINT UNICEF, UNFPA & WHO MEETING WITH MANUFACTURERS AND SUPPLIERS

30 November - 2 December 2020

WHO Prequalification Inspection Services:

Update on activities of inspections including quality guideline expectation

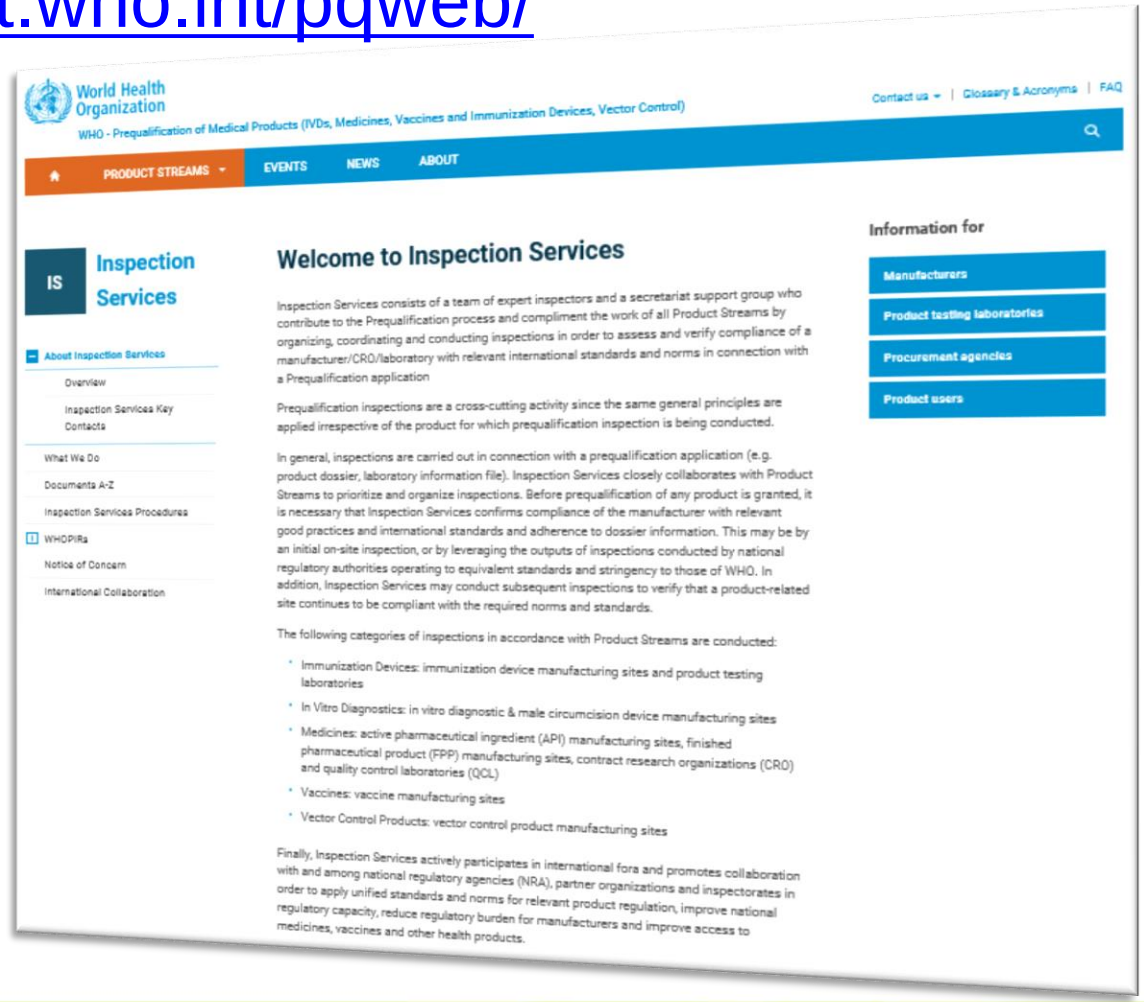
Inspection services, Prequalification Unit
Regulation and Prequalification Department
Access to Medicines and Health Products Division
World Health Organization,
Geneva, Switzerland

Agenda

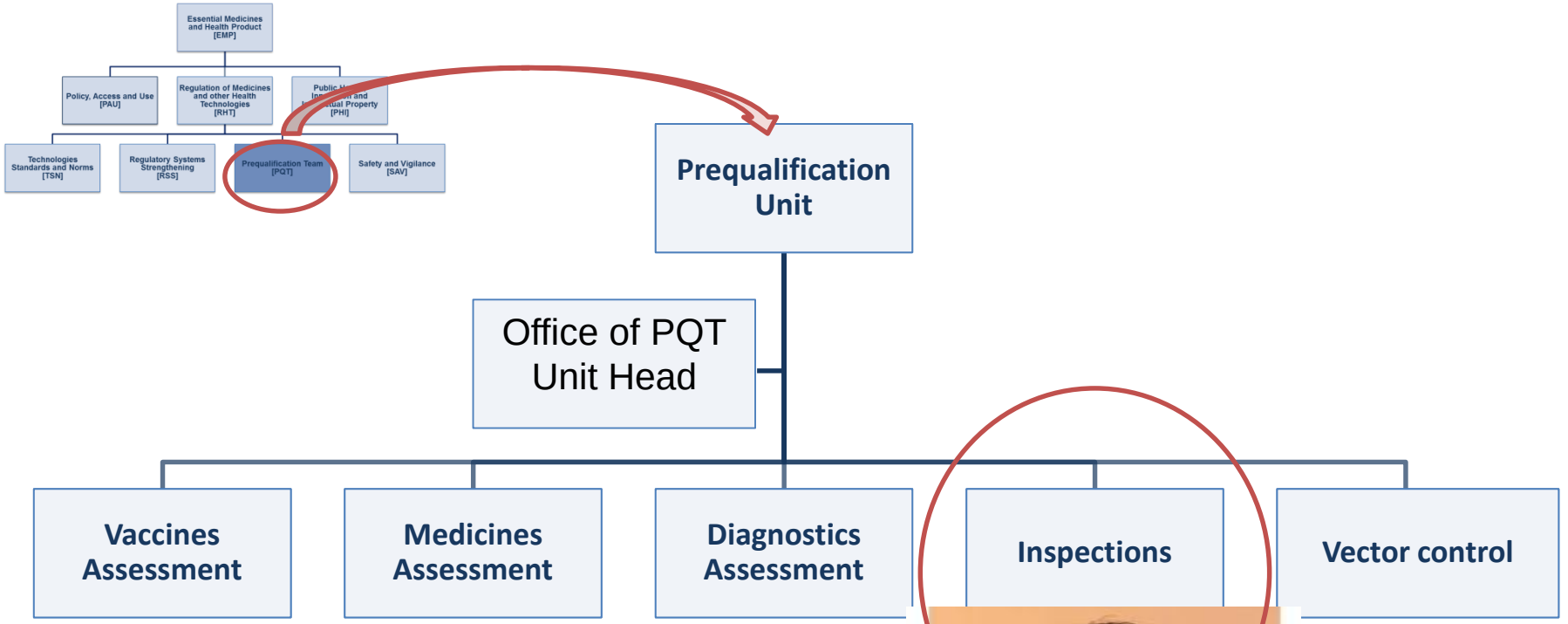
1. Introduction
2. WHO PQ Inspection Services
3. Updates related to inspections of
    a) Vaccine (Vx)
    b) Medicines (Mx)
    c) In-vitro diagnostics (Dx)
    d) Vector control (VCT) products
3. New and updated GxP guidelines
4. Take away message

New: Prequalification Website

https://extranet.who.int/pqweb/



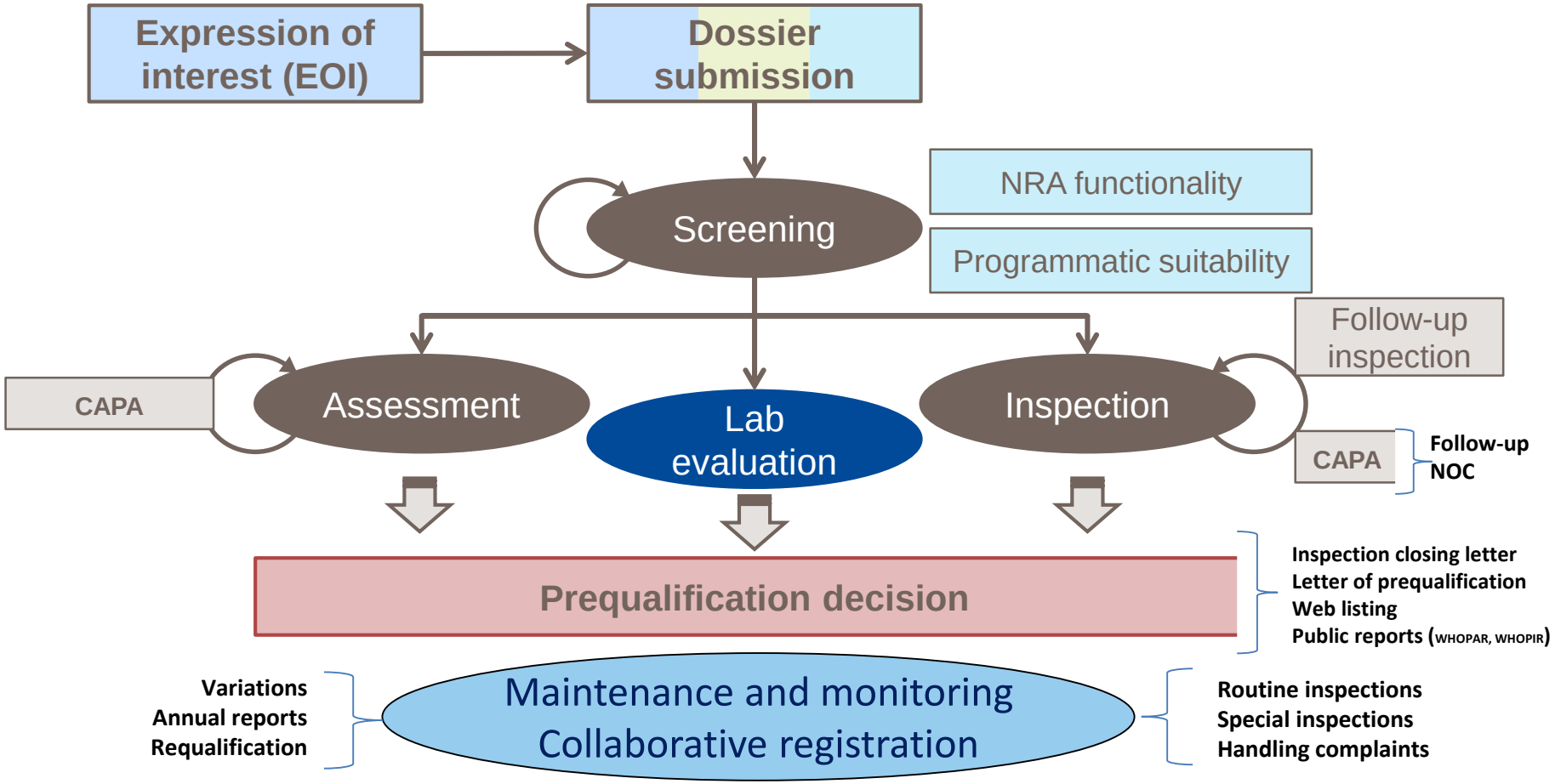
Structure of the Prequalification Unit



Prequalification inspections are a cross-cutting activity since the same general principles are applied irrespective of the product for which prequalification inspection is being conducted.

Prequalification workflow

For each type of product, prequalification includes a comprehensive dossier assessment and a manufacturing site inspection, as well as other product-specific elements of evaluation



Different Product Stream

Vaccines

- *Origin*:
  Request by UNICEF and PAHO to evaluate quality, safety and efficacy of vaccines in the context of national immunization programmes
- ***PQ beginning***:
  1987

Medicines

- *Origin*:
  Request by WHO MS to assess the quality, safety and efficacy of low-cost and new FDCs HIV/AIDS generic medicines
- ***PQ beginning***:
  2001

Diagnostics

- *Origin:*
  Substandard performance of HIV assays in sub-Saharan Africa
  → Response: HIV Test Kit Evaluation Programme (1988)
- **PQ beginning:**
  2010

Vector Control

- *Origin*:
  WHOPES set up in 1960 for evaluation of pesticides for public health. In 2015, WHO initiated reforms to foster innovation, improve efficiency, assure quality and align with other PQ programmes
- ***PQ beginning***:
  2017

Prequalification Inspection Services

1. An independent team of expert inspectors contribute to the Prequalification process by conducting inspections.
2. Inspections are carried out in connection with a prequalification application– dossier submission. **No dossier, no inspection**!
3. Risk based approach followed for planning, scheduling, conducting and closing of inspections (initial, surveillance and for-cause inspections)
4. Inspection Services closely collaborate with different product stream teams to prioritize and organize inspections.
5. Before prequalification of any product is granted, it is necessary that Inspection Services confirms compliance of the manufacturer/laboratory/CRO with relevant Good Practices (GxP), international standards and adherence to dossier information.

Prequalification Inspection Services

The objective of Prequalification inspections are to assess compliance with WHO GxP guidelines, ISO 13485:2016, ISO 9001:2015 or equivalent requirements and data verification.

The following categories of inspections in accordance with Product Streams are conducted:

1. **Immunization Devices:** immunization device manufacturing sites and product testing laboratories
2. **In Vitro Diagnostics:** in vitro diagnostic & male circumcision device manufacturing sites
3. **Medicines:** active pharmaceutical ingredient (API) manufacturing sites, finished pharmaceutical product (FPP) manufacturing sites, contract research organizations (CRO) and quality control laboratories (QCL)
4. **Vaccines:** vaccine manufacturing sites
5. **Vector Control Products:** vector control product manufacturing sites

Inspection Team and Timelines

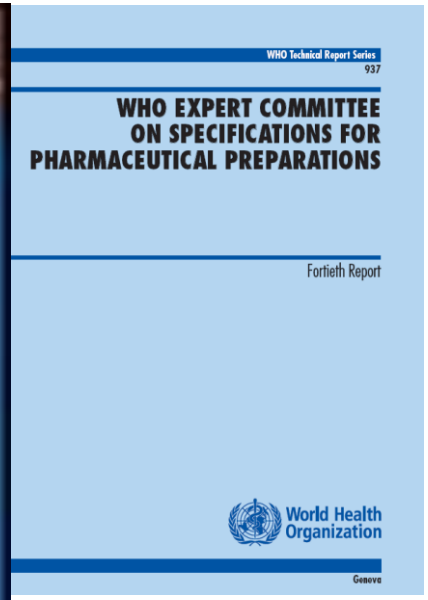
Inspection Team

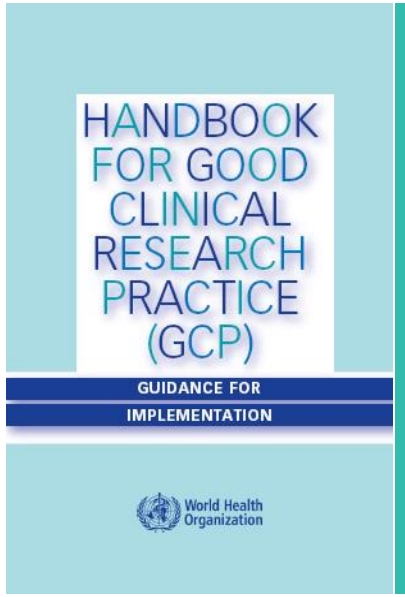
a) WHO staff (qualified inspector) lead the inspection
b) Co-inspector from well-established inspectorate (e.g. PIC/S)
c) Technical expert/product assessor, where required
d) Inspectors from the National Regulatory Authority (NRA) invited as observers
e) Representatives of procurement agencies and UN organizations invited as observers

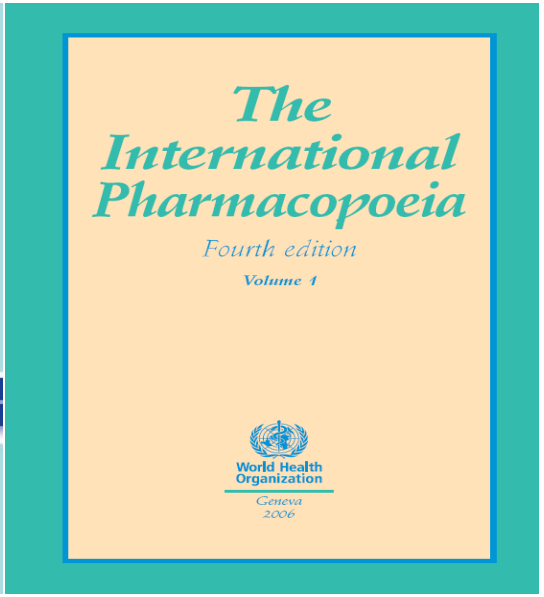
Inspection Timelines

a) Follow-up inspection: 6-9 months from inspection.
b) Routine inspection: 1–3 years
c) Special inspection: focusing on the specific causes (e.g. complaint) that triggered the inspection.

Prequalification Programme: International norms, standards and guidelines used in inspection activities to ensure wide applicability

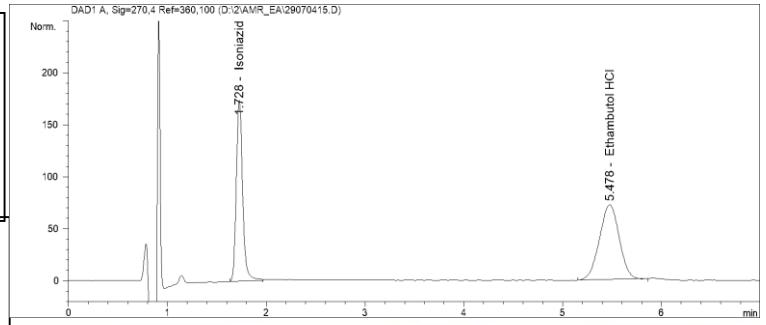






USP
BP
Ph. Eur.
Ph. Int., JP

Other guidelines
e.g. ICH, ISO



International norms, standards and guidelines used in inspection activities – GMP (APIs and FPPs)

- WHO GMP for **Active Pharmaceutical Ingredients**,, Technical Report Series/**TRS**, No 957, 2010, Annex 2
- WHO GMP for **Pharmaceutical Products: Main Principles,** TRS, No. 986, 2014, Annex 2
- WHO Good Practices for **Pharmaceutical Quality Control Laboratories,** TRS, No. 957, 2010, Annex 1
- WHO Good Practices for **Pharmaceutical Microbiology Laboratories,** TRS, No. 961, 2011, Annex 2
- WHO Guidelines on **Quality Risk Management,** TRS, No. 981, 2013 Annex 2,
- WHO GMP for Pharmaceutical Products containing **Hazardous Substances,** TRS, No. 957, 2010, Annex 3
- WHO Guidelines on **Heating, Ventilation and Air-Conditioning Systems** for non-sterile Pharmaceuticals Products, TRS, No. 1010, 2018 Annex 8,
- WHO Guidance on **Good Data and Record Management Practices**, TRS 996, 2016, Annex 5
- **WHO TRS No 1025, 2020:**
  a. Production of water for injection by means other than distillation, Annex-3,
  b. Good chromatography practices, Annex.-4,
  c. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing practices for the prevention of antimicrobial resistance, Annex-6 and
  d. Good storage and distribution practices, Annex-7.

International norms, standards and guidelines used in inspection activities – GCP/GLP/BE/ISO

- Guidelines for **Good Clinical Practice (GCP)** for trials on pharmaceutical products. World Health Organization, 1995, WHO Technical Report Series, No 850, Annex 3
- Guidance for **Organizations Performing in-vivo Bioequivalence Studies**. WHO Technical Report Series, No. 996, 2015, Annex 9
- Handbook for **Good Clinical Research Practice (GCP**) Guidance for implementation
- Guidelines for the preparation of a **Contract Research Organization Master File**. World Health Organization, WHO Technical Report Series, No. 957, 2010 Annex 7,
- WHO Guidance on **Good Data and Record Management Practices**. 2015, WHO Technical Report Series, No. 996, Annex 5
- **EMA** Guideline on **Bioanalytical Method Validation**
- **FDA** Guidance for Industry: **Bioanalytical Method Validation**
- **ISO 13485:2016 (for IVDs)** and **ISO 9001:2015 (for vector control products)**

Desk assessment of evidence of GXP compliance

1. **Objective** reduce duplication, frequency or duration of inspections
2. **Scope**
   - Finished pharmaceutical product (FPP)
   - Active pharmaceutical ingredient (API)
   - Contract research organizations (CROs)
   - Quality control laboratories (QCLs)
   - Devices and In-vitro Diagnostic (Dx- IVDs)
   - Vector control products (VCs)
3. **How it is done**
   - Review of recent inspection report and additional documentation
   - DA completed by finalizing desk assessment report

Please stay tuned for a full desk assessment presentation

Statistics at a Glance (1 Jan-7 Oct 2020)

	Initial	Follow-up	Reinspection	Desk review	Special
FPP	2	0	8	24	0
API	0	0	0	25	0
CRO	2	0	0	13	0
QCL	1	0	8	2	0
Dx (IVD)	2	0	0	3 & 71 EULs	0
Dx (MCD)	0	0	0	0	0
Vaccines	1	1	0	3	1
Vector Control	3	0	0	0	0

Total Inspections:

FPP: On-sites: 10, DA:24, Total: 34

API: On-sites: 0, DA:18, Total: 18

API Intermediates: DA: 7

CRO: On-sites: 2, DA:13, Total: 15

QCL: On-sites: 9, DA:2, Total: 11

Total for Mx: = 85

Dx IVD: On-sites: 2, DA:3

IVD-EUL: 71 Total: 76

Vaccine: On-site: 3, DA: 3, Total: 6

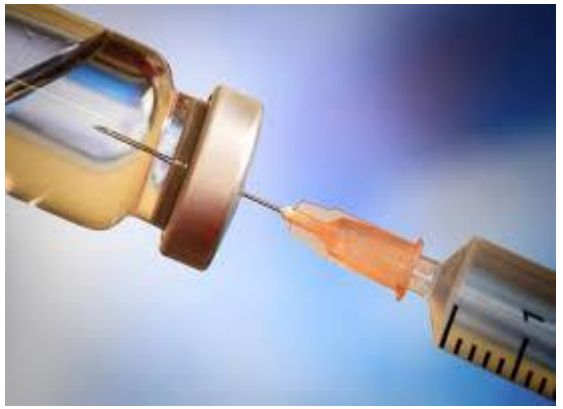
Vector Control: On-sites: 3, DA:0, Total: 3

Inspection Outcome Publicly Available

1. Public inspection reports are published on WHO Prequalification website for **transparency purposes** and as a result of **Resolution WHA57.14** of the World Health Assembly.
2. A WHOPIR is a publicly available summary of:
   - on-site inspection
   - desk assessment
3. A Notice of Concern (NOC) is issued when significant non-compliances have been identified with result in failure to comply with relevant standards and norms.

Vaccines






Vaccine Activities during 2020:

Pre-Covid 19:

2 on-site inspections:

- One initial inspection for the first ever EUL nOPV2 vaccine,
- One follow up inspection,
- Closure of two inspections conducted in 2019.

Post Covid 19:

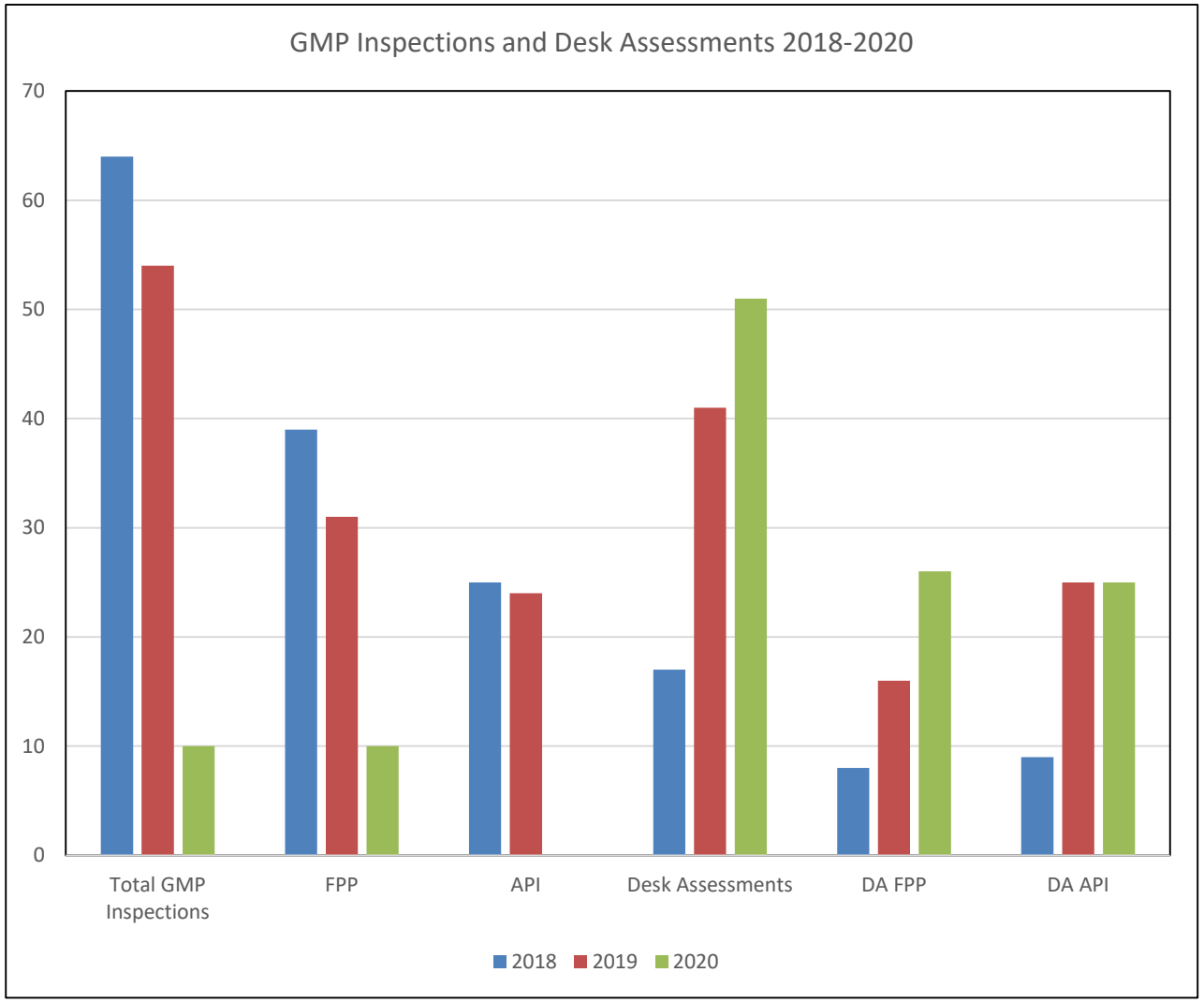
Several inspections cancelled, postponed due to Covid-19 Pandemic.

1. Follow up inspection of nOPV2 vaccine with the national regulatory authority;
2. Four Desk Reviews conducted;

- Two desk reviews included sIPV vaccines with three drug substances and one finished product each;
- One desk review included TCV vaccine with one drug substance, one carrier protein and one finished product;
- One desk audit for WHO contracted laboratory for vaccines testing for animal tests on Diphtheria, Tetanus and whole cell pertussis components.

Medicines Activities during 2020

(APIs, FPPs, CROs and QCLs)



	2018	2019	**2020**
Total GMP Inspections	64	54	**10**
FPP	39	31	**10**
API	25	24	**0**
Total Desk Assessments	17	41	**51**
DA FPP	8	16	**26**
DA API	9	25	**25**

CRO inspections

Year 2018

- 13 onsite - inspections

Year 2019

- 7 onsite - inspections

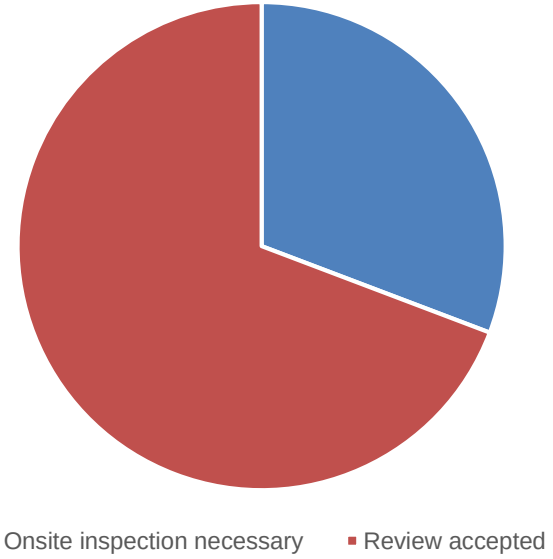
Year 2020

- No onsite inspection
- 13 Desk Reviews

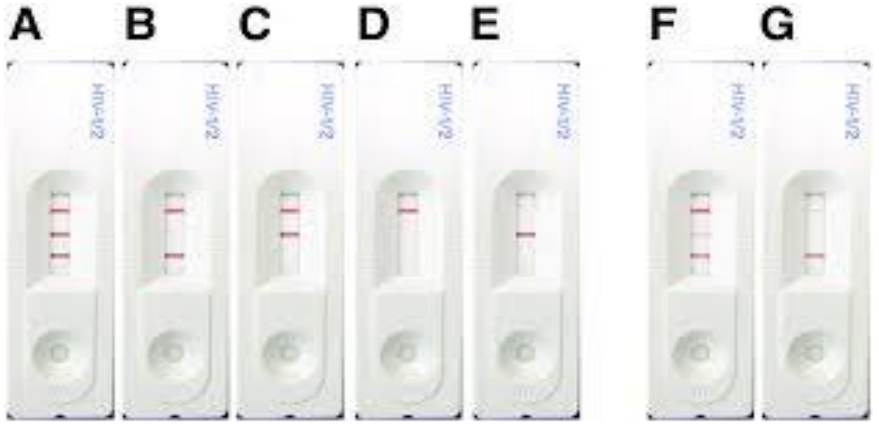
CRO Desk assessment 2020

13 Desk assessment Review of CROs were completed in 2020

- Recommended: on-site inspection 4 CROs
- Recommended: Desk review accepted 9 CROs



Dx-IVD activities during 2020 Emergency Use Listing (EUL)



Emergency Use Listing (EUL)

1. Risk-based procedure for assessing and listing in vitro diagnostics (IVDs) not (yet) undergone stringent regulatory assessment
2. Intended for use primarily during **public health emergencies** of international concern (PHEICs), or in other public health emergencies.
3. Based on an essential set of quality, safety and performance data.
4. NOT equivalent or alternative to WHO prequalification

WHO Member States alone hold the authority to decide whether or not to allow the emergency use of a product/medicine or vaccine into their country.

EUL: QMS review

	Accepted	Under review	Rejected or withdrawn	Awaiting submission	Total
NAT	34	6	14	1	55
Antibody	18	7	1	5	31
Antigen	2	1	1	3	7

Dx-IVD On-site inspections

Year 2020

- On-site inspections : 2
- Desk assessments: 3
- Products:
  - HIV RDT: 1
  - Malaria RDT: 5
  - HIV NAT: 3
  - HPV NAT: 2
  - SARS-CoV-2 NAT: 1
- Pandemic led to Travel restrictions (March 2020)

Vector Control Product inspection activities during 2020

Vector control on-site inspections

Year 2020

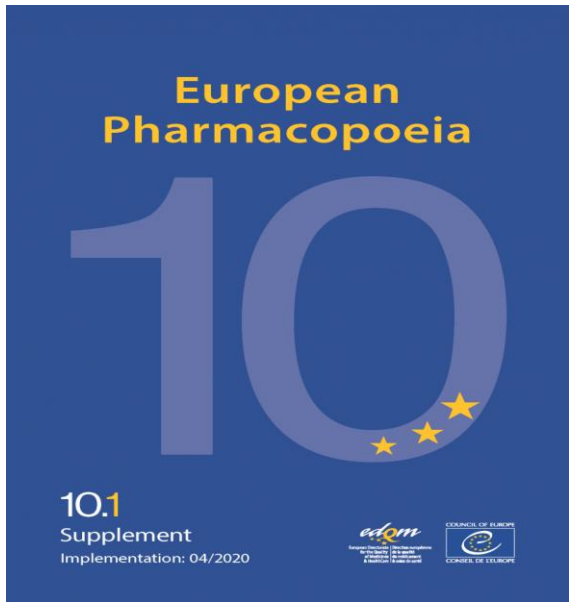
- On-site inspections : 3
- Pandemic led to Travel restrictions (since March 2020)
- Due to nature of sites, not possible to perform remote inspections
- Due to lack of inspection reports available from SRA, no desk reviews conducted

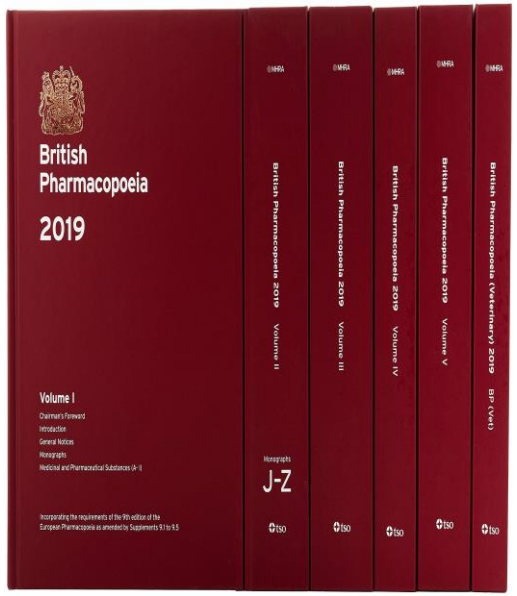
Vector manufacturers:

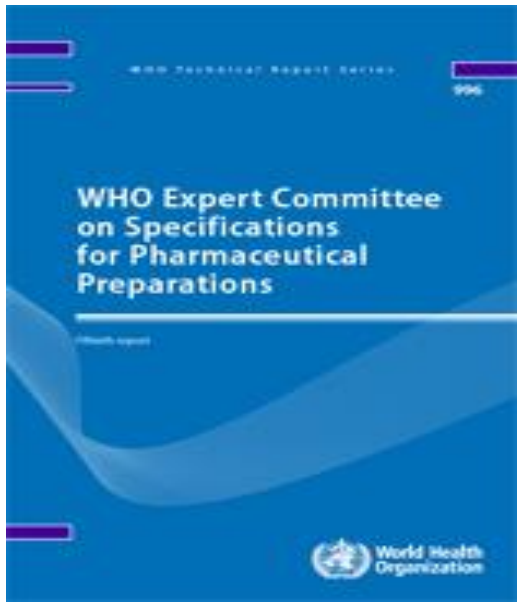
Examples of commonly cited NCs

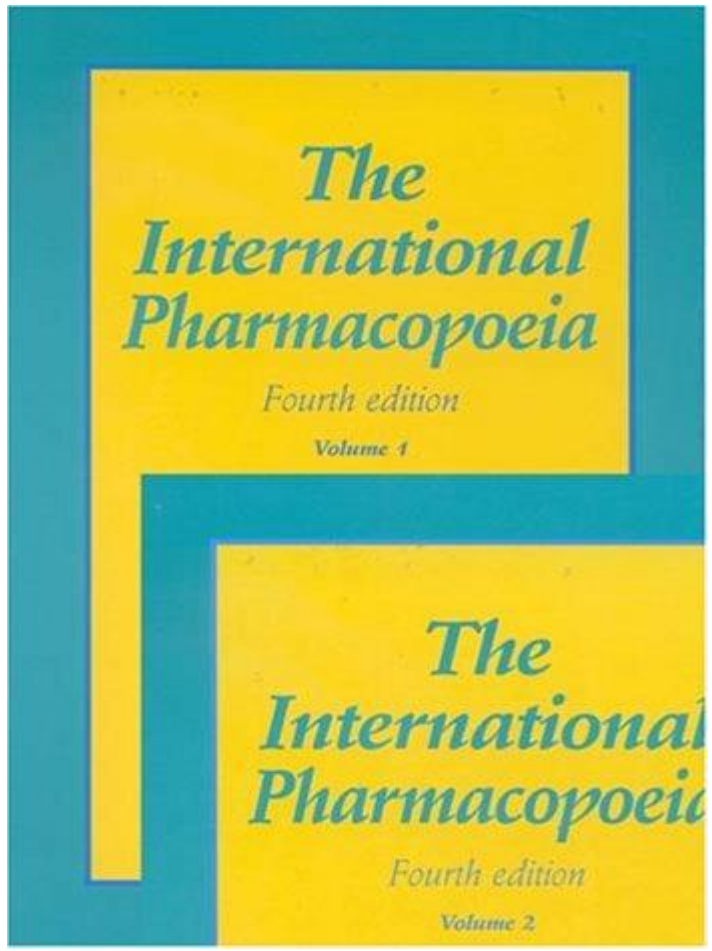
1. Equipment not calibrated and records not retained;
2. No recording of batch numbers of API or inactive ingredients on batch manufacturing records;
3. Product release not considering: review of the production process or related records;
4. Inadequate reconciliation of Printed Packaging Components:
    - Labels
    - Printed polybags
5. Data Integrity: Excel sheets used for calculation not locked to safe guard the formulas from unintentional changes or alterations.

New and updated GxP guidelines









Outcome of the 55th Expert Committee on Specifications for Pharmaceutical Preparations: October 2020

1. Points to consider when including **Health Based Exposure Limits (HBELs)** in cleaning validation (Annex-2)
2. Good manufacturing practices: **Water for pharmaceutical use** (Annex 3)
3. Guideline on **Data Integrity** (Annex 4)
4. UNFPA/WHO Recommendations for condom storage and shipping (Annex 5)
5. UNFPA/WHO Guidance on testing of male latex condoms (Annex 6)
6. UNFPA/WHO Guidance on conducting post-market surveillance of condoms (Annex 7)
7. WHO **"Biowaiver List"** (Annex 8)
8. WHO Certification Scheme on quality of pharma. products moving in international commerce (Annex 9)
9. **Good reliance practices** in the regulation of medical products (Annex 10)
10. **Good regulatory practices** for regulation of medical products (Annex 11)

Update on TRS 961 Annex 6 versus Annex 1 (Manufacturing of sterile medicinal products):

WHO TRS 961, annex 6 "*WHO GMP for sterile pharmaceutical products*" version 2011 updated

- To allow for a clear structure with a sensible sequence of its content and sections

Update on TRS 961 Annex 6 versus Annex 1

Annex 1: Manufacture of Sterile Products

Document map

Section Number	General overview
1. Scope	Includes additional areas (other than sterile products) where the general principles of the annex can be applied.
2. Principle	General principles as applied to the manufacture of sterile products.
3. Pharmaceutical Quality System (PQS)	Highlights the specific requirements of the PQS when applied to sterile products.
4. Premises	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of Barrier Technology.
5. Equipment	General guidance on the design and operation of equipment.
6. Utilities	Guidance with regards to the special requirements of utilities such as water, gas and vacuum.
7. Personnel	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance to the qualification of personnel.
8. Production and specific technologies	Discusses the approaches to be taken with regards to aseptic and terminal sterilization processes. Discusses approaches to sterilization of products, equipment and packaging components. Also discusses different technologies such as lyophilization and Form-Fill-Seal where specific requirements apply.
9. Viable and non-viable environmental and process monitoring	This section differs from guidance given in section 4 in that the guidance here applies to ongoing routine monitoring with regards to the design of systems and setting of action limits alert levels and reviewing trend data. The section also gives guidance on the requirements of Aseptic Process Simulation (APS).
10. Quality control (QC)	Gives guidance on some of the specific Quality Control requirements relating to sterile products.
11. Glossary	Explanation of specific terminology.

Key changes in summary:

No paradigm change but update relates:

- ❑ Introduction and emphasis of **QRM**,
- ❑ Need for a documented **contamination control strategy,**
- ❑ Based on QRM, **design is paramount to risk reduction**,
- ❑ Need to **use current technologies** (e.g. RABS, Isolators and even robotics),
- ❑ Old 70s technologies i.e. **open "grade A" or curtains not allowed**
- ❑ Needs to be designed to keep **operators outside of the Grade A,**
- ❑ …

Conclusion

1. **GxP inspections** are **fundamental elements of managing quality** in the pharmaceutical industry;
2. **Risk based approach** applied for planning, conducting and concluding GxP inspections.
3. **Desk assessments** are routinely conducted to leverage on the work performed by stringent regulatory authorities
4. Encouraging to receive applications from **manufacturers from developing countries**
5. Significant compliances observed however attention required in areas:
   - Understanding of “overall” requirements – move away from “silo” approach
   - Poor product understanding due to inadequate development
   - Poorly designed processes and validation
   - Poor laboratory practices
   - Poor data integrity practices

Acknowledgement

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1. Vx: Mustapha Chafai
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3. Dx: Kim Richards and Philippe Boeuf
4. VCT: Conrad Mark